Nucleophilic Substitution at Centers Other than Carbon: Reaction at the Chlorine of *N*-Chloroacetanilides with Triethylamine as the Nucleophile

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Received April 13, 1984

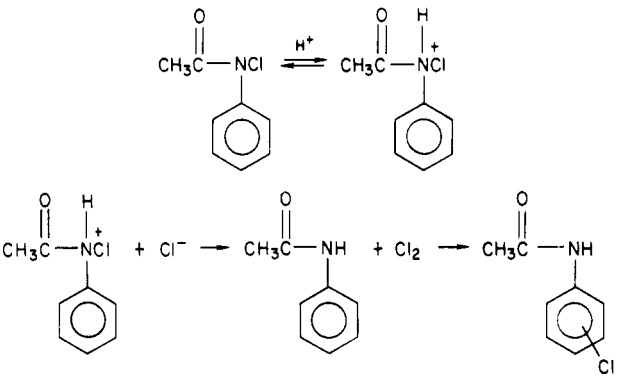
The reaction between triethylamine (TEA) and a series of para-substituted *N*-chloroacetanilides has been studied in aqueous solution buffered to pHs between 1 and 5. In these reactions, the exclusive product derived from the aromatic moiety is the corresponding acetanilide. The reaction occurs via two parallel pseudo-second-order paths, one acid catalyzed (the Orton-like mechanism), the other uncatalyzed. The uncatalyzed reaction is accelerated by the presence of electron-withdrawing substituents on the aromatic ring and can best be represented as nucleophilic displacement at chlorine. It therefore appears to be the prototype of a convenient class of reactions for the study of displacement reactions at chlorine. The ρ value for this reaction is 3.87 indicating substantial negative charge buildup in the aromatic ring during of the transition state. The acid-catalyzed reaction is more complex, presumably involving a protonation equilibrium for the *N*-chloroacetanilide prior to the rate-determining step similar to that in the Orton reaction.

Nucleophilic displacement reactions are among the most widely studied of all chemical reactions, although the center at which this reaction takes place is almost invariably a carbon atom. Other centers have been studied to a limited degree including platinum, sulfur, and oxygen.[2]

The rate constant for a bimolecular substitution reaction depends, to a large extent of course, on the nature of both the nucleophile and the electrophilic center with other factors playing roles of varying importance. In order to understand more fully how various factors influence the outcome of these reactions, a better knowledge of the effects of changes in the most obvious variable, the nature of the reaction center, would appear to be essential. The halogens represent the classical series of elements with well-defined gradations in chemical and physical properties, and it was thus considered of value to initiate our study of this subject with chlorine.

Nucleophilic substitutions at halogen have been reported in a few instances, for example, in 1-haloalkynes,[3] α-halo sulfones,[4] and vicinal dihalides.[5] The Orton rearrangement involves the migration of the chlorine of an *N*-chloroacetanilide to the ortho or para position in the presence of hydrochloric acid. The generally accepted mechanism[6] for this reaction requires protonation of the *N*-chloroacetanilide followed by nucleophilic attack on chlorine to produce, initially, molecular chlorine. Subsequent rechlorination of the aromatic ring then leads to the observed products (Scheme I).

Scheme I



Although this reaction has been quite extensively studied, the conditions for the rearrangement seem remarkably limited: acidic media and a halogen nucleophile. Since other sources of "positive halogen" have been shown to undergo reaction with a wide range of nucleophiles it seemed most reasonable to us that other nucleophiles should be equally capable of effecting the same reaction, or at least the same first step in this case.

The work reported in this paper represents a detailed examination of one aspect of nucleophilic substitution at the chlorine of *N*-chloroacetanilides. Our results indicate that this particular reaction *may* be acid catalyzed but that it also proceeds quite smoothly without catalysis. Moreover the range of nucleophiles[7] and of pH over which this reaction may occur are such that the Orton rearrangement must be considered as just one very specific example of a much more general class of displacements at chlorine.

After some preliminary study, it appeared that the best course of action would be to examine in detail the reaction of one nucleophile with several substituted *N*-chloroacetanilides. A particularly convenient nucleophile turned out to be triethylamine for a variety of reasons including the fact that the concentration of the free (unprotonated) nucleophile can be buffered to practically any value desired by the appropriate selection of the pH of the medium. The work described in this paper therefore deals with nucleophilic attack on the chlorine of *N*-chloroacetanilides by triethylamine. All reactions were carried out in buffered 10% aqueous acetonitrile maintained at a constant ionic

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Table I. Reaction Times and Yields for the Preparation of Substituted *N*-Chloroacetanilides

substituent	time	yield, %
none	15 min	66
p-nitro	15 min	44
p-chloro	75 min	48
m-chloro	24 h	34
p-cyano	4 h	42
p-acetyl	4 h	49

strength of 1.500 M with $NaClO_4$.

Experimental Section

All melting points were determined on a Thomas Hoover capillary melting point apparatus and are corrected. IR spectra were recorded in chloroform solution on a Perkin Elmer Model 137 double beam prism spectrometer. NMR spectra were recorded on a Perkin Elmer 60-MHz spectrometer. pH measurements were made with an Altex Model 3500 digital pH meter using a Corning Model 476051 combination electrode. The pH meter was standardized at the temperature of the reaction before each measurement by using NBS standards of either pH 4.00 ± 0.02 or 7.00 ± 0.02. The pH of all kinetic runs was monitored by taking measurements at at least three well-chosen intervals during the reaction. The pH for each kinetic run remained constant within the accuracy of the measurements (±0.05).[8] The high-performance liquid chromatography (HPLC) system used to monitor the reaction consisted of a Waters Associates Model M-45 solvent delivery system, a Rheodyne Model 7125 injector equipped with a 20-μL constant volume injection loop, and a Waters Associates Model 440 absorbance detector operating at 254 nm. All HPLC columns were reverse phase 4.6 mm × 250 mm packed with either Whatman R-Sil-C18HL (10 μm) or Alltech Associates Partisil 10-ODS2 (10 μm). Columns were packed with a slurry packing apparatus SLP-100 (Alltech Associates).

All buffer reagents were Baker Analyzed Reagent Grade of established purity. Sodium perchlorate monohydrate was Fischer Purified (98+%) and for the purpose of ionic strength calculation was assumed to be 99% pure.

Triethylamine was redistilled Baker Reagent Grade. *p*-Cyano- and *p*-acetylacetanilide were prepared from the corresponding commercially available amines by standard techniques. The *N*-chloroacetanilides were prepared by chlorination of the acetanilides by the following procedure. The acetanilide (2–5 g) was dissolved in the minimum volume of dimethoxyethane. This solution was added dropwise to a two molar excess of aqueous NaOCl (5%) containing a two molar excess of $NaHCO_3$, at 0 °C. The solution was stirred vigorously for a period of time dependent on the acetanilide used (see Table I). The solid *N*-chloroacetanilides were collected by filtration and were washed with 200 mL of cold water. The solid was dissolved in $CHCl_3$, dried ($MgSO_4$), and recrystallized from $CHCl_3$:petroleum ether. The *N*-chloroacetanilides were relatively stable if stored in the dark below 0 °C.

The following physical properties were recorded. **N-Chloroacetanilide**: mp 91.0–92.0 °C (lit.[12] mp 91 °C). **N-Chloro-*p*-chloroacetanilide**: mp 83.0–84.0 °C (lit.[13] mp 82 °C). **N-Chloro-*p*-nitroacetanilide**: red-orange solid; mp 97.7–99.7 °C. Anal. $C_8H_7N_2O_3Cl$: C; H; N. MNR ($CDCl_3$) δ 2.1 (s, 3 H), 7.65 (d, 2 H), 8.25 (d, 2 H); IR 1700, 1530, 1347 cm^{-1}. **N-Chloro-*p*-cyanoacetanilide**: red-orange solid; mp 110.6–111.6 °C. Anal. $C_9H_7N_2OCl$: C; H; N. NMR ($CDCl_3$) δ 2.35 (s, 3 H), 7.8 (m, 4 H); IR 1683, 2281 cm^{-1}. **N-Chloro-*p*-acetylacetanilide**: red-orange solid, mp 59.9–61.9 °C. Anal. $C_{10}H_{10}NO_2Cl$: C; H; N. NMR ($CDCl_3$) δ 2.1 (s, 3 H), 2.6 (s, 3 H), 7.45 (d, 2 H), 8.0 (d, 2 H); IR 1683 cm^{-1}. **N-Chloro-*m*-chloroacetanilide**: mp 85.9–87.4 °C. Anal. $C_8H_7NOCl_2$: C; H; N. NMR ($CDCl_3$) δ 2.1 (s, 3 H), 7.3 (s, 4 H); IR 1687 cm^{-1}. The infrared spectra of all *N*-chloroacetanilides were devoid of any N–H stretching frequency.

Products. In all reactions studied, the kinetics were monitored by HPLC. This enabled a determination of the concentration of the *N*-chloroacetanilide as a function of time, but, most usefully, it also permitted us to examine the reaction mixture at regular intervals for the appearance of products. In all the reactions between triethylamine and substituted *N*-chloroacetanilide, the only detectable product (more than 1%) containing an aromatic ring was the corresponding substituted acetanilide. During the reaction, copious quantities of acetaldehyde also were produced. Although the yield of this product was not determined quantitatively, when benzylamine was used as nucleophile, benzaldehyde was produced in close to quantitative yields.

Kinetics. All kinetic data were obtained under pseudo-first-order conditions with the nucleophile present in at least 8-fold excess and generally in much larger excess. The constant temperature bath could be maintained at ±0.005 °C and all reactions were run at 29.60 ± 0.01 °C. Concentrations of the *N*-chloroacetanilides were monitored as a function of time by removing aliquots and introducing them onto the HPLC column with a 20-μL injection loop. Insignificant reaction was shown to take place during the sampling and analysis periods. Peak heights, recorded on a strip chart recorder, were shown by the use of appropriate calibration curves to be directly proportional to concentration. An internal standard (nitrobenzene or *p*-chloronitrobenzene) was used to keep errors due to irreproducibility in sampling to below 1%. HPLC separations were effected using a mobile phase of 50:50 acetonitrile:water for all kinetic runs except for *N*-chloroacetanilide itself (50:50 methanol:water) and for *p*-cyano-*N*-chloroacetanilide (45:55 acetonitrile:water).

Pseudo-first-order rate constants, k_{obsd}, were obtained from the equation $\ln [h_0/(h_t - h_\infty) = k_{obsd}t$, where h_0 = initial HPLC peak height of *N*-chloroacetanilide, h_t = peak height at time t, and h_∞ = peak height at t_∞.

All kinetic runs were monitored to greater than 85% reaction, with 8–25 data points being obtained for each run, 20 points being usual unless reaction rate and analysis time precluded it. All correlation coefficients were in excess of 0.995, the average being greater than 0.998. Several reactions were repeated under practically identical conditions to give rate constants with a reproducibility of better than 5%.

For each reaction, three stock buffer solutions were prepared. For the pH range above 4.0 the solutions were 1.000 M sodium acetate, 1.000 M acetic acid, and 1.000 M triethylammonium acetate, while for the range of pH 1.5–4.0, they were 1.000 M monobasic sodium phosphate, 1.000 M phosphoric acid, and 1.000 M triethylammonium phosphate. All solutions were adjusted to ionic strength of 1.500 M with $NaClO_4$. By mixing the appropriate volumes of these three stock solutions, the concentration of both free and total triethylamine could be adjusted at will. The appropriate buffer solution (9 mL) was placed in the reaction vessel, stoppered, and placed in the constant temperature bath. After thermal equilibration, 1.0 mL of a stock solution containing the *N*-chloroacetanilide (approximately 0.14 M) was added. The vessel was sealed, and the solution was thoroughly mixed and returned to the constant temperature bath. Aliquots were then withdrawn at appropriate intervals.

Results

From a kinetic point of view, it is reasonable that several processes might be involved in the consumption of the starting materials, leading to the inclusion in the rate equation of terms involving the concentrations of any or all the species in solution. In particular we have examined the possibility of the involvement of acid and base catalysis and participation by the acidic and basic components of the buffers as well as both free and protonated reactants.

Under such circumstances, then, the pseudo-first-order rate constant, k_{obsd}, would be given by the following expression:

$$k_{obsd} = k_{solv} + k_{HA}[HA] + k_A[A] + k_H[H^+] + k_{OH}[OH^-] + k_1[TEAH^+] + k_2[TEA] \quad (1)$$

(8) In spite of some vendors' claims to the contrary, this appears to be the best accuracy currently attainable.

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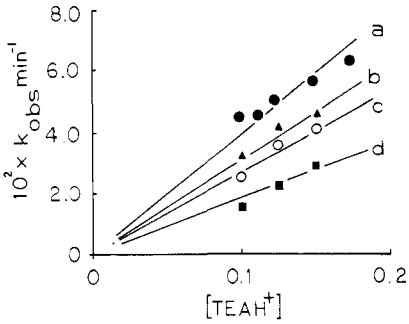


Figure 1. Plots of k_{obsd} vs. concentration of protonated triethylamine for the reaction of triethylamine with *N*-chloroacetanilide. Data obtained at the same pHs are represented by the same symbol: a, pH = 5.24 ± 0.03; b, pH = 5.05 ± 0.02; c, pH = 4.80 ± 0.01; d, pH = 4.51 ± 0.01. All lines were constrained to pass through the origin since there was negligible reaction in the absence of triethylamine. The slopes and correlation coefficients of the lines: a, 0.039, 0.950; b, 0.312, 0.991; c, 0.279, 0.976; d, 0.181, 1.000.

HA is the conjugate acid of the buffer, A is its conjugate base, TEA is triethylamine, $TEAH^+$ is protonated triethylamine, and the k's represent the various individual rate constants.

Experimentally it was observed that, in the absence of triethylamine, no appreciable reaction occurred with any of the buffers used, so eq 1 simplifies[15] to the following:

$$k_{obsd} = k_1[TEAH^+] + k_2[TEA] \quad (2)$$

The term $k_1[TEAH^+]$ might be associated with the reaction of $TEAH^+$ but is kinetically indistinguishable from the acid-catalyzed reaction with TEA itself. This is because the $[TEAH^+]$ is related to the [TEA] by the acid–base equilibrium constant:

$$K_{BN} = [TEAH^+]/[TEA][H^+] \quad (3)$$

For the purposes of facile analysis of the data, we define γ such that

$$\gamma = [TEAH^+]/[TEA] \quad (4)$$

Then eq 2 reduces to the following:

$$k_{obsd} = (k_1 + k_2/\gamma)[TEAH^+] \quad (5)$$

In this form, a plot of k_{obsd} vs. $[TEAH^+]$ should give a straight line with a slope of $(k_1 + k_2/\gamma)$. If this procedure is repeated at several pHs, a family of straight lines, passing through the origin, should be obtained. Plotting the *slopes* of these lines vs. $1/\gamma$ should yield another straight line with a slope of k_2 and an intercept of k_1. This is merely a specific application of the well-known Bell–Darwent[9] procedure.

An easier, more direct, and more precise method for obtaining the two rate constants is simply to treat eq 2 as a problem in three dimensions, rather than trying to reduce it to the more pictorial two-dimensional equivalent as was done by Bell and Darwent, that is, to carry out a direct regression analysis on eq 2. The concentrations of TEA and $TEAH^+$ were determined by using the Henderson–Hasselbach equation, knowing the pH, the total concentration of amine (free and protonated), and the pK_a of triethylamine determined under the reaction conditions (pK_a = 10.67).

(15) General acid catalysis, leading to a term of the form k[HA][TEA] was demonstrated to make a negligible contribution by the appropriate buffer dilution study with acetic acid/sodium acetate at pH 4.75.

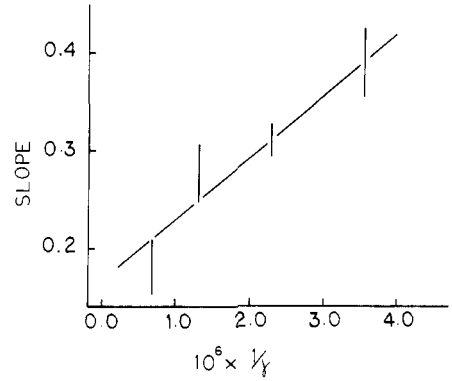


Figure 2. A plot of the slopes of the lines a–d from Figure 1 vs. $1/\gamma$. Error bars represent 95% confidence limits.

Table II. The Apparent Pseudo-Second-Order Rate Constants k_1 and k_2 for the Reaction of Triethylamine with Substituted *N*-Chloroacetanilides[a]

substituent	K_1, M^{-1} min^{-1}	k_2, M^{-1} min^{-1}	σ	σ^-
none	$(5.24 \pm 0.78) \times 10^4$	$(1.85 \pm 0.24) \times 10^{-1}$	0.00	0.00
m-Cl	$(1.97 \pm 0.18) \times 10^6$	$(8.07 \pm 2.38) \times 10^{-2}$	0.37	0.37
p-Cl	$(6.77 \pm 0.97) \times 10^5$	$(1.58 \pm 0.33) \times 10^{-1}$	0.24	0.24
p-$COCH_3$	$(1.23 \pm 0.11) \times 10^7$	$(5.26 \pm 0.77) \times 10^{-2}$	0.50	0.87
p-CN	$(2.55 \pm 0.20) \times 10^7$	$(7.50 \pm 1.57) \times 10^{-2}$	0.67	1.00
p-NO_2	$(5.05 \pm 0.20) \times 10^7$	$(8.25 \pm 1.32) \times 10^{-2}$	0.78	1.23

[a] The conditions are described in the Experimental Section. The uncertainties given represent standard deviations from a linear least-squares regression analysis. Values of σ and σ^- are taken from ref 14.

The kinetic data were treated by both procedures and the agreement between the two was adequate (9% for k_2, 6% for k_1). Plots of k_{obsd} vs. $[TEAH^+]$ are given in Figure 1 for reactions with *N*-chloroacetanilide, and plots of the slopes of these lines vs. $1/\gamma$ in Figure 2. This gives a convenient visual display of the data. However, simple statistical analysis shows that, for a given number of data points, the simultaneous treatment of all data must give better confidence limits. Therefore, all values of the rate constants given in this paper were obtained by this latter procedure.

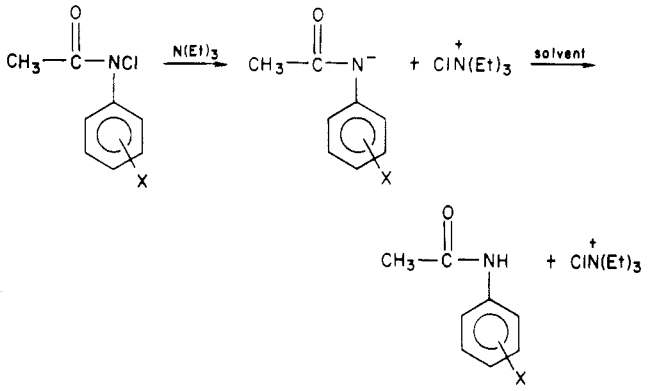
A summary of the rate constants k_1 and k_2 for all the acetanilides studied are given in Table II.

Discussion

An examination of the data in Table II shows that the reaction between *N*-chloroacetanilides and triethylamine can be described by two parallel pseudo-second-order reactions: one acid dependent and the other acid independent. However, in all the reactions reported here, the sole detectable aromatic product was the substituted acetanilide irrespective of the pH employed, i.e., irrespective of the relative degree of utilization of each pathway. Thus both paths lead to the same products. While this observation is consistent with a variety of conceivable mechanisms, the fact that substitution at the para position with electron-withdrawing substituents leads to a very substantial rate increase for the pH-independent process suggests that it can best be described in terms of a nucleophilic displacement at chlorine.

Plots of the logarithms of the rate constants, k_2, for these acid-independent reactions (Scheme II) reveals a better correlation with σ than with σ^- (correlation coefficient 0.989 compared with 0.972). This result is somewhat surprising for a reaction in which it is proposed that the negative charge is developing on an atom directly adjacent to the aromatic ring. Under such conditions a better correlation

Scheme II[a]



[a] a, X = H; b, X = p-NO_2; c, X = p-OCH_3, d, X = p-CN; e, X = m-Cl; f, X = p-Cl.

Table III. A Summary of Reaction ρ Values for Reactions Related to the Present Study

reactn	ρ	ref
$ArCHClSO_2Ph + :PPh_3$ rates	2.33	4f
$NH_2COCArCl_2 + :PPh_3$ rates	2.60	4e
$ArNHCOCH_3 + CH_3O^-$ rates	2.151	10
Ar–OH dissociation equilibria	2.229	14
Ar–SH dissociation equilibria	2.236	10
$Ar-NH_3^+$ dissociation equilibria	2.767	14

with σ^- should be expected. One possible explanation for this observation might be that, in the transition state, the breaking N–Cl bond is orientated essentially in the plane of the aromatic ring such that the developing charge derives little stabilization from delocalization into the π-system. There may be some justification for this particular orientation since this conformation would allow maximum overlap between the π-system of the amide group and that of the aromatic system. It is known[10] that, in reactions in which a negative charge is developing on the nitrogen of an amine, correlations are better with σ^- but it has been pointed out[10] that the dependence of the kinetic acidity of the N–H proton of amides on σ or σ^- has not been established.

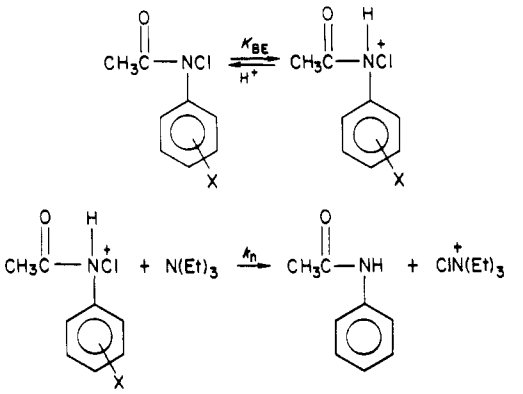
The work by Jarvis and Saukatis[4e] on nucleophilic displacements at chlorine in α-halo sulfones showed better correlation with σ^- than with σ, but this system is not complicated in the same way by the possibility of delocalization into the aromatic system from an orbital orthogonal to the reacting bond.

The ρ value determined for the reaction between triethylamine and the N-chloroacetanilides is 3.87 ± 0.29. This value is a qualitative measure of the charge separation as the reactants proceed from their initial condition to the transition state, i.e., there is significant heterolytic breakage of the N–Cl bond. ρ values for model reactions are given in Table III for comparison.

The second, acid-catalyzed pathway for this reaction could involve any one of several alternative combinations of reactants. The most plausible mechanism, however, appears to us to involve rapid reversible protonation of the N-chloroacetanilide followed by a rate-determining attack on the chlorine by unprotonated amine, essentially the Orton reaction (Scheme III). The exact position of protonation of the amide group is immaterial. The Orton reaction is usually written with protonation occurring at nitrogen, although most evidence seems to favor protonation at oxygen.

Values for the apparent pseudo-second-order rate constants for this acid-catalyzed portion of the reaction are given in Table II. These rate constants show no significant correlation with either σ or σ^-, but none should be expected

Scheme III



since this "constant" is, in fact, a complex term. If the mechanism outlined in Scheme III is in fact operative, then the apparent pseudo-second-order rate constant k_1 can be shown to be given by the following expression:

$$k_1 = k_n K_{BE} K_{BN} \quad (6)$$

where K_{BE} is the equilibrium constant for protonation of the N-chloroacetanilide and k_n is the rate constant for the reaction of triethylamine with protonated N-chloroacetanilide (Scheme III).

Under such circumstances, no simple relationship should be expected between k_1 and the nature of the substituent; k_n increases as the substituent is better able to withdraw electrons while K_{BE} decreases with this change. If the mechanism of Scheme III is accepted, and therefore, eq 6, it should, in principle, be possible to extract values of k_n from k_1 provided we have good estimates of K_{BE} and K_{BN}. While K_{BN} has been determined, the values of K_{BE} are not readily available since their determination would require conditions under which considerable protonation of the substrate was occurring. These are precisely the conditions of the Orton reaction and thus preclude facile determination of this quantity. The values for the acid dissociation constants of the corresponding protonated acetanilides, have been reported[11] but only for a few of the substituents employed in this study, and then, of course, under substantially different conditions than were used here. Moreover, it is far from clear whether protonation of the acetyl- and cyanoacetanilides takes place at the amide function or at the para substituent or whether protonation of the N-chloro analogues occurs at the same position as for the acetanilides. Thus we consider that any correlations we might, or might not, be able to obtain in such an analysis would be largely illusionary.

The production of acetaldehyde from the triethylamine is also thoroughly compatible with this proposal since the produced chlorotriethylammonium ion $(C_2H_5)_3NCl^+$ should readily eliminate HCl and hydrolyze to the aldehyde. The mechanism shown in Scheme II is therefore proposed to account for that portion of the reaction which is not acid dependent.

Conclusions

The reaction between triethylamine and substituted N-chloroacetanilides is an excellent model reaction for examining nucleophilic substitutions at chlorine. In these reactions, the exclusive product derived from the aromatic moiety is the corresponding acetanilide. The reaction occurs via two parallel pseudo-second-order paths, one acid catalyzed (the Orton-like mechanism), the other uncatalyzed. The uncatalyzed reaction is accelerated by the presence of electron-withdrawing substituents on the aromatic ring and can best be represented as nucleophilic

displacements at chlorine. The ρ value for this reaction is 3.87 indicating substantial negative charge buildup in the aromatic ring during the transition state. The acid-catalyzed reaction is more complex, presumably involving a protonation equilibrium for the *N*-chloroacetanilide prior to the rate-determining step. Consequently no clear correlation is discernable between the nature of the substituent and the rate of reaction.

Acknowledgment. Supported in part by Grants CA 25073 and CA28038 from the National Cancer Institute of the National Institutes of Health and by the Department of Energy contract DE-A C02-81 ER60015.

Registry No. *N*-Chloroacetanilide, 579-11-3; *N*-chloro-*p*-chloroacetanilide, 29551-85-7; *N*-chloro-*p*-nitroacetanilide, 79272-04-1; *N*-chloro-*p*-cyanoacetanilide, 14596-61-3; *N*-chloro-*p*-acetylacetanilide, 91238-44-7; *N*-chloro-*m*-chloroacetanilide, 29551-86-8; acetanilide, 103-84-4; *p*-chloroacetanilide, 539-03-7; *p*-nitroacetanilide, 104-04-1; *p*-cyanoacetanilide, 35704-19-9; *p*-acetylacetanilide, 2719-21-3; *m*-chloroacetanilide, 588-07-8; triethylamine, 121-44-8; phenoxide anion, 3229-70-7; phenol, 108-95-2.

Supplementary Material Available: A summary of specific reaction conditions and pseudo-first-order reaction rate constants (4 pages). Ordering information is given on any current masthead page.

Intramolecular Participation by a Neighboring Amide Group in the Hydrolysis of *N*-Acylimidazoles

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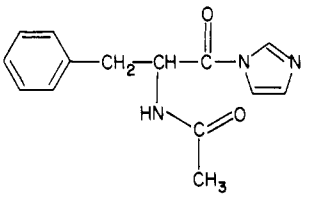
Received March 20, 1984

Rate constants have been determined for the disappearance of the *N*-acylimidazole derivatives of *N*-acetylphenylalanine and *N*-acetylvaline in H_2O at 30 °C. The pH–rate constant profiles are characterized by large pH-independent regions. These reactions are 2-fold slower in D_2O than in H_2O. The pH-independent reactions show rate enhancements of 100–250-fold in comparison with hydrolysis of the corresponding compounds *N*-(β-phenylpropionyl)imidazole and *N*-isovalerylimidazole, which lack an acetamido substituent. Thus, the neighboring acetamido groups are participating in the neutral species reactions. Nucleophilic attack by the acetamido oxygen occurs to form oxazolinone derivatives that were identified both spectrally and kinetically. Reversibility of this reaction was demonstrated in imidazole buffer. The reactions are general acid catalyzed by $H_2PO_4^-$. Therefore, proton transfer may take place in concert with nucleophile attack. The intramolecular nucleophilic reactions do not compete effectively with OH^--catalyzed hydrolysis, which illustrates the great facility of the latter reaction in the hydrolysis of *N*-acylimidazoles.

The hydrolysis reactions of *N*-acylimidazoles have been extensively studied.[1-8] General acid and general base catalysis by various buffers has been observed in these reactions.[2,4] However, there is little knowledge of intramolecular participation by neighboring groups other than carboxyl in the hydrolysis of such compounds.[9] Chemical intramolecular reactions bear a striking resemblance to the intracomplex reactions of enzymes.[10] Therefore, in view of the importance of determining the factors governing intramolecular reactions, we have studied the hydrolysis of the *N*-acylimidazole derivatives of *N*-acetylphenylalanine and *N*-acetylvaline (I and II), compounds having a neighboring acetamido group. Neighboring amide groups have been found to be powerful intramolecular nucleophiles in reactions of esters and amides.[1,11,12]



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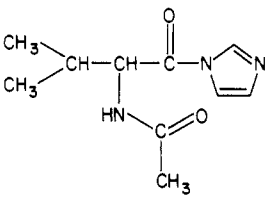

II

Experimental Section

Materials. The *N*-acylimidazoles I and II were prepared from *N*-acetyl-L-phenylalanine or *N*-acetyl-L-valine by reaction in dichloromethane with equimolar amounts of imidazole and dicyclohexylcarbodiimide. After 2 h at room temperature the mixture was filtered, and the dichloromethane was evaporated under reduced pressure. The residue was dissolved in chloroform and filtered. Ether was then added to the filtrate. The product crystallized from this mixture upon standing in the cold and was recrystallized from the same solvent. *N*-[α-(acetylamino)-β-phenylpropionyl]imidazole (I) had mp 99–101 °C. Anal. Calcd for $C_{14}H_{15}N_3O_2$: C, 65.35; H, 5.88; N, 16.33. Found: C, 65.14; H, 6.09; N, 16.09. *N*-[α-(Acetylamino)isovaleryl] imidazole (II) had mp 95–97 °C. Anal. Calcd for $C_{10}H_{15}N_3O_2$: C, 57.38; H, 7.22;

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0022-3263/84/1949-5229$01.50/0