Structure–Activity Considerations in Kinetics and Mechanism of Chlorine Exchange between Chloramine-T and Secondary Amines

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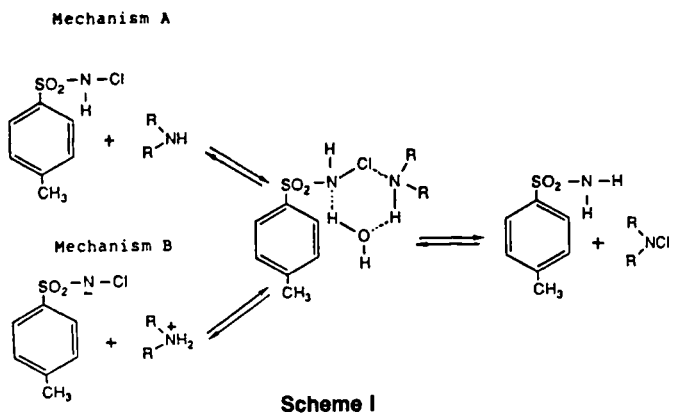
Abstract □ To study the mechanism of *N*-chlorination of secondary amines by chloramine-T, the kinetics of the reactions of some aromatic-substituted analogues of *N*-chlorobenzenesulfonamide with various secondary amines were determined. The importance of amine basicity and reactivity of the N–Cl bond of the *N*-chlorobenzenesulfonamide was also assessed. The results indicate that a mechanism involving the un-ionized species of both reactants (i.e., a molecular mechanism), rather than an ionic mechanism, is operating and that the reaction most likely proceeds via a six-membered-ring transition state that incorporates a water molecule.

In our previous work,[1] chlorine exchange between chloramine-T hydrate (CAT) and secondary amines (Scheme I) was shown to be first-order with respect to each reactant. The rate of the reaction is independent of *p*-toluenesulfonamide (TSA) concentration, a fact suggesting that the chlorine exchange is not mediated by dichloramine-T formation.[2] The profile of pH versus rate for the reaction was constructed, and two mechanisms were proposed (Scheme I): (1) mechanism A (nonionic or molecular mechanism), which involves the un-ionized species of both CAT and the amine, and (2) mechanism B (ionic or ionized mechanism), which involves the ionized species of both reactants. In both cases, the reaction proceeds through a six-membered-ring transition state that incorporates a water molecule. These two mechanisms are kinetically indistinguishable, because both fit the observed profiles of pH versus rate. The effect of ionic strength, if present, would be the same for both mechanisms.[1] On the basis of the magnitude of the rate constants of the reaction between the same amines and other un-ionizable chlorinating agents, however, the chlorination of amines by CAT may involve the un-ionized forms of both the amine and CAT.

In this present study, attempts were made to distinguish further the ionic and the nonionic mechanisms, to study the role of electron-inductive effects on the reactivity of the N–Cl bond of *N*-chlorobenzenesulfonamide compounds, and to determine the effect of amine basicity on the rate of chlorine transfer from *N*-chloro compounds to secondary amines.



Scheme I

Experimental Section

Reagents—Glass-distilled water was used to prepare all stock solutions and reaction mixtures. The following reagents were purchased from Aldrich Chemical Company (Milwaukee, WI): benzenesulfonamide (BSA), 4-nitrobenzenesulfonamide, 4-methoxybenzenesulfonyl chloride, CAT, chloramine-B hydrate (CAB), and sodium hypochlorite solution (5%). Morpholine, TSA, and piperidine (PIP) were purchased from Eastman Kodak Company (Rochester, NY). Diethylamine (DEA)[3] and diisopropylamine (DIP) were purchased from Fluka AG, Busch SG, Switzerland. Dibasic, anhydrous sodium phosphate was purchased from Mallinckrodt Inc., St. Louis, MO.

CAT was prepared free from possible contamination by dichloramine-T by washing several times with carbon tetrachloride and drying in a vacuum desiccator over phosphorus pentoxide.[3] The final purity was confirmed by iodometric titration.

TSA and BSA were recrystallized from glacial acetic acid[4] prior to use. Dimethylamine hydrochloride was recrystallized from chloroform–ether. The other dialkylamines were purified by vacuum distillation.

Synthesis of Ring-Substituted Derivatives of *N*-Chlorobenzenesulfonamides—*Preparation of p-Methoxybenzenesulfonamide*—4-Methoxybenzenesulfonamide was prepared by bubbling ammonia gas into an ice-cooled solution of 4-methoxybenzenesulfonyl chloride (7.7 g) in ethanol (75 mL) until a heavy precipitate was formed. The reaction mixture was left at room temperature for ~4 h, and the crude product was filtered, extracted with sodium hydroxide (1 N), and reprecipitated from the sodium hydroxide solution by addition of concentrated hydrochloric acid. The product was recrystallized from benzene as described by Ludwing et al.[5] Additional amounts of the product were obtained from the ethanol solution by evaporation, extraction, and recrystallization from benzene; mp 108 °C (literature value, 110–111 °C[5]). The product was identified spectrophotometrically (UV and IR) and by nuclear magnetic resonance spectroscopy.

Preparation of Sodium Salts of N-Chloro-p-Methoxybenzenesulfonamide (CAM), N-Chloro-p-Nitrobenzenesulfonamide (CAN), and N-Chloro-p-Chlorobenzenesulfonamide (CAC)—The sodium salts of the *N*-chloro derivatives CAM, CAN, and CAC were synthesized by dissolving 0.4 M of each of the appropriate benzenesulfonamides in 10 mL of a solution containing sodium hypochlorite (5%, w/v) and sodium hydroxide (0.4 M). The product precipitated after a few minutes of stirring and was filtered, washed with carbon tetrachloride and ether, and dried under reduced pressure over phosphorus pentoxide. Melting points were 175 °C for CAM, 189 °C for CAN (literature value, 188–189 °C[6]), and 185 °C for CAC (literature value, 190 °C[7]). The compounds melted with decomposition.

Apparatus—Kinetic experiments were carried out with a Cary 219 spectrophotometer (Varian Associates, Inc., Palo Alto, CA) connected to a circulating water bath (Haake Instrument Company, Inc., Saddlebrook, NJ, and Forma-Temp, Jr., Forma Scientific Company, Marietta, OH) to maintain constant temperature. The pHs of the reaction mixtures were determined with a digital ionizer pH meter (model 501, Orion Research, Inc., Cambridge, MA).

Methods—The reactions between *N*-chlorobenzenesulfonamides and secondary amines (forward reactions) and the reactions between

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BSA derivatives and *N*-chloroamines (reverse reactions) were followed as described previously (Cary 219 spectrophotometer; 1-cm cells), by observing the disappearance or appearance of *N*-chlorobenzenesulfonamides at wavelengths of 240, 250, 256.5, 260, and 310 nm for CAB, CAT, CAC, CAM, and CAN, respectively. This method was based on the fact that *N*-chlorobenzenesulfonamides have much higher molar absorptivities than the corresponding unchlorinated sulfonamides and *N*-chlorodialkylamines at these wavelengths. Sodium phosphate (0.05 M) buffers were used as the reaction media, and the pH was checked after each kinetic measurement.

Kinetic Measurements—*Forward Reaction Rates*—Experiments were performed under pseudo-first-order conditions by maintaining the amines in at least a sixfold molar excess over the *N*-chlorobenzenesulfonamides. Stock solutions (0.1 and 0.2 M) of each amine were prepared in water. A calculated volume of each stock solution was transferred to a volumetric flask and brought to the mark with water and 0.2 M phosphate buffer at the desired pH to produce a solution containing twice the desired amine concentration in 0.1 M buffer. The pHs of the solutions were then readjusted to the original values by using either 0.1 M phosphoric acid or 0.1 M sodium hydroxide. After temperature equilibration, 1.5 mL of a 1×10^{-3} M *N*-chlorobenzenesulfonamide solution was placed in a spectrophotometer cell in the instrument, and 1.5 mL of temperature-equilibrated amine solution was rapidly injected. The reactions were monitored by following the decrease in absorbance at the appropriate absorption maxima. Thus, the disappearance of the *N*-chlorobenzenesulfonamide was followed in each case. Blank experiments were performed under identical conditions in the absence of the amines, and no appreciable change in absorbance was observed.

Reverse Reaction Rates—Aqueous solutions of each sulfonamide were freshly prepared at a concentration of 2×10^{-2} M. A calculated volume of the sulfonamide solution was injected into the spectrophotometer cell containing a calculated volume of *N*-chloramine solution at the desired pH and at a concentration of either 3.6×10^{-4} or 5×10^{-4} M.[8] The concentrations and volumes of the solutions were chosen so that the sulfonamide was present in a 10- to 20-fold molar excess over the *N*-chloramine. The absorbances due to the relatively high concentrations of the sulfonamides were canceled by placing a solution of equivalent sulfonamide concentration in the reference cell. The increase in absorbance corresponding to the appearance of the particular *N*-chlorobenzenesulfonamide was monitored at the appropriate wavelength. All kinetic reactions were carried out in duplicate or triplicate, and the rate constants from individual experiments did not vary by more than ±10%.

Determination of Dissociation Constants of *N*-Chlorobenzenesulfonamides by UV Spectrophotometry—Acetate buffer solutions (0.2 M) with approximate pHs of 1.5, 2, 3, 4, 5, 6.14, and 6.6 were prepared, and 1.5 mL of each buffer was injected into a spectrophotometer cell containing 1.5 mL of *N*-chlorosulfonamide (10^{-3} M). The initial absorbances were recorded immediately at the following wavelengths (nm): 240 (CAB), 250 (CAT), 256.5 (CAC), 260 (CAM), and 310 (CAN). These wavelengths were chosen to maximize the differences between the absorbances of fully ionized and un-ionized forms of each *N*-chlorosulfonamide (i.e., at pH 6.6 and 1.5, respectively). The pH of each solution was accurately determined after each spectral measurement, and the ionic strength was calculated for each solution.

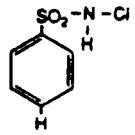
The mixed ionization constants (pK_m) (involving both activities and concentrations) were calculated by using the following equation: $pK_m = pH - \log (A - A_{HP})/(A_P - A)$. A_{HP} is the absorbance of the un-ionized form (measured at the buffer of the lowest pH), A_P is the absorbance of the ionized form (measured at the buffer of the highest pH), and A is the absorbance at any pH.

The thermodynamic ionization constants (pK_a) were calculated from the experimental pK_m values by using the Debye–Hückel equation, which applies to a neutral acid at 25 °C in aqueous solution[9]: $pK_a = pK_m + 0.509\mu/(1 + \mu)$, in which μ is the ionic strength. The mean pK_a value for each *N*-chlorosulfonamide was calculated from the set of pK_a values obtained at the various pHs studied.

Results

Effect of *para* Substitution—*Forward Reaction Rate*—The effect of *para* substitution in the benzene ring of *N*-chlorobenzenesulfonamide was studied by using the *N*-chlorobenzenesulfonamides listed in Table I. The *para* substituents ranged from a nitro group, with an electron-withdrawing effect, to a methoxy group, with an electron-donating effect. These inductive effects are illustrated in the Hammett plot (Figure 1) of pK_a versus Hammett substituent constants (σ_p values).

Table I—Thermodynamic Ionization Constants (pK_a) and Hammett Substituent Constants (σ_p) of *N*-Chlorobenzenesulfonamides



Amide (Abbreviation)	*para* Group	pK_a	σ_p
N-Chloro-*p*-nitrobenzenesulfonamide (CAN)	NO_2	3.50	0.78
N-Chloro-*p*-chlorobenzenesulfonamide (CAC)	Cl	4.00	0.23
N-Chlorobenzenesulfonamide (CAB)	H	4.34	—[a]
N-Chloro-*p*-toluenesulfonamide (CAT)	CH_3	4.41	−0.17
N-Chloro-*p*-methoxybenzenesulfonamide (CAM)	OCH_3	4.56	−0.27

[a] Not determined.

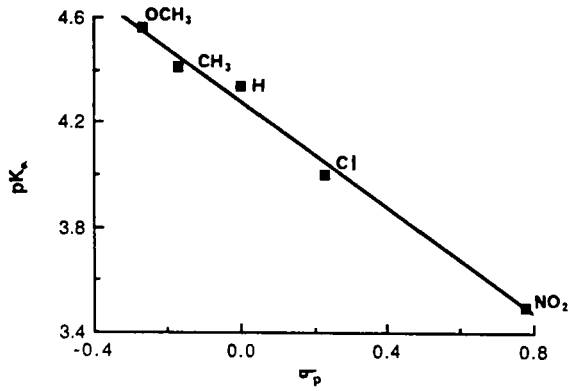


Figure 1—Correlation of pK_a values of *para*-substituted *N*-chlorobenzenesulfonamide with Hammett substituent constant (σ_p).

Table II—Structures, Nomenclature, and Acid Dissociation Constants (pK_a) of Amines

Structure	Name (Abbreviation)	pK_a[a]
$(CH_3CH_2)_2NH$	Diethylamine (DEA)	10.98
$(CH_3)_2CHNHCH(CH_3)_2$	Diisopropylamine (DIP)	11.05
$CH_2CH_2NHCH_2CH_2CH_2$	Piperidine (PIP)	11.28
$CH_2CH_2NHCH_2CH_2O$	Morpholine	8.40

[a] Data taken from ref 10.

The kinetics of the reactions of each chloramine with DEA, DIP, PIP, and morpholine (Table II) were studied for the ionic and nonionic mechanisms by using eqs 1 and 2, respectively:[1]

$$k_{obs} = k_2 \cdot K_a/([H^+] + K_a) \cdot [H^+]/([H^+] + K_a 1) \quad (1)$$

$$k_{obs} = k_3 \cdot [H^+]/([H^+] + K_a) \cdot K_a/([H^+] + K_a 1) \quad (2)$$

In eqs 3 and 4, k_{obs} is the pH-dependent, second-order rate constant; k_2 and k_3 are the pH-independent, second-order rate constants calculated for the ionic and nonionic mechanisms, respectively; and K_a and $K_a 1$ are the dissociation constants of

Table III—pH-Independent, Second-Order Rate Constants for Reactions between *para*-Substituted *N*-Chlorobenzenesulfonamides and Secondary Amines according to the Ionic Mechanism[a]

Amine	Second-Order Rate Constant for Reaction with *N*-Chlorobenzenesulfonamide with *para* Substituent of:				
	NO_2	Cl	H	CH_3	OCH_3
DEA	0.36	0.70	1.32	1.73	1.89
DIP	0.09	0.31	0.33	0.43	0.48
PIP	0.30	1.15	1.72	2.47	3.21
Morpholine	12.8	12.2	11.3	10.9	—[b]

[a] Scheme I, mechanism B; pH 7.3–7.5. [b] Not determined.

the chlorinating agents and the amine, respectively.

The resulting pH-independent, rate constants for the ionic mechanism (Scheme I, mechanism B) are summarized in Table III, and those for the nonionic mechanism (Scheme I, mechanism A) are summarized in Table IV. The rate constants calculated on the basis of the ionic mechanism increased with DEA, DIP, and PIP as the electron-donating effect of the aromatic substituent increased, whereas the opposite trend was observed in the case of morpholine. However, when the rate constants were calculated on the basis of the nonionic mechanism, the rate of the reaction between the chlorosulfonamides and morpholine decreased as the electron-donating effect increased. This effect was less pronounced when DEA was used and became insignificant with DIP and PIP.

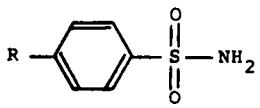
Reverse Reaction Rate—The effect of *para* substitution on the reverse reaction rate was determined by examining the reaction between *N*-chlorodiisopropylamine and the sulfonamides corresponding to the chloramines listed in Table I. The results (Table V) indicate that the effect of *para* substitution on the rate of the reverse reaction was insignificant.

Discussion

It was thought that any *para* substituents on the benzene ring that affect the activation of the N–Cl bond should also affect the rates of reactions between *N*-chlorobenzenesulfonamides (Table I) and dialkylamines (Table II). The *para* substituents ranged from a nitro group with an electron-withdrawing effect, which decreases the electron density on the sulfonamide nitrogen and consequently weakens the N–Cl bond, to a methoxy group with an electron-donating effect, which increases the electron density on the sulfonamide nitrogen and causes the N–Cl bond to be stronger, the effect resulting in an expected decrease in the reaction rate. These substituents have a dramatic effect on the electron density around the sulfonamide nitrogen, as reflected by the pK_as of the sulfonamides.

If the molecular (nonionic) mechanism (Scheme I, mechanism A) is operating, the un-ionized species of both the chlorinating agent and the amine would be the reactive species, and the electron-donating or electron-withdrawing effect of the *para* substituent on the reaction rate would be very pronounced. For the reactions of morpholine (pK_a = 8.4) with *para*-substituted *N*-chlorobenzenesulfonamides, the rate constants calculated with eq 2 increased as the electron-withdrawing effect of the *para* substituent increased (Table IV); the result is a Hammett plot with a p value (slope) of 1.27 (Figure 2). This effect was less pronounced as the amine became more basic. For example, the Hammett plot for the reaction between DEA (pK_a = 10.98) and the *para*-substituted *N*-chlorobenzenesulfonamides resulted in a p value of 0.334 (Figure 2), whereas the substitution effect diminished (Table IV) with DIP and PIP (pK_a = 11.05 and 11.28, respectively). This observation can be explained by the fact that the strong basicity of the amine (therefore greater affinity for chlorine) masks any electron-donating or electron-withdrawing effect of the *para* substituent. However, eliminating the basicity factor (e.g., in the case of morpholine) uncovered these electronic effects and gave results that are in good agreement with the nonionic mechanism.

Table V—pH-Independent Rate Constants for Reaction between *N*-Chloro-DIP and *para*-Substituted BSAs[a]



R	k_{true}, $M^{-1}s^{-1}$
$-NO_2$	0.91
–H	1.02
$-CH_3$	1.04
$-OCH_3$	1.11

[a] pH, 7.5–7.7; phosphate buffer, 0.33 M; *N*-chloro-DIP, 1.2×10^{-4} M; BSA, 1.33×10^{-3} M.

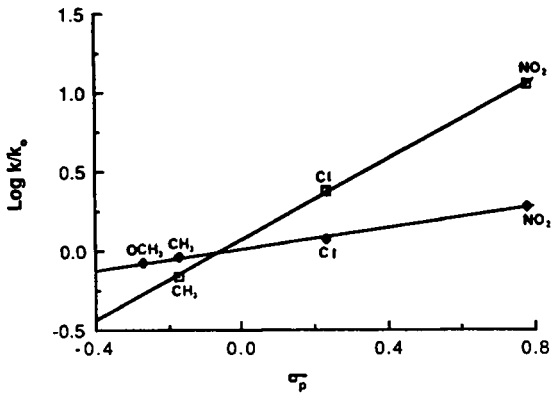


Figure 2—Hammett plots for reactions between (◆) DEA and (□) morpholine with the *para*-substituted benzenesulfonamides via the nonionic mechanism.

Table IV—pH-Independent, Second-Order Rate Constants for Reaction between *para*-Substituted *N*-Chlorobenzenesulfonamides and Secondary Amines according to the Nonionic Mechanism[a]

Amine	Second-Order Rate Constant for Reaction with *N*-Chlorobenzensulfonamide with *para* Substituent of:				
	NO_2	Cl	H	CH_3	OCH_3
DEA	1.09×10^7	6.71×10^6	5.70×10^6	5.24×10^6	4.80×10^6
DIP	3.20×10^6	3.48×10^6	1.70×10^6	1.50×10^6	1.48×10^6
PIP	1.80×10^7	2.19×10^7	1.50×10^7	1.80×10^7	1.68×10^7
Morpholine	1.68×10^6	3.55×10^5	1.50×10^5	1.03×10^5	—[b]

[a] Scheme I, mechanism A; pH 7.3–7.5. [b] Not determined.

On the other hand, inconsistencies in the rate constants calculated for the ionic mechanism with eq 1 are apparent. For example, the rate constants for the reactions of DEA, DIP, and PIP with the *N*-chlorobenzenesulfonamides decreased as the electron-withdrawing character of the *para* substituent increased, whereas the opposite trend was observed for the reactions of morpholine with the *N*-chlorosulfonamides (Table III). The observed variation in the rates of the reactions between the chlorinating agent and the two structurally similar amines PIP and morpholine is consistent with the nonionic mechanism. As the basicity of the amine increases, the reaction rates should increase. This trend was, in fact, observed (i.e., the *N*-chloro compounds reacted with PIP at faster rates than with morpholine). The magnitude of the differences in the rate constants is parallel to the differences in the basicities of the amines.

In summary, examining the evidence kinetically (by comparing the rate constants obtained for each proposed mechanism with the rate constants of similar chlorination reactions) and mechanistically [by examining the effects of amine basicity and of *para* substituents on the benzene ring of CAT on the rate constants calculated for the ionic and nonionic (molecular) mechanisms] reveals that the molecular mechanism is more probable. An energetically stable, six-membered-ring transition state (Scheme I) probably is essential for chlorination reactions that require the displacement of chlorine from an N–Cl bond, because displacement of chlorine by a simple nucleophilic attack is a relatively high energy process.

References and Notes

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Acknowledgments

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