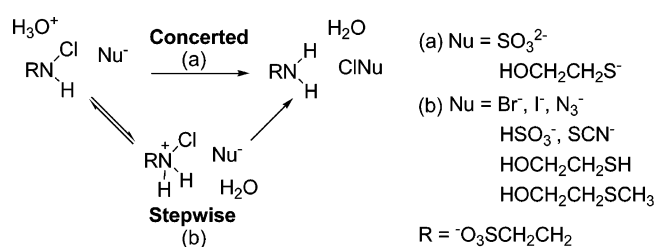# Nucleophilic Substitution Reactions of *N*-Chloramines: Evidence for a Change in Mechanism with Increasing Nucleophile Reactivity

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Third-order rate constants ($k_{Nu})_H$ ($M^{-2} s^{-1}$) for the hydronium ion catalyzed reactions of a range of nucleophiles with *N*-chlorotaurine (**1**) in water at 25 °C and $I = 0.5$ ($NaClO_4$) are reported. The solvent deuterium isotope effects on hydronium ion catalysis of the reaction with **1** of bromide and iodide ion are $(k_{Br})_H/(k_{Br})_D = 0.30$ and $(k_I)_H/(k_I)_D = 0.54$, respectively. The inverse nature of these isotope effects and the absence of general acid catalysis are consistent with a stepwise mechanism involving protonation of **1** in a fast preequilibrium step. The appearance of strong catalysis by general acids for the reaction of the more nucleophilic SO_3^{2-} and $HOCH_2CH_2S^-$ with the chloramine indicates a change to a concerted mechanism, with protonation of the chloramine at nitrogen and chlorine transfer to the nucleophile occurring in a single step. A rough estimate of the lifetime of the protonated chloramine in the presence of the thiolate anion suggests that the concerted mechanism is enforced by the absence of a significant lifetime of the protonated substrate in contact with the nucleophile. Theoretical calculations provide evidence against an electron-transfer mechanism for chlorination of the nucleophiles by protonated **1**.

Introduction

It is well-known that *N*-chloro compounds are formed in vivo and play an important role in immunity.[1] Activated phagocytes generate a large number of highly reactive oxidants, including hypochlorous acid (HOCl), a product of the myeloperoxidase−H_2O_2−Cl^- system. HOCl is the major microbiocidal agent in neutrophils, but its excessive production leads to tissue damage. Taurine, a sulfur-containing amino acid ($^-O_3SCH_2CH_2NH_3^+$) present in mammalian plasma and cells, acts as a major trap for HOCl forming the more stable and weaker oxidant taurine chloramine ($^-O_3SCH_2CH_2NHCl$ (**1**)).[2] This species exerts a protective effect in neutrophils and helps to preserve the bacteriocidal potential for prolonged periods. Recent studies

suggest that **1** may function as a physiological modulator of inflammation, inhibiting the production of proinflammatory agents.[3]

The large number of reports in the literature on the biological activity of **1**, nowadays a very active area of research, shows the crucial role that this *N*-chloro amino acid plays in the human immune system.[4,5] In contrast, there have been few studies of the chemical reactivity of this compound, despite its importance in biology and medicine. Although the chemical properties of **1** have been analyzed recently,[6] kinetic studies which could

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provide important information about the mechanism of its reactions with nucleophilic reagents are scarce. The reactivity of this and other chloramines toward thiols has been previously examined,[7] but the precise mechanism for this process has not been established. This information is important for understanding the potential of *N*-chloro compounds to oxidize the thiol groups in proteins and therefore to alter their functional properties.

Nucleophilic substitution reactions are among the most studied reaction classes in physical organic chemistry, although the greatest effort has been put into understanding substitution at carbon. The lack of information on the mechanism of nucleophilic reactions involving the attack of a nucleophile on a halogen atom has recently been pointed out.[8] We are interested in understanding the mechanisms for halogen transfer reactions and how they are affected by changes in the nature of the reactants. We report here the results of a study of the reactions of **1** with several nucleophilic reagents. The transfer of chlorine from **1** to a nucleophile requires protonation at nitrogen before or during the transfer step. This avoids the formation of the unstable nitranion of taurine ($pK_a \sim 30$). The reaction may be subject to specific-acid catalysis, with proton transfer to the nitrogen atom of the chloramine in an initial equilibrium step, or to general-acid catalysis when there is significant proton transfer during nucleophilic attack at chlorine.

In previous studies of the acid-catalyzed oxidation of iodide by chloramines,[9,10] it was proposed that the addition of iodide to chlorine proceeds through a mechanism involving simultaneous chlorine and proton transfer in the rate-determining transition state. This conclusion was based on the observation of weak buffer catalysis of this chlorine transfer reaction. In this work, we have not detected significant catalysis by general acids of the reaction of *N*-chlorotaurine with iodide and less reactive nucleophiles. We present here evidence that the acid-catalyzed transfer of chlorine to these nucleophiles involves a stepwise mechanism that proceeds through a N-protonated chloramine intermediate. We have also found that increasing the reactivity of the nucleophile results in a change to a concerted mechanism, which seems to be enforced by the absence of a significant lifetime for the protonated intermediate in the presence of the nucleophilic reagent.

Results

Observed second-order rate constants, $(k_2)_{obsd}$ ($M^{-1} s^{-1}$), for the reactions of Br^-, N_3^-, SCN^-, I^-, SO_3^{2-}, $HOCH_2CH_2SCH_3$, and $HOCH_2CH_2S^-$ with **1,** in the presence of buffers at 25 °C and $I = 0.5$ (NaClO₄), were determined as the slopes of linear pseudo-first-order plots of k_{obsd} (s^{-1}) against the total concentration of the nucleophile (not shown) or as $(k_2)_{obsd} = k_{obsd}/[Nu]_T$. The rate constants $(k_2)_{obsd}$ for the reaction of Br^-, N_3^-, SCN^-, I^-, and $HOCH_2CH_2SCH_3$ with **1** in the presence of 0.02–0.05 M buffer are equal to the rate constants $(k_2)_o$ ($M^{-1} s^{-1}$) for the reaction catalyzed by solvent species alone, because there is
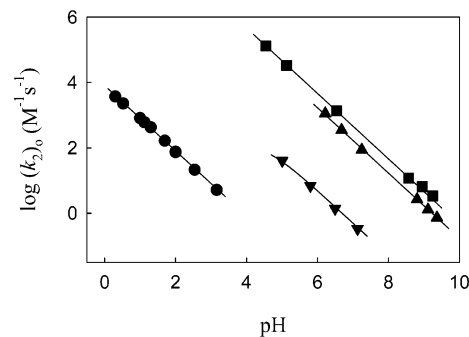
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FIGURE 1. pH−rate profiles of $(k_2)_o$ ($M^{-1} s^{-1}$) for the reaction of (●) Br^-, (▼) N_3^-, (▲) SCN^-, and (■) I^- with *N*-chlorotaurine at 25 °C and $I = 0.5$ (NaClO₄). The solid lines for bromide ion, thiocyanate ion, and iodide ion were calculated from the values of $(k_{Nu})_H$ ($M^{-2} s^{-1}$, Table 1) using the logarithmic form of eq 1. The line through the data for azide ion was calculated using eq 2 and the values of $(k_{Nu})_H$ and $(K_a)_{NuH}$ that are given in Table 1.

no significant change in $(k_2)_{obsd}$ with increasing buffer concentration up to 0.4 M for any of these nucleophiles. Figure 1 shows pH−rate profiles of $(k_2)_o$ for the reaction of Br^-, N_3^-, SCN^-, and I^- with **1**. The values of $(k_2)_o$ for bromide ion, thiocyanate, and iodide ion decrease with increasing pH according to eq 1.

$$(k_2)_o = (k_{Nu})_H[H_3O^+] \tag{1}$$

The plot (not shown) of $(k_2)_o$ against $[H_3O^+]$ for each of these nucleophiles is linear and the slope gives the third-order rate constant, $(k_{Nu})_H$ ($M^{-2} s^{-1}$), for the reaction of the nucleophile with **1** catalyzed by hydronium ion (Table 1). The lines through the data in Figure 1 were calculated from the values of $(k_{Nu})_H$ using the logarithmic form of eq 1.

In studies with azide ion, where it was possible to work at pH values close to $p(K_a)_{NuH}$, the value of $(k_{Nu})_H$ ($M^{-2} s^{-1}$, Table 1) was determined as the average of the values of $(k_2)_o/[H_3O^+]f_{Nu}$, where f_{Nu} is the fraction of the nucleophile present in the basic form. The solid line drawn through the data in Figure 1 was calculated according to eq 2, using the values of $(k_{Nu})_H$ and $(K_a)_{NuH}$ given in Table 1.

$$(k_2)_o = (k_{Nu})_H[H_3O^+]\left[\frac{(K_a)_{NuH}}{(K_a)_{NuH} + [H_3O^+]}\right] \tag{2}$$

Third-order rate constants $((k_{Nu})_D$, $M^{-2} s^{-1})$ for the reaction of Br^- and I^- with **1** catalyzed by D_3O^+ in D_2O at 25 °C and $I = 0.5$ (NaClO₄) were determined as the average of the values of $(k_2)_o/[D_3O^+]$ (eq 1) and are given in Table 1.

The dependence on pH of the observed second-order rate constants for the reaction of **1** with sulfite dianion, extrapolated to zero buffer concentration $((k_2)_o$, $M^{-1} s^{-1})$, is shown in Figure 2. The linear region of slope −1.0 below pH 4.5 corresponds to the acid-catalyzed reaction of HSO_3^- with **1** (Scheme 1), detected under conditions in which >99% of the nucleophile is protonated. The value of the third-order rate constant $(k_{NuH})_H$ ($M^{-2} s^{-1}$) (Table 1) for this acid-catalyzed reaction was calculated as the average of the values of $(k_2)_o/[H_3O^+]f_{NuH}$ at pH < 4.5, where f_{NuH} is the fraction of nucleophile present as the acid form.

Above pH 4.5, the reaction of sulfite dianion with **1** (Scheme 1) becomes significant, and this is the only detectable reaction at pH > 6. The rate constant $(k_{Nu})_H$ ($M^{-2} s^{-1}$) (Table 1) for the

TABLE 1. Third-Order Rate Constants for the Acid-Catalyzed Reaction of Nucleophiles with *N*-Chlorotaurine (1) in Water[a]

nucleophile	p(K_a)$_{NuH}$[b]	n[c]	N_+[d]	$(k_{Nu})_H$ (M^{-2} s^{-1})[e]	$(k_{NuH})_H$ (M^{-2} s^{-1})[f]
HOCH$_2$CH$_2$S$^-$	9.7	6.95[h]	8.87	$(2.1 \pm 0.5) \times 10^{10}$	$(5.0 \pm 0.1) \times 10^6$
SO$_3$$^{2-}$	6.7	5.67	8.01	$(5.6 \pm 0.8) \times 10^9$	$(1.4 \pm 0.2) \times 10^8$
I$^-$	-12[g]	4.93	4.0	$(4.6 \pm 0.1) \times 10^9$	
				$(8.5 \pm 0.2) \times 10^9$ (D$_2$O)	
HOCH$_2$CH$_2$SCH$_3$	-5[g]			$(2.0 \pm 0.2) \times 10^9$	
SCN$^-$	0.9[g]	4.80		$(1.7 \pm 0.1) \times 10^9$	
N$_3$$^-$	4.5	3.92	7.54	$(4.8 \pm 0.5) \times 10^6$	
Br$^-$	-10[g]	4.02	2.2	$(7.8 \pm 0.4) \times 10^3$	
				$(2.6 \pm 0.1) \times 10^4$ (D$_2$O)	

[a] At 25 °C and $I = 0.5$ (NaClO$_4$). [b] Apparent pK_a of the conjugate acid of the nucleophile, determined under the experimental conditions as described in the Experimental Section, unless noted otherwise. [c] Swain–Scott n values in water from ref 32, unless noted otherwise. [d] Ritchie's N_+ parameters taken from ref 36. [e] Third-order rate constant for the hydronium ion catalyzed reaction of the basic form of the nucleophile with **1**, determined as described in the text. [f] Third-order rate constant for the specific-acid-catalyzed reaction of the acid form of the nucleophile with **1**. [g] Data from ref 33b. [h] Assumed to be the same as for propanethiolate ion (ref 36), on the basis of the similar reactivity of these two thiol anions toward a simple quinone methide (ref 35).
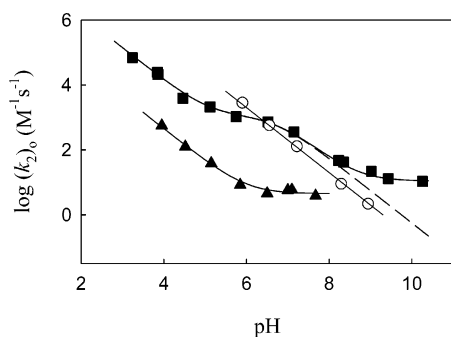

FIGURE 2. pH–rate profiles of $(k_2)_o$ (M^{-1} s^{-1}) for the reaction of (■) sulfite, (▲) 2-mercaptoethanol, and (○) 2-(methylthio)ethanol with *N*-chlorotaurine (**1**) at 25 °C and $I = 0.5$ (NaClO$_4$). The solid line for sulfite was calculated using eq 3 and the reported values of $(k_{NuH})_H$, $(k_{Nu})_H$, k_{Nu}, and $(K_a)_{NuH}$. The line through the data for 2-mercaptoethanol shows the fit of the data to eq 5, and the line for 2-(methylthio)ethanol was calculated from the value of $(k_{Nu})_H$ (M^{-2} s^{-1}, Table 1) using the logarithmic form of eq 1.

SCHEME 1
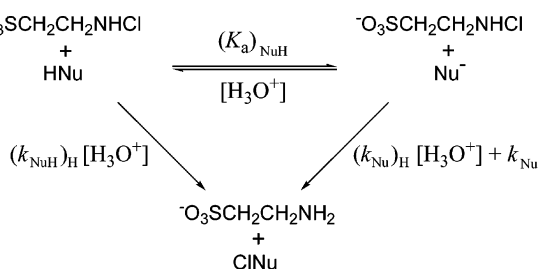
acid-catalyzed reaction of SO$_3$$^{2-}$ with **1** was determined as the slope of a linear plot of $[(k_2)_o - (k_{NuH})_H[H_3O^+]f_{NuH}]/f_{Nu}$ against $[H_3O^+]$, according to eq 3, derived for Scheme 1.

$$(k_2)_o = (k_{NuH})_H[H_3O^+]f_{NuH} + ((k_{Nu})_H[H_3O^+] + k_{Nu})f_{Nu} \quad (3)$$

The pH–rate profile for the acid-catalyzed reaction of sulfite with the chloramine should follow a slope of -1.0 at pH $\gg$ (pK_a)$_{NuH}$, as shown by the dashed line in Figure 2. This line represents values of $(k_2)_o$ for the reaction of sulfite with **1**, calculated using eq 3 with $k_{Nu} = 0$ and the values of $(k_{NuH})_H$ and $(k_{Nu})_H$ reported in Table 1. The experimental values of $(k_2)_o$ in this pH region become pH independent and are consistent with the existence of an uncatalyzed pathway for the reaction of SO$_3$$^{2-}$ with **1**, k_{Nu} (M^{-1} s^{-1}, Scheme 1), which involves a water molecule acting as an acid. A value of $k_{Nu} = 11.0 \pm 0.5$ M^{-1} s^{-1} was calculated as the average of the values of $[(k_2)_o -$
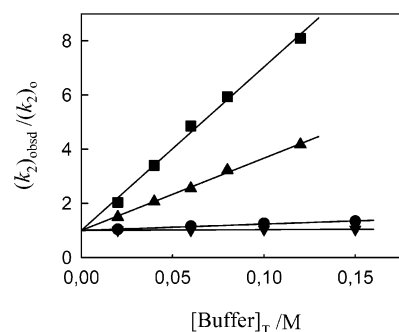

FIGURE 3. Dependence of the normalized observed second-order rate constant, $(k_2)_{obsd}/(k_2)_o$, for the reaction of sulfite with *N*-chlorotaurine on the total concentration of buffer at 25 °C and $I = 0.5$ (NaClO$_4$). (▼) Acetate buffer at pH 4.5. (●) Acetate buffer at pH 5.1. (▲) Phosphate buffer at pH 5.8. (■) Phosphate buffer at pH 6.5.

$(k_{Nu})_H [H_3O^+]f_{Nu}/f_{Nu}$ determined for reactions at pH > 9.0, for which the contribution of the acid-catalyzed reaction of HSO$_3$$^-$ with **1** is negligible. The solid line through the data for the reaction of sulfite with the chloramine in Figure 2 was calculated using eq 3 and the values of $(k_{NuH})_H$, $(k_{Nu})_H$, and $(K_a)_{NuH}$ given in Table 1 and k_{Nu} reported above.

Figure 3 shows the effect of increasing the concentration of buffers on the normalized observed second-order rate constants, $(k_2)_{obsd}/(k_2)_o$, for the reaction of sulfite with **1**, which varies as a function of pH. Up to pH 4.5, the observed reaction corresponds solely to the acid-catalyzed nucleophilic attack of HSO$_3$$^-$ at chlorine and $(k_2)_{obsd}$ is independent of buffer concentration up to 0.15 M. At higher pH, the reaction of sulfite dianion with **1** becomes a significant reaction pathway, and the observed reaction is subject to buffer catalysis (see Figure 3). Third-order rate constants $(k_3)_{buffer}$ (M^{-2} s^{-1}) for catalysis by the buffer of the reaction of sulfite dianion with **1** were calculated as the slopes of linear plots of $(k_2)_{obsd}$ against [buffer]. The catalytic constants determined at different buffer compositions yielded the same value of $(k_{Nu})_{AH}$ (M^{-2} s^{-1}), the third-order rate constant for general-acid catalysis of the reaction of sulfite dianion with **1**, after division by the fraction of sulfite present as the dianion and the fraction of buffer present as the acid form, according to eq 4. Table 2 summarizes the rate constants obtained for different general acids.

$$(k_3)_{buffer} = (k_{Nu})_{AH}f_{AH}f_{Nu} \quad (4)$$

Buffer-independent second-order rate constants, $(k_2)_o$, for the reaction between 2-mercaptoethanol and **1** were determined by

TABLE 2. Third-Order Rate Constants for General-Acid Catalysis of the Reaction of Sulfite Dianion with N-Chlorotaurine (1) in Water[a]

catalyst	pK_a[b]	$(k_{Nu})_{AH}$ ($M^{-2} s^{-1}$)[c]
CH_3COOH	4.6	$(1.1 \pm 0.1) \times 10^6$
$H_2PO_4^-$	6.5	$(2.1 \pm 0.1) \times 10^5$
boric acid	8.9	$(1.43 \pm 0.05) \times 10^3$
HCO_3^-	9.8	$(3.5 \pm 0.6) \times 10^2$

[a] At 25 °C and $I = 0.5$ ($NaClO_4$). [b] Apparent pK_a's of the general acids under the experimental conditions, given by $pK_a = pH - log([A^-]/[AH])$, determined from the pH of the buffer solutions and the concentration ratios $[A^-]/[AH]$. [c] Third-order rate constant for general-acid catalysis of the reaction of sulfite dianion with 1, determined as described in the text.
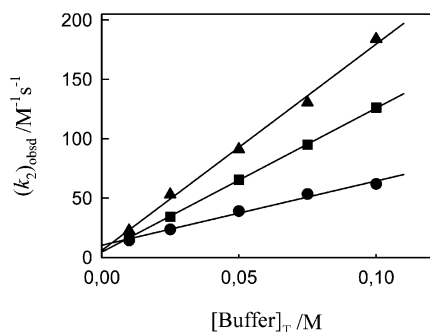

FIGURE 4. Catalysis of the reaction of 2-mercaptoethanol with **1** by phosphate buffers at 25 °C and $I = 0.5$ ($NaClO_4$). (▲) 80% free base, pH 7.10. (■) 50% free base, pH 6.49. (●) 20% free base, pH 5.86.
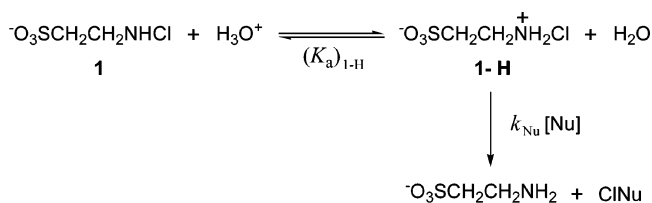
extrapolation of the observed second-order rate constants to zero buffer concentration. The pH−rate profile for this reaction at pH ≪ p$(K_a)_{NuH}$ shows two distinct regions (see Figure 2). The profile follows a slope of −1.0 below pH 5, and the observed reaction is due to the acid-catalyzed reaction of RSH with **1** (Scheme 1). The third-order rate constant $(k_{NuH})_H$ ($M^{-2} s^{-1}$) reported in Table 1 for this nucleophile was calculated as the slope of a linear plot of $(k_2)_o$ against $[H_3O^+]$ according to eq 5, derived for Scheme 1 when $[H_3O^+] \gg (K_a)_{NuH}$ and k_{Nu} is not significant. The pH-independent region above pH 7 represents the acid-catalyzed reaction of the thiolate anion with the chloramine, $(k_{Nu})_H$ in Scheme 1. The value of $(k_{Nu})_H$ given in Table 1 was calculated from the average of the values of $(k_2)_o - (k_{NuH})_H [H_3O^+]$ at pH > 6 and the reported value of $(K_a)_{NuH}$ (Table 1).

$$(k_2)_o = (k_{NuH})_H[H_3O^+] + (k_{Nu})_H(K_a)_{NuH} \qquad (5)$$

There is no detectable catalysis of the reaction of mercaptoethanol with **1** by acetate buffers between pH 4−5. However, there is strong buffer catalysis for this reaction at pH > 5.5, where the observed reaction is essentially due to the nucleophilic attack of the thiolate anion. Figure 4 shows plots of $(k_2)_{obsd}$ against the total concentration of phosphate buffers for the reaction of **1** with the thiol at different buffer ratios. The slopes of these plots are $(k_3)_{buffer}$, the third-order rate constants for catalysis of the reaction by the buffer. A value of $(k_{Nu})_{AH} = (4.0 \pm 0.5) \times 10^6 M^{-2} s^{-1}$ was calculated as an average of the values of $(k_3)_{buffer}/f_{AH}f_{Nu}$, according to eq 4.

The dependence on pH of the buffer-independent observed second-order rate constants, $(k_2)_o$ ($M^{-1} s^{-1}$), for the reaction of **1** with 2-(methylthio)ethanol is shown in Figure 2. The values of $(k_2)_o$ increase with $[H_3O^+]$ according to eq 1, and a value of $(k_{Nu})_H = (2.0 \pm 0.2) \times 10^9 M^{-2} s^{-1}$ for the third-order rate

SCHEME 2

$$^-O_3SCH_2CH_2NHCl + H_3O^+ \underset{(K_a)_{1-H}}{\overset{}{\rightleftharpoons}} {}^-O_3SCH_2CH_2\overset{+}{N}H_2Cl + H_2O$$

1   **1- H**

$$\downarrow k_{Nu}\,[Nu]$$

$$^-O_3SCH_2CH_2NH_2 + ClNu$$

constant for reaction of this nucleophile with **1** catalyzed by hydronium ion (Table 1) was calculated as the slope of a linear plot of $(k_2)_o$ against $[H_3O^+]$ (not shown). The line through the data in Figure 2 was calculated from the value of $(k_{Nu})_H$ using the logarithmic form of eq 1.

Discussion

The literature on the chemistry of N-chloramines shows that in aqueous solution they transfer a chlorine to nucleophiles such as amines,[11] iodide ion,[9,10] sulfite dianion,[12] and thiols.[7] However, some reports on the reaction of chloramine with amines in aqueous solution conclude that this reaction proceeds through two competitive pathways: (1) chlorine transfer to the amine leading to a new chloramine and (2) nucleophilic attack at nitrogen to form a substituted hydrazine.[13] Although these studies suggest that nucleophilic substitution at nitrogen may be significant for these N-chlorocompounds under certain conditions, we have found no evidence for reaction at nitrogen in our study of the reactions of different nucleophiles with N-chlorotaurine. Furthermore, the observed acid catalysis of the addition of nucleophiles to **1** reported in this work is consistent with the requirement that protonation at nitrogen takes place before or during chlorine transfer. Such catalysis would not be expected for nucleophilic attack at nitrogen with chloride ion as the leaving group.

Mechanism of the Addition of Nucleophiles to 1. The pH− rate profiles of Figures 1 and 2 show that the reactions of Br^-, N_3^-, SCN^-, I^-, and $HOCH_2CH_2SCH_3$ with **1** proceed through the specific-acid-catalyzed reaction of these nucleophiles with the chloramine. The failure to detect catalysis by general acids together with the inverse solvent deuterium isotope effects on these acid-catalyzed processes, $(k_{Nu})_H/(k_{Nu})_D = (0.30 \pm 0.02)$ for bromide ion and (0.54 ± 0.02) for iodide ion (Table 1), indicate that these reactions occur by a mechanism involving protonation of **1** in a fast preequilibrium step (Scheme 2).[14] According to this mechanism, the correlations shown for Br^-, SCN^-, and I^- in Figure 1 and for $HOCH_2CH_2SCH_3$ in Figure 2 should break to a slope of zero at pH = p$(K_a)_{1-H}$, as a result of complete substrate protonation. Saturation of acid catalysis has not been observed for bromide ion up to 0.5 M perchloric acid, and this is consistent with a recently reported value of $(K_a)_{1-H} = (1.14 \pm 0.09)$ M for the acidity constant of protonated **1** in water at 25 °C and $I = 0.5$ ($NaClO_4$), determined in a

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TABLE 3. Second-Order Rate Constants, k_{Nu}, for the Reaction of Nucleophiles with N-Protonated Chlorotaurine, 1-H, in Water[a]

|	k_{Nu} ($M^{-1} s^{-1}$)	
nucleophile	**1-H**[b]	**2**[c]
I^-	5.2×10^9	68
$HOCH_2CH_2SCH_3$	2.3×10^9	
SCN^-	1.9×10^9	
HSO_3^-	1.6×10^8	
$HOCH_2CH_2SH$	5.7×10^6	0.12^d
N_3^-	5.5×10^6	5.5×10^5
Br^-	8.9×10^3	1.4

[a] At 25 °C and $I = 0.5$ (NaClO$_4$). [b] Second-order rate constant for the reaction of the nucleophile with **1-H**, determined as described in the text. [c] Second-order rate constant for addition of the nucleophile to the quinone methide 4-[bis(trifluoromethyl) methylene]cyclohexa-2,5-dione (**2**), taken from ref 36, unless noted otherwise. [d] Data from ref 35.

study of the disproportionation of this chloramine in aqueous solution.[15] Table 3 gives the values of the second-order rate constant, k_{Nu} ($M^{-1} s^{-1}$), for the reactions of Br^-, N_3^-, SCN^-, I^-, and $HOCH_2CH_2SCH_3$ with **1-H**, calculated from the observed values of $(k_{Nu})_H$ (Table 1) and $(K_a)_{1-H} = 1.14$ M using the relationship $k_{Nu} = (k_{Nu})_H (K_a)_{1-H}$ (Scheme 2).

Several studies of the nucleophilic addition of thiocyanate anion to alkyl halides[16] and carbocations[17] show the preferential reaction of this ambident nucleophile at sulfur, with k_S/k_N ratios ranging from 10^2 to 10^4. The observation of a large difference in reactivity between the S and N nucleophilic centers of thiocyanate in these reactions suggests that this nucleophile reacts with **1-H** through the sulfur atom to give the unstable chlorine thiocyanate, ClSCN, which rapidly decomposes to form thiocyanogen.[18]

The rate profiles in Figure 2 show that the reaction of each of sulfite and 2-mercaptoethanol with the chloramine occurs by two pathways. The linear regions of the profiles at low pH represent the acid-catalyzed reaction of the protonated form of these nucleophiles (HSO_3^- and $HOCH_2CH_2SH$) with **1**. The absence of catalysis by general acids of both reactions in this pH region is consistent with preequilibrium substrate protonation followed by the reaction of the acid form of the nucleophiles with **1-H** (Scheme 2). Second-order rate constants for this last step, k_{Nu} ($M^{-1} s^{-1}$), determined as indicated above, are given in Table 3. At higher pH, the dominant pathway for the reaction of these sulfur nucleophiles with **1** is the acid-catalyzed reaction of SO_3^{2-} and $HOCH_2CH_2S^-$. These reactions show strong general-acid catalysis, which suggests that a proton is being transferred in the rate-determining step.

Nucleophilic attack at the neutral chloramine generates a strongly basic nitranion ($pK_a \sim 30$). Therefore, general acid catalysis of the reaction of either SO_3^{2-} or $HOCH_2CH_2S^-$ with **1** cannot be attributed to trapping of the initially formed nitranion by the buffer acid. The reaction must proceed through a preassociation mechanism in which the attack of the nucleophile at chlorine must take place in the presence of the acid catalyst. This mechanism could be either concerted or stepwise (Scheme 3). It is likely that the activation barrier for the largely favorable

SCHEME 3
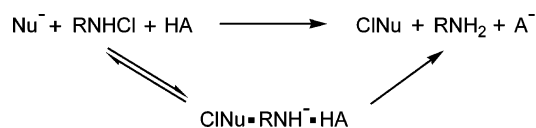
SCHEME 4
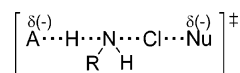
SCHEME 5
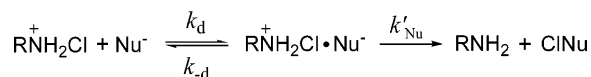
proton transfer from the catalyst to the nitranion ($\Delta pK_a \sim 20$) within the intermediate complex of the stepwise mechanism is negligible. If there is no barrier to this proton transfer, the intermediate cannot exist and the reaction must occur by a concerted mechanism, where protonation of the chloramine at nitrogen and chlorine transfer takes place in a single step (Scheme 4). A Brønsted plot (not shown) for general-acid catalysis of the reaction of sulfite dianion with **1** yields a Brønsted coefficient of $\alpha = (0.74 \pm 0.07)$. This suggests that proton transfer to nitrogen is ca. 70% complete at the transition state.

The data in Table 3 show that the value of k_{Nu} approaches the expected limit of 5×10^9 $M^{-1} s^{-1}$ for a diffusion-controlled bimolecular reaction for the most reactive nucleophiles. The value of k_{Nu} for the reaction with iodide ion suggests that the reaction of this nucleophile with **1-H** is diffusion-limited and is consistent with a rate constant k_{Nu}' for reaction within an encounter complex larger than k_{-d} for diffusional separation of the ion pair (Scheme 5). The values of $K_{as} = k_d/k_{-d} \leq 1.0$ M^{-1} for the weak association of the two ions in water to form an encounter complex[19] and $k_d = 5 \times 10^9$ $M^{-1} s^{-1}$ for the diffusion-limited reaction of iodide ion give $k_{-d} \geq 5 \times 10^9$ s^{-1} and, therefore, $k_{Nu}' \geq 10^{11}$ s^{-1} for this nucleophile. This suggests that the rate constant k_{Nu}' for the reaction of **1-H** with more nucleophilic species could reach the value of 10^{13} s^{-1} for a bond vibration frequency. A correlation of log k_{Nu} for the activation-limited reactions of **1-H** with log k_{Nu} for the attack of the same nucleophiles at the fluorine atom in Selectfluor (1-chloromethyl-4-fluoro-1,4-diazoniabicyclo [2.2.2]octane bis(tetrafluoroborate))[20] gives a good linear fit with a slope of 1.6. According to this correlation, we can predict that the rate constants for the reaction of **1-H** with I^- and $HOCH_2CH_2S^-$ should be 30 and 1 $\times 10^5$-fold larger, respectively, than that for SCN^-. The estimated rate constant for collapse of the ion pair, [RNH$_2$-Cl$^+$·Nu$^-$], is $k_{Nu}' \geq 10^{11}$ s^{-1} for iodide ion and $k_{Nu}' \geq 10^{14}$ s^{-1} for the thiolate anion. The latter value suggests that there is no chemical barrier to the collapse of **1-H** in the presence of this strong nucleophile. This is consistent with a change to a concerted mechanism, which is enforced by the absence of a significant lifetime for the protonated chloramine when it is in contact with the thiolate ion.[21]

Our experimental observations are not consistent with the conclusions of earlier studies of the reaction of iodide ion with

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different *N*-chloramines.[9,10] It has been proposed, on the basis of the observation of weak buffer catalysis for this reaction, that the mechanism involves proton transfer from the general acid to the developing nitrogen anion as the chlorine is being transferred to iodide ion. However, most of the chloramines that have been investigated previously are less reactive than *N*-chlorotaurine, since they have more basic leaving groups. Therefore, for these less reactive chloramines, there should be a significant barrier for chlorine transfer to iodide ion from the protonated chloramine. Our results suggest that the concerted mechanism is followed only when it is enforced by the nonexistence of the protonated chloramine in the presence of the nucleophile, and therefore the reaction of iodide ion with chloramines, which are less reactive than chlorotaurine, should proceed through the stepwise mechanism shown in Scheme 2. We are currently carrying out a more extensive study of the reaction of chloramines with iodide ion to determine whether the weak catalytic effect observed previously can in fact be attributed to general acid catalysis of the addition reaction.

Feasibility of an Electron-Transfer (ET) Mechanism. Recent studies on the mechanism by which *N*-fluoro compounds transfer the fluorine atom to nucleophiles have focused on the distinction between nucleophilic substitution and electron-transfer pathways.[22–25] Differding and Ruegg have looked at the mechanism of electrophilic fluorinations by using a cyclizable radical probe and found that free radicals are not involved in the formation of fluorinated products.[22] They have also shown that the observed rate constants for fluorination of several nucleophiles by *N*-fluoro-saccharin sultam are much faster than the rate constants for the hypothetical electron-transfer reaction, estimated using electron-transfer theory, and concluded that nucleophilic substitution at fluorine is the only pathway that leads to fluorination.[23] In addition, the one-electron electrochemical reduction of this *N*-fluoro compound has been found to follow a dissociative mechanism with simultaneous electron transfer and breaking of the N−F bond, to give a nitrogen-centered sultam radical and fluoride ion.[26] This supports the conclusion that fluorination of nucleophiles by this N−F reagent proceeds by an S_N2 mechanism. We have previously suggested that fluorination of nucleophiles such as iodide ion, thiocyanate ion, and bromide ion by *N*-fluorobenzenesulfonimide in aqueous solution occurs by direct nucleophilic attack at fluorine, with nucleophilic reactivity at this center being largely determined by the ease of one-electron oxidation of the nucleophile.[27] We would like to know whether the related reaction of nucleophiles at chlorine proceeds by a direct substitution or by initial electron transfer from the nucleophile to the electrophile to form radical intermediates followed by a radical-coupling step.

The reduction of **1-H** by transfer of an electron from the nucleophile involves the cleavage of the N−Cl bond, and the reaction may proceed by a concerted mechanism or in two successive steps through the intermediate radical **1-H•** (Scheme

SCHEME 6
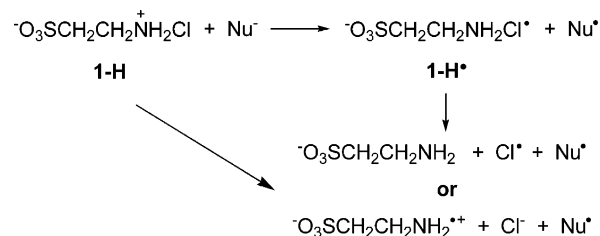
6). The latter pathway can only be followed if **1-H•** has a lifetime in aqueous solution longer than a bond vibration. Independently of the mechanism by which reduction takes place, the reductive cleavage of **1-H** may lead to formation of the chlorine radical, which would then couple with Nu• to give ClNu. Alternatively, a nitrogen-centered radical and chloride ion could be the preferred products, in which case chlorination of the nucleophile can only occur by direct substitution at chlorine.

To investigate whether an electron-transfer mechanism can lead to chlorinated products, we have carried out a series of quantum chemical calculations to analyze the stability in aqueous solution of the radical **1-H•** formed by electron transfer to **1-H** and the nature of the products formed after reduction. Figure 5 shows the potential energy profile for the cleavage of the corresponding radical in the gas phase, obtained from density functional theory (DFT) calculations using the UB3LYP functional in combination with the 6-31+G(d) basis set, together with the optimized geometry of the minimum.

There is only a shallow energy minimum on this surface at a nitrogen−chlorine distance of 2.47 Å. This is much larger than the expected bonding distance for these two atoms and shows that the radical **1-H•** is an unstable species. The long-distance energy minimum corresponds to a complex with a dissociation energy of 58.8 kJ/mol, in which the electron spin density is distributed almost equally between nitrogen (0.45) and chlorine (0.52) and the latter carries about half of the negative charge. The distance of 1.909 Å between one of the oxygen atoms of the SO3 group and a hydrogen bound to nitrogen is consistent with the existence of a hydrogen bond. Similar complexes between the fragments formed upon dissociative one-electron transfer have been experimentally detected in the reduction of haloalkanes in polar solvents.[28] At longer N−Cl distances, the nitrogen atom tends to accumulate negative

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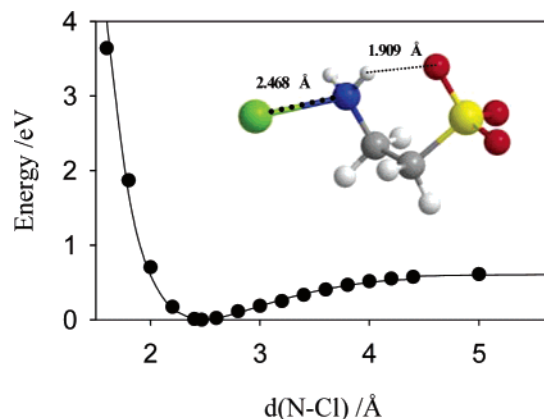

FIGURE 5. Gas-phase potential energy of the reduced form of **1-H**, calculated at the UB3LYP/6-31+G(d) level, versus the N−Cl distance. Inset: Optimized geometry of **1-H** + e− in the gas phase.

charge and this, together with the low spin density on this atom, supports the conclusion that the amine (taurine), and not a nitrogen-centered radical, is formed upon one-electron reduction of **1-H** in the gas phase (see Table S2 in the Supporting Information). The calculated energy of the two possible sets of products, obtained by adding the energies of the two fragments, shows that the reductive cleavage of **1-H** in the gas phase to give chloride ion and a nitrogen-centered radical is less favorable than the cleavage to chlorine radical and the amine by ca. 38 kJ/mol. Geometry optimization of the amine radical results in the transfer of a proton from the amino to the sulfonate group, which is then hydrogen bonded to nitrogen. However, the results of calculations using a continuum solvation model show that the behavior in water is different. The interactions that give rise to the long-distance complex in the gas phase disappear in aqueous solution and the absence of energy minima suggests that the reduction of **1-H** in this solvent takes place by a concerted mechanism. The results of single-point calculations, using the optimized gas-phase geometries, indicate that at long N−Cl distances the negative charge accumulates on the chlorine whereas essentially all the spin density is located on the nitrogen. This observation is consistent with formation of the amine radical and chloride ion by the reduction of **1-H** in aqueous solution. This is in good agreement with recent experimental studies which show that *N*-chloro compounds undergo reductive cleavages to yield a nitrogen-centered radical and chloride ion.[29] Our attempts to fully optimize the geometry of this system in aqueous solution were not successful, but intermediate results suggest that a proton moves from nitrogen to oxygen and a hydrogen bond is formed between this hydrogen and the nitrogen atom. In fact, geometry optimization in both the gas phase and in aqueous solution of the hypothetical amine radical, $^-O_3SCH_2CH_2NH_2^{\bullet+}$, results in the transfer of a proton from the amino to the sulfonate group to give $HO_3SCH_2CH_2NH\bullet$, in a conformation that allows the formation of a hydrogen bond to nitrogen. In aqueous solution, the nitrogen radical and chloride ion are more stable than the amine and chloride radical by ca. 40 kJ mol^{-1}. In conclusion, the fact that electron transfer to **1-H** in aqueous solution results in the formation of chloride ion provides evidence that chlorination by **1-H** proceeds by nucleophilic substitution at the chlorine atom.

Structure−Reactivity Correlations. Previous reports on the reactions of electrophilic chlorine and fluorine compounds have shown a very large sensitivity of *N*-halo compounds to the strength of the attacking nucleophile, and the observed slopes of Swain−Scott correlations for these reactions are in the range $s = 4-5$.[27,30] The observed increase in k_{Nu} for the reaction of nucleophiles with N-protonated chlorotaurine (Scheme 2) from 8.9×10^3 M^{-1} s^{-1} for bromide ion to 5.2×10^9 M^{-1} s^{-1} for iodide ion (Table 3) is also much larger than predicted by the Swain−Scott and Ritchie nucleophilicity scales.[31−34] However,

the rate constant for the reaction of $HOCH_2CH_2SCH_3$ with **1-H** is 400-fold larger than that for the reaction of $HOCH_2CH_2SH$, and this effect is similar to the observed 600-fold difference in the reactivities of CH_3SCH_3 and CH_3SH toward the quinone methide 4-[bis(trifluoromethyl) methylene]cyclohexa-2,5-dione.[35] Furthermore, the estimated 3×10^7-fold increase in reactivity toward **1-H** on moving from $HOCH_2CH_2SH$ to $HOCH_2CH_2S^-$, on the basis of a comparison of nucleophile reactivities toward **1-H** and Selectfluor,[20] is not significantly different from the 2×10^7-fold difference between the rate constants for addition of these two nucleophiles to the same quinone methide.[35] These data suggest similar nucleophile selectivities for displacement by sulfur nucleophiles on chlorine and for addition of sulfur nucleophiles to carbocations. However, bromide ion reacts with **1-H** 600-fold slower than $HOCH_2CH_2$-SH, whereas this same nucleophile is ca. 10 times more reactive than $HOCH_2CH_2SH$ toward carbocations.[35,36] Also, the observed reactivity difference between iodide ion and bromide ion of at least 6×10^5-fold for reaction with **1-H** is much larger that the 50-fold difference in reactivity for the two nucleophiles toward carbocations. Therefore, the large nucleophile selectivities observed for nucleophilic substitution at halogen, on the basis of the reactivities of a very small number of sulfur nucleophiles and halide ions, could be due to the anomalous reactivity of halide ions. We are currently studying the reaction of some *N*-halo compounds with a wide range of nucleophilic reagents to fully characterize the reactivity of these substrates toward nucleophilic substitution at chlorine. Azide ion is less reactive than iodide ion and thiocyanate anion, showing a reactivity pattern toward **1-H** similar to that found for alkyl halides. However, its reaction with **1-H** is ∼2900-fold faster than what would be expected from the *n* value for this nucleophile. Larger positive deviations have been found for the addition of this species to carbocations, but the origin of the enhanced nucleophilic reactivity shown by azide ion in certain reactions is still not clear.[36]

Experimental Section

Materials. The sodium salt of *N*-chlorotaurine (**1**) was prepared by reaction of taurine with chloramine-T in ethanol. Deuterium oxide and deuterium chloride (35% w/w) were 99.9% D and 99.5% D, respectively. Inorganic salts and organic chemicals were reagent grade from commercial sources and were used without further purification. Stock solutions of sodium sulfite were prepared daily, and their concentrations were determined immediately after their use in a kinetic run by titration with starch iodine.[37]

Buffer Solutions and pH Measurements. The following buffers (0.05 M) were used to maintain constant pH in studies of the reaction of **1** with nucleophiles: methoxyacetate, pH 3.2−4.0; chloroacetate, pH 2.5−3.2; acetate, pH 4.5−5.2; phosphate, pH 5.8−7.2; *N*-2-hydroxyethyl-piperazine-*N*′-2-ethanesulfonic acid (HEPES), pH 7.6; borate, pH 8.2−9.6; taurine, 9.0; 1,1,1,3,3,3-hexafluoroisopropanol (HFIP), pH 8.6−9.9; carbonate, pH 9.4−10.3. In some experiments with azide ion, the nucleophile also served as the solution buffer (pH 5.0). Solution pH was measured at 25 °C using a Radiometer PHM82 pH-meter equipped with a GK3401C combined glass electrode. In reactions monitored by

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conventional UV spectroscopy, the pH was determined at the end of the reaction. In kinetic experiments involving fast reactions that were monitored using a stopped-flow device, the pH was measured for control solutions identical to the solutions used in the stopped-flow experiments. Values of pD were obtained by adding 0.4 to the observed reading of the pH meter. The apparent pK_a's of the nucleophiles at 25 °C and $I = 0.5$ (NaClO$_4$), given by $p(K_a)_{NuH} = pH - \log([Nu]/[NuH])$, were determined from the solution pH and the stoichiometric concentrations of [Nu] and [NuH].

Kinetic Studies. All reactions were carried out in water at 25 °C and at constant ionic strength of $I = 0.5$ maintained with sodium perchlorate. Kinetic experiments always employed at least a 10-fold excess of nucleophile over substrate. Reactions of **1** with halftimes of less than 15 s were studied by using the DX17MV stopped-flow device from Applied Photophysics. An aqueous solution of the substrate and a buffered solution of the nucleophile were mixed in a ratio of 1:1 to give a final reaction mixture containing a concentration of **1** of 1×10^{-5} to 1×10^{-3} M. The slower reactions of **1** were monitored using a conventional UV spectrophotometer and were initiated by making a 100-fold dilution of a solution of substrate into the reaction mixture to give a final substrate concentration between 1×10^{-5} and 1×10^{-3} M. The reactions with bromide and iodide ions were followed by monitoring the appearance of Br$_3^-$ at 266 nm and I$_3^-$ at 287 nm, respectively. Reactions with azide ion were difficult to follow because of the large background absorbance of this nucleophile and were studied in the presence of a fixed concentration of iodide ion by monitoring the increase in absorbance at 287 nm because of formation of I$_3^-$. Other reactions of **1** were followed by monitoring the disappearance of the substrate at the following wavelengths: SCN$^-$, 270 nm; SO$_3^{2-}$, 287 nm; HOCH$_2$CH$_2$SCH$_3$, 240 nm; HOCH$_2$CH$_2$S$^-$, 250 nm. First-order rate constants, k_{obsd} (s^{-1}), were obtained from the fit of the absorbance data to a single-exponential function and were reproducible to ±5%.

Quantum Chemical Calculations. All calculations were performed using the Gaussian 03 package.[38] Molecular geometries were optimized at the DFT/UB3LYP level using the 6-31+G(d) basis set. Frequency calculations were carried out to characterize all stationary points as minima or transition states on the potential energy surface. DFT/UB3LYP calculations with different basis sets (6-311G**, CEP121g or aug-cc-pVTZ) and MP2/6-31G* calculations led to essentially the same results. The effects of solvent were simulated at 300.0 K by the PCM solvent model using Pauling radii for the solute atoms with a scaling coefficient of 1.21 and mapping the internal surface of the cavity with 70 elements.

Supporting Information Available: Rate constants $(k_2)_{obsd}$ (M^{-1} s^{-1}) for the reaction of nucleophiles with *N*-chlorotaurine (**1**) in water at 25 °C and $I = 0.5$ (NaClO$_4$). Calculated electronic energies, electron spin densities, and atomic charges of the reduced form of N- protonated chlorotaurine (**1-H•**) as a function of the N−Cl distance. Calculated energies of the possible products formed upon reduction of N-protonated chlorotaurine (**1-H**) in the gas phase and in aqueous solution. This material is available free of charge via the Internet at http://pubs.acs.org.

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