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# Kinetic and Thermodynamic Barriers to Chlorine Transfer between Amines in Aqueous Solution

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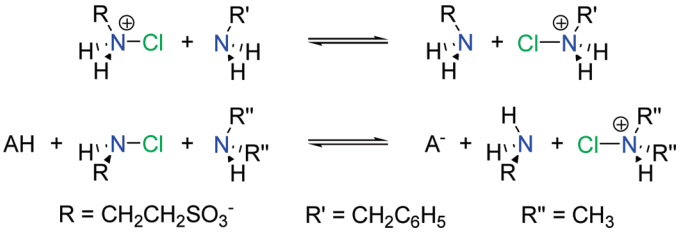


Third-order rate constants for the acid-catalyzed reversible reaction of *N*-chlorotaurine with benzylamine and dimethylamine were determined in water at 25 °C and $I = 0.5$ ($NaClO_4$). The reaction with benzylamine shows inverse solvent deuterium isotope effects of $k_H/k_D = 0.57$ and 0.47 in the forward and reverse directions, respectively. These isotope effects, together with the absence of detectable general acid catalysis for this reaction, provide evidence for a stepwise mechanism involving fast equilibrium protonation of *N*-chlorotaurine followed by rate-determining chlorine transfer from the protonated chloramine to benzylamine. The observation of strong catalysis by general acids of the reaction of dimethylamine with *N*-chlorotaurine suggests a change to a concerted mechanism with proton and chlorine transfer occurring in a single step. This change in mechanism is enforced by the absence of a significant lifetime for protonated chlorotaurine in contact with this strongly nucleophilic amine. The kinetic and thermodynamic parameters for the reaction between protonated chlorotaurine and benzylamine are used to estimate a Marcus intrinsic reaction barrier of $\Delta G_0^{\ddagger} = 4.1$ kcal/mol for chlorine transfer between amines. Comparison of this intrinsic barrier with those reported previously for bromine transfer between carbanions points to the existence of certain similarities between halogen and proton transfer reactions.

## Introduction

*N*-Chloramines play a significant role in important biological processes. They have been implicated as intermediates in the myeloperoxidase/$H_2O_2$/$Cl^-$ initiated oxidation of biomolecules, which is involved in the microbiocidal response of phagocytic cells.[1−3] More recently, it has been suggested that a lysine chloramine is the chlorinating species responsible for conversion of free tryptophan to 7-chlorotryptophan at the active site of the flavin-dependent halogenase RebH.[4,5] *N*-Chloramines are formed in vivo by reaction of HOCl with amino groups of amino acids, peptides, and proteins.[6] These *N*-chloro compounds are longer lived than HOCl but retain an effective oxidizing and chlorinating capacity, being able to react with a variety of nucleophilic groups in biological substrates. In the past few years, significant efforts have been made to identify possible targets for *N*-chloramines in biological systems.[7−12] However, relatively little is known about the mechanisms

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of chlorine transfer from *N*-chloramines to other substrates.[13−16]

We have recently reported that chlorine transfer from *N*-chloramines to sulfur nucleophiles and halide ions requires protonation of the chloramine at nitrogen before or during the rate-limiting step, to avoid the formation of an unstable nitranion.[16] Most of these reactions proceed with specific acid catalysis, consistent with protonation of the chloramine in an initial equilibrium step. However, some of them are subject to general acid catalysis, which indicates that chlorine transfer is assisted by proton transfer to the chloramine nitrogen in the rate-limiting step. We have followed the suggestion of Jencks[17−19] that reaction mechanisms are dictated by the lifetimes of possible reaction intermediates and have analyzed the observed change in mechanism in terms of the estimated lifetime of the protonated chloramine in the presence of the nucleophile. The results show that as the nucleophile becomes stronger, a point is reached where there is no chemical barrier for collapse of the complex $[RNH_2Cl^+ \cdot Nu]$ to products, and therefore, the reaction becomes concerted. We have now extended this work and report here the results of a study of the reaction of *N*-chlorotaurine ($^-O_3S(CH_2)_2NHCl$) with amines, designed to provide evidence for a similar change in mechanism with increasing the strength of the nitrogen nucleophile. This work was undertaken for the following reasons:

(1) An analysis of the mechanistic information available in the literature on the reaction of chloramines with amines in aqueous solution shows important discrepancies between the conclusions reached in different studies. Snyder and Margerum[13] have reported specific acid catalysis of chlorine transfer from chloramine ($NH_2Cl$) to methylamine and amino acids and have concluded that these reactions occur through a stepwise mechanism involving the protonated chloramine. Limited studies by Isaac and Morris[20,21] describe the reaction of chloramine with amines, but the presence or absence of general acid catalysis was not investigated. In later studies, Ferriol et al.[22,23] reported general acid catalysis of the reaction of chloramine with methylamine and other amines and suggested that these reactions follow a concerted mechanism, which could occur concurrently or not with a stepwise process involving the protonated chloramine. We therefore conclude that there is currently not a clear understanding of the mechanism of these reactions. The available data provide no evidence for the disappearance of the barrier for collapse of the protonated chloramine in the presence of a sufficiently nucleophilic amine. We show here that an expected transition from a stepwise to a concerted mechanism, where protonation of the chloramine and chlorine transfer to the amine occur in a single step, is observed as the amine becomes more reactive.

(2) Chlorine transfer between the nitrogen atoms of amines is a reversible reaction for which it is possible to experimentally determine the corresponding rate and equilibrium constants. This allows for an estimation of the Marcus intrinsic barrier for chlorine transfer between amines, which can be compared with the very small intrinsic barrier of ca. 1 kcal $mol^{-1}$ for direct proton transfer between electronegative atoms.[24] To the best of our knowledge, there is only one report in the literature providing values of intrinsic barriers for halogen transfer reactions.[25] This study surprisingly reveals that bromine transfer between carbanions is *intrinsically* faster than the parallel proton transfer reaction and shows the nitro anomaly, a typical feature of proton transfer. We report here that the intrinsic barriers for halogen transfer between electronegative atoms are much lower than those for halogen transfer involving carbon. These results leave an open question about the origin of the observed similarities between proton and halogen transfer reactions.

(3) A detailed elucidation of the mechanisms of reaction of *N*-chloramines with small nucleophilic molecules, as models for the reactive groups in the more complex biomolecules, could help to understand the roles that *N*-chloramines play in biological systems.

## Results

**Chlorine Transfer to Benzylamine.** The observed first-order rate constants, $k_{obsd}$ ($s^{-1}$), for the reaction of *N*-chlorotaurine with benzylamine in the presence of 5 mM taurine at pH 6.5 (buffered by 0.1 M phosphate) show a linear dependence on the total concentration of benzylamine. The linear plot of $k_{obsd}$ against $[RNH_2]_T$ (●, Figure 1A) has a positive intercept characteristic of a reversible reaction, first-order in both directions, and this indicates that the reaction proceeds to an equilibrium mixture of *N*-chlorotaurine and *N*-chlorobenzylamine. The rate constants $k_{obsd}$ ($s^{-1}$) for the reversible chlorine transfer reaction are therefore equal to the sum of the rate constants for reaction in the forward and reverse directions (eq 1). Figure 1A shows the dependence of $k_{obsd}$ ($s^{-1}$) for chlorine transfer approaching equilibrium on the concentration of benzylamine in the presence of fixed concentrations of taurine. The slopes of these linear correlations give the same second-order rate constant $(k_{RNH_2})_{obsd} = (6.0 \pm 0.2) \times 10^{-2}$ $M^{-1}$ $s^{-1}$ for formation of *N*-chlorobenzylamine in the forward direction. The intercepts, $(k_r)_{obsd}$ ($s^{-1}$), increase with increasing the concentration of taurine according to eq 2, and the slope of a linear plot of $(k_r)_{obsd}$ against $[TauNH_2]_T$ (Figure 1B) gives $(k_{TauNH_2})_{obsd} = (7.4 \pm 0.2) \times 10^{-2}$ $M^{-1}$ $s^{-1}$

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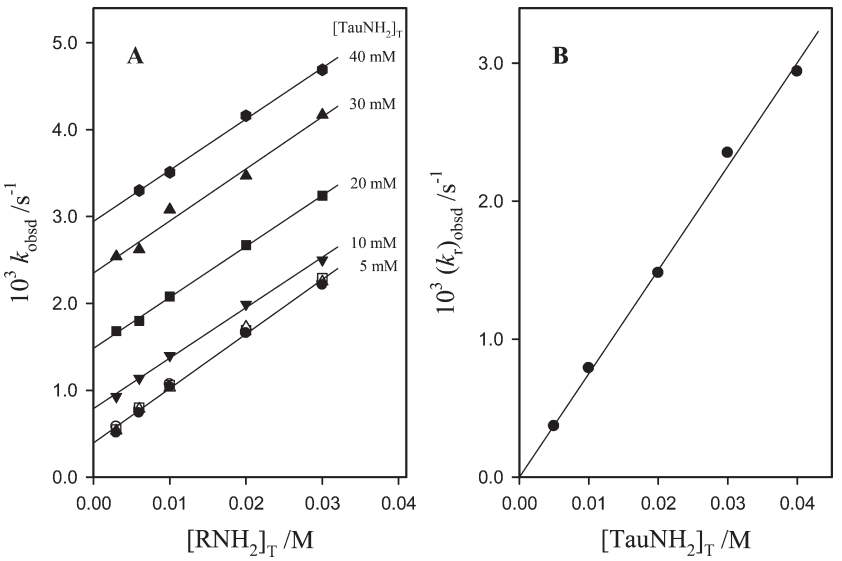



**FIGURE 1.** (A) Dependence of $k_{obsd}$ ($s^{-1}$) for the reaction of *N*-chlorotaurine with benzylamine on the concentration of amine at pH 6.5 in the presence of different concentrations of taurine and phosphate buffer in $H_2O$ at 25 °C and $I$ = 0.5 ($NaClO_4$). Key: (○) [buffer] = 0.03 M; (□) [buffer] = 0.05 M; (●, ▼, ■, ▲, ⬢) [buffer] = 0.1 M; (△) [buffer] = 0.15 M. (B) Dependence of $(k_r)_{obsd}$ ($s^{-1}$) for the reaction of *N*-chlorobenzylamine with taurine on the total concentration of taurine at pH 6.5 (buffered by 0.1 M phosphate) in $H_2O$ at 25 °C and $I$ = 0.5 ($NaClO_4$).

**TABLE 1. Third-Order Rate Constants for Reversible Acid-Catalyzed Chlorine Transfer from *N*-Chlorotaurine to Amines**[a]

| amine | $(k_{RR'NH})_H$[b] ($M^{-2}$ $s^{-1}$) | $(k_{TauNH_2})_H$[c] ($M^{-2}$ $s^{-1}$) | $(k_{RR'NH})_{H_2PO_4^-}$[d] ($M^{-2}$ $s^{-1}$) | $(k_{TauNH_2})_{H_2PO_4^-}$[e] ($M^{-2}$ $s^{-1}$) |
|---|---|---|---|---|
| $C_6H_5CH_2NH_2$ (in $H_2O$) | $(1.87 \pm 0.06) \times 10^8$ | $(8.84 \pm 0.06) \times 10^7$ | | |
| $C_6H_5CH_2ND_2$ (in $D_2O$) | $(3.3 \pm 0.3) \times 10^8$ | $(1.9 \pm 0.3) \times 10^8$ | | |
| $(CH_3)_2NH$ | $(9.0 \pm 1.3) \times 10^7$ | $(1.1 \pm 0.2) \times 10^5$ | $(2.63 \pm 0.08) \times 10^3$ | $(3.91 \pm 0.12)$ |

[a] At 25 °C and $I$ = 0.5 ($NaClO_4$). [b] Third-order rate constant for the hydronium ion catalyzed chlorine transfer from *N*-chlorotaurine to amines. [c] Third-order rate constant for the hydronium ion catalyzed chlorine transfer from the corresponding *N*-chloramine to taurine in the reverse direction. [d] Third-order rate constant for catalysis by phosphate monoanion of chlorine transfer from *N*-chlorotaurine to amines. [e] Third-order rate constant for catalysis by phosphate monoanion of chlorine transfer from the corresponding *N*-chloramine to taurine in the reverse direction.

for formation of *N*-chlorotaurine from *N*-chlorobenzylamine and taurine in the reverse direction.

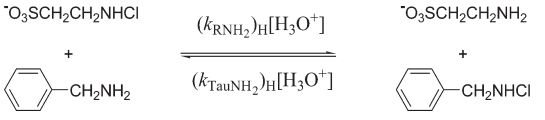
$$k_{obsd} = (k_{RNH_2})_{obsd}[RNH_2]_T + (k_r)_{obsd} \quad (1)$$

$$(k_r)_{obsd} = (k_{TauNH_2})_{obsd}[TauNH_2]_T \quad (2)$$

Figure 1A also shows that $k_{obsd}$ does not depend on the concentration of 50% free base phosphate buffer at pH 6.5 and 25 °C ($I$ = 0.5, $NaClO_4$). The absence of a significant increase in $k_{obsd}$ upon increasing the buffer concentration from 30 to 150 mM shows that there is no general acid−base catalysis of chlorine transfer in the forward or reverse directions. Table S1 of Supporting Information gives second-order rate constants $(k_{RNH_2})_{obsd}$ ($M^{-1}$ $s^{-1}$, eq 1) and $(k_{TauNH_2})_{obsd}$ ($M^{-1}$ $s^{-1}$, eq 2) obtained from the slope and intercept, respectively, of linear plots of $k_{obsd}$ against $[RNH_2]_T$ at pH 5.8, 6.5, and 7.1. An analysis of the data reported in this table shows that there is no significant change in these second-order rate constants with changing pH in the interval 5.8−7.1. This pH-independent pathway is due to the acid-catalyzed reaction of the neutral amine with the chloramine (Scheme 1) in a pH region where the amine is mainly protonated and the increase in the fraction of reactive amine with increasing pH is compensated for by the corresponding decrease in $[H_3O^+]$.

At pH ≪ $(pK_a)_{RNH_3^+}$, eq 3, derived for the forward reaction in Scheme 1, simplifies to eq 4, and a value of $(k_{RNH_2})_H$ = (1.87 ± 0.06) × $10^8$ $M^{-2}$ $s^{-1}$ (Table 1) for the acid-catalyzed reaction of benzylamine with *N*-chlorotaurine was determined from this equation, using the average of the values of $(k_{RNH_2})_{obsd}$ determined at different pH values and $(K_a)_{RNH_3^+}$ = 3.31 × $10^{-10}$ M for the apparent acidity constant of protonated benzylamine. Similarly, a third-order rate constant $(k_{TauNH_2})_H$ = (8.84 ± 0.06) × $10^7$ $M^{-2}$ $s^{-1}$ (Table 1) for the acid-catalyzed reaction of taurine with *N*-chlorobenzylamine in the reverse direction was calculated as $(k_{TauNH_2})_{obsd}/(K_a)_{TauNH_3^+}$, using the average value of $(k_{TauNH_2})_{obsd}$ and $(K_a)_{TauNH_3^+}$ = 8.71 × $10^{-10}$ M for the apparent acidity constant of protonated taurine.[26]

**SCHEME 1**




$$(k_{RNH_2})_{obsd} = (k_{RNH_2})_H[H_3O^+]f_{RNH_2} \quad (3)$$

$$(k_{RNH_2})_{obsd} = (k_{RNH_2})_H(K_a)_{RNH_3^+} \quad (4)$$

Rate measurements in phosphate buffer solutions in $D_2O$ at 25 °C and $I$ = 0.5 ($NaClO_4$) provided second-order rate

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**TABLE 2. Rate and Equilibrium Constants for Reversible Chlorine Transfer from *N*-Chlorotaurine to Amines in Water at 25 °C and $I = 0.5$ ($NaClO_4$)**

| Reaction | $k_f$[a] | $k_r$[b] | $K$[c] |
|---|---|---|---|
| $^{-}O_3S(CH_2)_2\overset{\oplus}{N}H_2Cl + PhCH_2NH_2 \underset{k_{TauNH_2}}{\overset{k_{RNH_2}}{\rightleftharpoons}} {}^{-}O_3S(CH_2)_2NH_2 + Ph\overset{\oplus}{C}H_2NH_2Cl$ | $(2.13 \pm 0.13) \times 10^8$ $M^{-1}s^{-1}$ | $(1.32 \pm 0.04) \times 10^7$ $M^{-1}s^{-1}$ | $(16.1 \pm 1.1)$ |
| $^{-}O_3S(CH_2)_2NHCl + (CH_3)_2NH + H_3O^+ \underset{(k_{TauNH_2})_o}{\overset{(k_{R_2NH})_H}{\rightleftharpoons}} {}^{-}O_3S(CH_2)_2NH_2 + (CH_3)_2\overset{\oplus}{N}HCl$ | $(9.0 \pm 1.3) \times 10^7$ $M^{-2}s^{-1}$ | $(2.2 \pm 0.4) \times 10^4$ $M^{-1}s^{-1}$ | |
| $^{-}O_3S(CH_2)_2NHCl + (CH_3)_2NH + H_2PO_4^- \underset{(k_{TauNH_2})_{A^-}}{\overset{(k_{R_2NH})_{AH}}{\rightleftharpoons}} {}^{-}O_3S(CH_2)_2NH_2 + (CH_3)_2\overset{\oplus}{N}HCl + HPO_4^{2-}$ | $(2.63 \pm 0.08) \times 10^3$ $M^{-2}s^{-1}$ | $(2.20 \pm 0.07) \times 10^6$ $M^{-2}s^{-1}$ | |

[a]Rate constant for the forward reaction, determined as described in the text. [b]Rate constant for the reverse reaction, determined as described in the text. [c]Equilibrium constant for the reaction calculated as $K = k_f/k_r$.

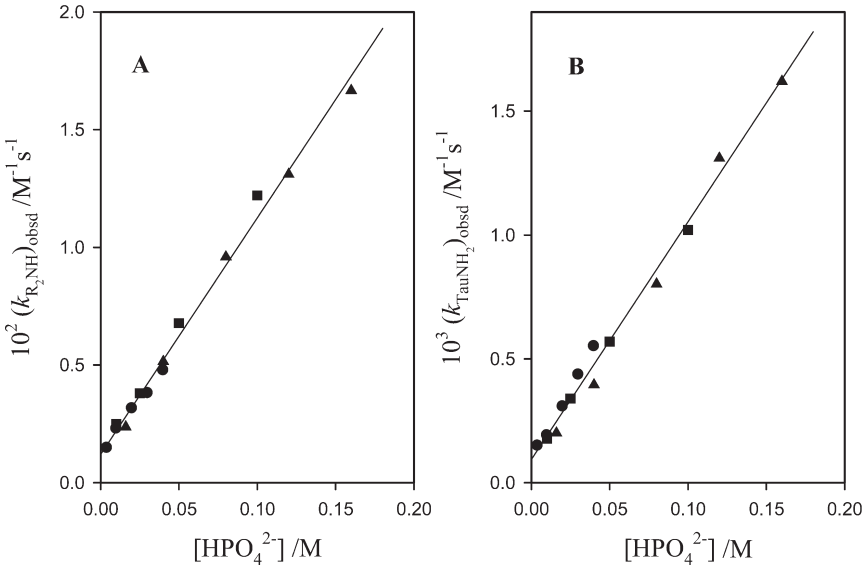


**FIGURE 2.** (A) Dependence of $(k_{R_2NH})_{obsd}$ ($M^{-1}$ $s^{-1}$) for the reaction of *N*-chlorotaurine with dimethylamine on the concentration of the basic form of phosphate buffer in $H_2O$ at 25 °C and $I = 0.5$ ($NaClO_4$). (B) Dependence of $(k_{TauNH_2})_{obsd}$ ($M^{-1}$ $s^{-1}$) for the reaction of *N*-chlorodimethylamine with taurine in the reverse direction on the concentration of the basic form of phosphate buffer in $H_2O$ at 25 °C and $I = 0.5$ ($NaClO_4$). Key: (●) 20% free base, pH = 5.8; (■) 50% free base, pH = 6.4; (▲) 80% free base, pH = 7.1.

constants $(k_{RND_2})_{obsd} = (3.2 \pm 0.3) \times 10^{-2}$ $M^{-1}$ $s^{-1}$ for the reaction of *N*-chlorotaurine with benzylamine and $(k_{TauND_2})_{obsd} = (4.8 \pm 1.0) \times 10^{-2}$ $M^{-1}$ $s^{-1}$ for the reaction of *N*-chlorobenzylamine with taurine. Third-order rate constants $(k_{RND_2})_D = (3.3 \pm 0.3) \times 10^8$ $M^{-2}$ $s^{-1}$ and $(k_{TauND_2})_D = (1.9 \pm 0.3) \times 10^8$ $M^{-2}$ $s^{-1}$ (Table 1) for the acid-catalyzed chlorine transfer reactions in the forward and reverse directions (Scheme 1) were determined using eq 4 and a solvent isotope effect on the acid ionization constant of the protonated amines of $(K_a)_{H_2O}/(K_a)_{D_2O} = 3.36$.[27]

**Chlorine Transfer to Dimethylamine.** First-order rate constants, $k_{obsd}$ ($s^{-1}$), for the reaction of *N*-chlorotaurine with dimethylamine in the presence of different fixed concentrations of taurine at pH 5.8−7.1 (buffered by phosphate) correspond to the approach to an equilibrium mixture of *N*-chlorotaurine and *N*-chlorodimethylamine. Observed second-order rate constants, $(k_{R_2NH})_{obsd}$ ($M^{-1}$ $s^{-1}$), for the reaction in the forward direction were determined as the slopes of linear correlations of $k_{obsd}$ against $[R_2NH]_T$ (not shown) according to eq 1. The intercepts of these linear plots give $(k_r)_{obsd}$ ($s^{-1}$, eq 1) for the reverse reaction and observed second-order rate constants, $(k_{TauNH_2})_{obsd}$ ($M^{-1}$ $s^{-1}$), for chlorine transfer from *N*-chlorodimethylamine to taurine were determined as the slopes of linear plots of $(k_r)_{obsd}$ against $[TauNH_2]_T$ or as $(k_{TauNH_2})_{obsd} = (k_r)_{obsd}/[TauNH_2]_T$ (eq 2). The values of $(k_{R_2NH})_{obsd}$ increased linearly with increasing phosphate buffer concentration up to 0.2 M according to eq 5, where $(k_2)_o$ ($M^{-1}$ $s^{-1}$) is the second-order rate constant for solvent-catalyzed chlorine transfer at the pH of the experiment and $(k_3)_{buffer}$ ($M^{-2}$ $s^{-1}$) is the observed third-order rate constant for the buffer-catalyzed reaction.

$$(k_{R_2NH})_{obsd} = (k_2)_o + (k_3)_{buffer}[buffer]_T \qquad (5)$$

The buffer-independent rate constants, $(k_2)_o$, obtained by extrapolation of the observed rate constants $(k_{R_2NH})_{obsd}$ to zero buffer concentration, were found to be pH-independent within experimental error in the pH range 5.8−7.1. The increase in $(k_3)_{buffer}$ with increasing the fraction of buffer base is consistent with a general base catalysis rate law. Figure 2A shows a plot of $(k_{R_2NH})_{obsd}$ against the concentration of the

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basic form of the phosphate buffer, according to eq 6. The data obtained at different buffer ratios $[HPO_4^{2-}]/[H_2PO_4^-]$ fall on the same correlation line, which indicates that there is no significant catalysis of this reaction by the acidic form of the buffer. The slope of this plot gives the third-order rate constant for catalysis of chlorine transfer from *N*-chlorotaurine to dimethylamine by $HPO_4^{2-}$, $(k_{A^-})_{obsd} = (1.00 \pm 0.03) \times 10^{-1}\ M^{-2}\ s^{-1}$. A value of $(k_2)_o = (1.21 \pm 0.18) \times 10^{-3}\ M^{-1}\ s^{-1}$ for the pH-independent rate constant for chlorine transfer was determined as the intercept of the plot in Figure 2A.

$$(k_{R_2NH})_{obsd} = (k_2)_o + (k_{A^-})_{obsd}[A^-] \quad (6)$$

The values of $(k_{TauNH_2})_{obsd}$ for chlorine transfer in the reverse direction, determined at increasing concentrations of phosphate buffer, were plotted against the total buffer concentration. The slopes of the linear correlations observed at different fixed ratios of the buffer acid and conjugate base increased with increasing the fraction of the buffer present in the basic form. The *y*-intercepts of these plots were found to be pH-independent at pH values between 5.8 and 7.1. Figure 2B shows the dependence of $(k_{TauNH_2})_{obsd}$ on the concentration of the basic form of the phosphate buffer. The slope and intercept of this plot give $(k_{A^-})_{obsd} = (9.6 \pm 0.3) \times 10^{-3}\ M^{-2}\ s^{-1}$ and $(k_2)_o = (9.5 \pm 1.9) \times 10^{-5}\ M^{-1}\ s^{-1}$ for catalysis by $HPO_4^{2-}$ and uncatalyzed chlorine transfer from *N*-chlorodimethylamine to taurine, respectively (eq 6).

At pH 5.8−7.1, dimethylamine and taurine exist mainly as the *N*-protonated species and the fraction of amine present in the reactive neutral form is given by $f_{R_2NH} = (K_a)_{R_2NH_2^+}/[H_3O^+]$, where $(K_a)_{R_2NH_2^+}$ is the equilibrium constant for dissociation of the conjugate acid of the amine. The experimentally observed general base catalysis rate law for both the forward and reverse reactions (eq 6) is therefore consistent with catalysis by general acids of the reaction of the neutral amine with the chloramine, as shown in Scheme 2.

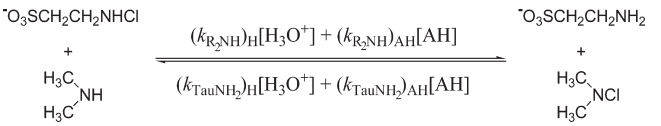
At pH $\ll (pK_a)_{R_2NH_2^+}$, eq 7, derived for the forward reaction in Scheme 2, simplifies to eq 8, where $(K_a)_{AH}$ is the acidity constant of the general acid. Comparison of eqs 6 and 8 shows that $(k_2)_o = (k_{R_2NH})_H(K_a)_{R_2NH_2^+}$, and a third-order rate constant $(k_{R_2NH})_H = (9.0 \pm 1.3) \times 10^7\ M^{-2}\ s^{-1}$ (Table 1) for catalysis by $H_3O^+$ of chlorine transfer from *N*-chlorotaurine to dimethylamine (Scheme 2) was calculated from the value of $(k_2)_o$ given above using $(K_a)_{R_2NH_2^+} = 1.35 \times 10^{-11}$ M for protonated dimethylamine. The rate constant $(k_{A^-})_{obsd} = (1.00 \pm 0.03) \times 10^{-1}\ M^{-2}\ s^{-1}$ for catalysis by $HPO_4^{2-}$ of chlorine transfer to dimethylamine, which in terms of eq 8 is equal to $(k_{R_2NH})_{AH}[(K_a)_{R_2NH_2^+}/(K_a)_{AH}]$, may be combined with $(K_a)_{R_2NH_2^+} = 1.35 \times 10^{-11}$ M and $(K_a)_{AH} = 3.55 \times 10^{-7}$ M to give $(k_{R_2NH})_{AH} = (2.63 \pm 0.08) \times 10^3\ M^{-2}\ s^{-1}$ (Table 1) as the third-order rate constant for catalysis by $H_2PO_4^-$ of chlorine transfer from *N*-chlorotaurine to dimethylamine (Scheme 2).

$$(k_{R_2NH})_{obsd} = ((k_{R_2NH})_H[H_3O^+] + (k_{R_2NH})_{AH}[AH])f_{R_2NH} \quad (7)$$

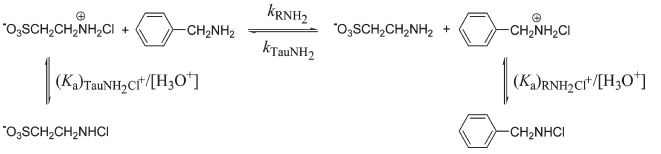
$$(k_{R_2NH})_{obsd} = (k_{R_2NH})_H(K_a)_{R_2NH_2^+} + (k_{R_2NH})_{AH}\frac{(K_a)_{R_2NH_2^+}}{(K_a)_{AH}}[A^-] \quad (8)$$

A similar treatment of the data for the reverse reaction gives $(k_{TauNH_2})_H = (1.1 \pm 0.2) \times 10^5\ M^{-2}\ s^{-1}$ and

**SCHEME 2**




**SCHEME 3**




$(k_{TauNH_2})_{AH} = (3.91 \pm 0.12)\ M^{-2}\ s^{-1}$ (Table 1) as the third-order rate constants for chlorine transfer from *N*-chlorodimethylamine to taurine catalyzed by $H_3O^+$ and $H_2PO_4^-$, respectively.

## Discussion

Chlorine transfer from *N*-chloramines to nucleophiles occurs through an acid-catalyzed reaction pathway that involves protonation of the leaving amine before or during the rate-limiting step to avoid the formation of an extremely unstable nitranion.[16] We showed previously that the transfer of a chlorine atom from *N*-chlorotaurine to iodide and less reactive nucleophiles occurs through a stepwise mechanism involving a protonated chloramine intermediate. We also provided evidence for a change to a concerted mechanism with increasing the reactivity of the nucleophile and suggested that this is enforced by the absence of a significant lifetime of *N*-protonated chlorotaurine in contact with the nucleophile. We have now examined the reaction of *N*-chlorotaurine with amines in order to determine whether there is a similar change in mechanism with increasing amine reactivity.

**Reaction Mechanisms.** The experimental data obtained in this work show that there is no detectable general acid catalysis of the reversible reaction of benzylamine with *N*-chlorotaurine. This provides evidence that protonation of the chloramine on nitrogen takes place in a rapid equilibrium step followed by rate-determining chlorine transfer to the neutral amine (Scheme 3). Additional support for this mechanism comes from the observed inverse solvent deuterium isotope effects $(k_{RNH_2})_H/(k_{RND_2})_D = (0.57 \pm 0.05)$ and $(k_{TauNH_2})_H/(k_{TauND_2})_D = (0.47 \pm 0.07)$ on the acid-catalyzed forward and reverse reactions, respectively, which are typical of preequilibrium substrate protonation mechanisms.[28] The introduction of a chlorine substituent at the nitrogen atom of taurine ($pK_a = 9.06$) to give *N*-chlorotaurine brings down its $pK_a$ by ca. 9 units.[26] *N*-Chlorotaurine is therefore weakly basic ($pK_a \approx 0$), so that it would be necessary to work in concentrated acid solutions to observe a shift in the position of the preequilibrium to the protonated chloramine species. A second-order rate constant $k_{RNH_2} = (2.13 \pm 0.13) \times 10^8\ M^{-1}\ s^{-1}$ for chlorine transfer from protonated *N*-chlorotaurine to neutral benzylamine was determined from the value of $(k_{RNH_2})_H$ and $(K_a)_{TauNH_2Cl^+} = 1.14$ M[26] using

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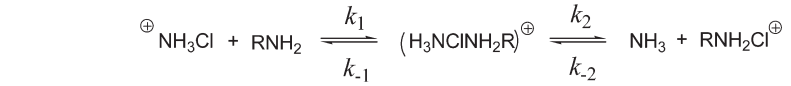
the relationship $k_{RNH_2} = (k_{RNH_2})_H (K_a)_{TauNH_2Cl^+}$ (Scheme 3, $pH \gg (pK_a)_{TauNH_2Cl^+}$). Similarly, the value of $(k_{TauNH_2})_H$ can be combined with $(K_a)_{RNH_2Cl^+} = 0.149$ M (see Experimental Section) to give $k_{TauNH_2} = (1.32 \pm 0.04) \times 10^7\ M^{-1}\ s^{-1}$ as the second-order rate constant for the reaction of taurine with protonated *N*-chlorobenzylamine in the reverse direction. The overall equilibrium constant $K_{Cl} = (16.1 \pm 1.1)$ for the reaction of protonated *N*-chlorotaurine with benzylamine to form taurine and protonated *N*-chlorobenzylamine was calculated as $K_{Cl} = k_{RNH_2}/k_{TauNH_2}$ from the values of $k_{RNH_2}$ and $k_{TauNH_2}$ reported above.

The kinetic behavior found in this work for the reaction of *N*-chlorotaurine with benzylamine is similar to that observed in earlier studies of the kinetics of chlorine transfer from $NH_2Cl$ to nitrogen nucleophiles.[13,20,21] However, Snyder and Margerum[13] suggested that the reaction between protonated chloramine and methylamine occurs through a mechanism involving the formation of a hypervalent chlorine species, as shown in Scheme 4. Their mechanistic proposal was based on an analysis of the dependence of the second-order rate constants for chlorine transfer from $NH_3Cl^+$ to nitrogen compounds on amine nitrogen basicity, which showed a limiting value of ca. $2 \times 10^8\ M^{-1}\ s^{-1}$ for compounds more basic than ammonia. The observed break in this Brønsted-type correlation was attributed to a change in rate-limiting step from nucleophilic attack of the amine at chlorine ($k_1$, Scheme 4) to N−Cl bond breaking ($k_2$, Scheme 4) with increasing amine reactivity. After extensive studies on amine nucleophilicities in aqueous solution,[29−32] it is now well-known that basicity is generally not a good measure of the nucleophilicity of amines. In fact, the three nitrogen compounds (glycine, $\beta$-alanine and methylamine) that define the observed limiting region in the Brønsted-type plot mentioned above react at similar rates with electrophiles such as 1-methyl-4-vinylpyridinium cation,[31] methyl 4-nitrobenzenesulfonate,[30] and benzhydrylium ions[29,33] despite their different basicities. Therefore, the kinetic data reported by Snyder and Margerum are consistent with the expected similar reactivity of these nucleophiles and there is no experimental evidence to support the existence of the intermediate shown in Scheme 4. We propose that chlorine transfer from the protonated chloramine to the amine takes place in a single step involving both breaking of the bond to the leaving group and formation of a bond to the incoming amine in the transition state.

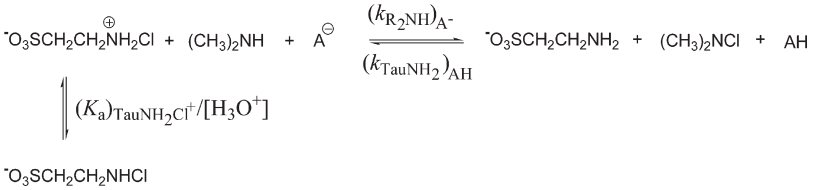
We have shown that $H_2PO_4^-$ is an effective catalyst of the reversible reaction of *N*-chlorotaurine with dimethylamine in both directions. This is consistent with either of the kinetically equivalent mechanisms shown in Schemes 5 and 6. The mechanism of Scheme 5 involves protonation of *N*-chlorotaurine in a preequilibrium step, followed by slow chlorine transfer assisted by removal of a proton from the attacking amine by a general base. This corresponds to true general acid catalysis of the reaction of *N*-chlorodimethylamine with taurine in the reverse direction. The mechanism of Scheme 6 involves proton donation from a general acid to the nitrogen atom of *N*-chlorotaurine in the forward direction and proton removal from the nitrogen atom of taurine by the conjugate general base in the reverse direction. A choice between these two mechanisms may be made from a comparison of the relative stabilities of the two *N*-protonated chloramines in the presence of the incoming nucleophilic amine. The reaction pathway shown in Scheme 5 avoids the formation of the complex $(CH_3)_2NHCl^+ \cdot NH_2(CH_2)_2SO_3^-$, whereas that in Scheme 6 avoids the formation of the kinetically and thermodynamically more unstable $^-O_3S(CH_2)_2NH_2Cl^+ \cdot NH(CH_3)_2$ complex. Since the latter species is more reactive than the former, it is more likely to be avoided in a concerted mechanism, and it seems therefore reasonable to conclude that the reaction of *N*-chlorotaurine with dimethylamine follows the mechanism shown in Scheme 6.

Scheme 6 shows that the observed acid-catalyzed forward reaction corresponds to "true" general acid catalysis of chlorine transfer from *N*-chlorotaurine to dimethylamine, and third-order rate constants $(k_{R_2NH})_H$ and $(k_{R_2NH})_{AH}$ for catalysis by $H_3O^+$ and $H_2PO_4^-$, respectively, were determined above (see Results). The acid-catalyzed reverse reaction corresponds to preequilibrium protonation of *N*-chlorodimethylamine followed by catalysis by general bases of chlorine transfer from this protonated chloramine to taurine. Rate constants $(k_{TauNH_2})_o = (2.2 \pm 0.4) \times 10^4\ M^{-1}\ s^{-1}$

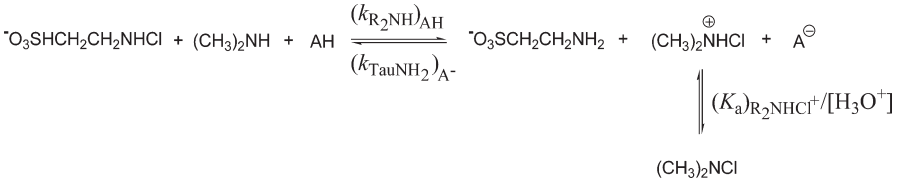
**SCHEME 4**




**SCHEME 5**




**SCHEME 6**



and $(k_{TauNH_2})_{A^-} = (2.20 \pm 0.07) \times 10^6\ M^{-2}\ s^{-1}$ for catalysis by $H_2O$ and $HPO_4^{2-}$, respectively, can be calculated from $(K_a)_{(CH_3)_2NHCl^+} = 0.2$ M[34] and $(K_a)_{AH} = 3.55 \times 10^{-7}$ M using the relationships $(k_{TauNH_2})_o = (k_{TauNH_2})_H\,(K_a)_{(CH_3)_2NHCl^+}$ and $(k_{TauNH_2})_{A^-} = (k_{TauNH_2})_{AH}\,((K_a)_{(CH_3)_2NHCl^+}/(K_a)_{AH})$ derived for Scheme 6.

We have previously suggested that the acid-catalyzed reaction of *N*-chlorotaurine with the highly reactive sulfur nucleophiles $HOCH_2CH_2S^-$ and $SO_3^{2-}$ follows a concerted mechanism, which is enforced by the absence of a significant lifetime of the protonated chloramine in the presence of the nucleophile.[16] The $N_+$ and $n$ nucleophilicity scales, predict that dimethylamine ($N_+ = 7.95$,[31] $n = 5.83$[30]) will show a reactivity toward electrophiles similar to that of $SO_3^{2-}$ ($N_+ = 8.01$,[35] $n = 5.67$[36]). It is therefore likely that the barrier for collapse of an encounter complex between *N*-protonated chlorotaurine and dimethylamine is insignificant, which forces chlorine transfer to occur through a mechanism in which proton transfer to the nitrogen atom of the chloramine and chlorine transfer merge into a single step.

**Intrinsic Barriers.** The reversibility of the reaction between *N*-chlorotaurine and benzylamine allowed the determination of the corresponding rate and equilibrium constants for this process. This set of data may now be analyzed in the context of Marcus theory,[37,38] which provides a relationship (eq 9) between the activation barrier, $\Delta G^{\ddagger}$, and the thermodynamic driving force for a reaction, $\Delta G°$, in terms of what is commonly called the intrinsic activation barrier, $\Delta G_0^{\ddagger}$, defined as the kinetic barrier for the hypothetical thermoneutral process ($\Delta G° = 0$). The Marcus eq 9 applies to the chemical step of the reaction and, therefore, the observed activation and thermodynamic barriers, $(\Delta G^{\ddagger})_{obsd}$ and $(\Delta G°)_{obsd}$, should be corrected for the free energy changes associated to formation of a reactive complex ($w_r$) and separation of the product complex to give free products ($w_p$) according to eqs 10 and 11.

$$\Delta G^{\ddagger} = \Delta G_0^{\ddagger}\left(1 + \frac{\Delta G^0}{4\Delta G_0^{\ddagger}}\right)^2 \quad (9)$$

$$\Delta G^{\ddagger} = (\Delta G^{\ddagger})_{obsd} - w_r \quad (10)$$

$$\Delta G^0 = (\Delta G^0)_{obsd} - w_r + w_p \quad (11)$$

It is generally difficult to identify the different processes involved in forming a reactive complex and to estimate their energetic contributions to the observed reaction barrier. For this reason, in most of the cases where the Marcus formalism has been applied to organic reactions the work terms have been neglected. An apparent intrinsic barrier of $\Delta G_0^{\ddagger} = 6.9$ kcal/mol for chlorine transfer can be determined by substituting the observed values of $(\Delta G^{\ddagger})_{obsd} = 6.1$ kcal/mol and $(\Delta G°)_{obsd} = -1.7$ kcal/mol for the reaction of *N*-protonated chlorotaurine with benzylamine (Scheme 3) into eq 9, using the assumption that the observed activation barrier corresponds entirely to the chemical transformation of the reactants to the transition state ($w_r = w_p = 0$). However, a better estimate of the chemical intrinsic barrier may be obtained if we are able to evaluate the significance of the work terms for this reaction.

The reactant and product pairs are strikingly similar, and it is reasonable to assume that there is not a significant difference in the work terms for formation of the reactant and product complexes ($w_r = w_p$). The work term $w_r$ should include the entropic cost of bringing the two reactants together, the cost of the partial desolvation required to create a complex in which the chlorine atom of the chloramine and the nitrogen of the amine are in contact with the correct orientation for the transfer of chlorine to take place, and possible interactions between the two species in the encounter complex. The free energy change involved in the approach of the two reactants to form a complex may be estimated following the work of Hine[39] as 2.8 kcal/mol, assuming that there is only one possible position for the nucleophilic nitrogen atom in the complex and that there are no interactions between the two reactants. There is evidence in the literature that complete desolvation of amines, to free the lone electron pair, must occur before nucleophilic attack takes place.[40−42] Berg and Jencks have provided estimates of the equilibrium constants for dissociation of amine−water complexes and have shown that desolvation becomes less favorable as the amine becomes more basic.[43] Interpolation of their data to a $pK_a = 9.5$ gives an energetic cost for breaking the hydrogen bond between water and benzylamine of 1.8 kcal/mol. Finally, it is necessary to consider the existence of stabilizing interactions between the amine and the protonated chloramine within the precursor complex. It is well-known that halogenated organic molecules form weak complexes with electron donor species, in which the halogen atom acts as an electron acceptor site.[44−46] This type of intermolecular interaction has been named halogen bonding to stress that many of its properties parallel those of the analogous hydrogen bonds. It is difficult to quantify the strength of an interaction between the nucleophilic nitrogen of the amine and the electrophilic chlorine atom of the protonated chloramine in the reactive complex. However, the stabilizing energy associated with formation of a chlorine bond has been estimated to be not much different from that involved in formation of a similar hydrogen bond.[47−49]

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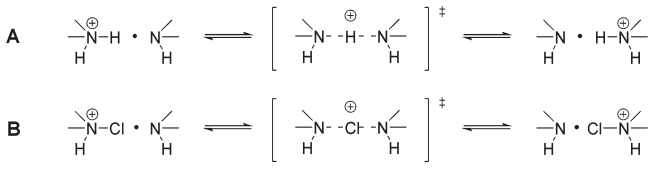
**SCHEME 7**



Therefore, the energetic cost of breaking the hydrogen bond to a water molecule in the solvated amine is expected to be compensated for, to a large extent, by the stabilization energy associated to formation of a halogen bond to the protonated chloramine. If this is so, the value of $w_r$ should be close to the 2.8 kcal/mol needed to bring the reactants together, giving $\Delta G_0^{\ddagger} = 4.1$ kcal/mol as the intrinsic barrier for the chemical step.

Literature reports on the calculation of intrinsic barriers for organic reactions are scarce,[50−54] and to the best of our knowledge there have been no previous determinations of these barriers for chlorine transfer. Our results show that chlorine transfer between amines is intrinsically slower than the apparently similar *direct* transfer of a proton between nitrogen atoms, for which an intrinsic barrier of 1 kcal/mol was estimated.[24] Proton transfer between nitrogen atoms along a preformed hydrogen bond is a very fast process because it occurs through a symmetrical transition state in which hydrogen is involved in a stable three-centered interaction with the electronegative atoms (Scheme 7A). There is strong experimental evidence for the formation of stable bis(amine)−iodine and bromine complexes.[55−57] However, to the best of our knowledge, similar stable hypervalent chlorine compounds have not been described. The intrinsic barrier of ca. 4 kcal/mol determined here for chlorine transfer between amines provides evidence that the hypervalent chlorine species (Scheme 7B) is ca. 4 kcal/mol higher in energy than the pre-reactive protonated chloramine−amine complexes.

It has been shown that bromine transfer between carbanions is faster than the corresponding proton transfer between the same species.[25] This reactivity order was tentatively attributed to the fact that bromine can expand its valence shell better than hydrogen. The increasing ability of halogens to expand the valence shell on going from fluorine to iodine provides a successful explanation for the observed reactivity order of hypohalous acids[58] (HOI > HOBr > HOCl) and *N*-halosuccinimides[59,60] (NBS > NCS) with nucleophiles. These reactivity trends are consistent with an easier transfer of bromine than of chlorine between the same nucleophilic centers, and therefore we expect the intrinsic barriers to chlorine transfer between carbanions to be larger than the 10.9 and 16.3 kcal/mol reported for the analogous bromine transfer between cyano- and nitro-activated carbanions, respectively.[25]

A comparison of the intrinsic barrier reported here for chlorine transfer between amines with that expected for the corresponding transfer between carbanions shows that the reaction at carbon is intrinsically slower than that between nitrogen atoms, and therefore, halogen transfer reactions seem to share this exceptional feature with proton transfer reactions. Moreover, it has been shown that the nitro anomaly, typical of proton transfer reactions, is also a peculiarity of halogen transfer.[25,61] The anomalous behavior of carbanions in protonation and halogenation reactions contrasts with their behavior in nitrosation reactions, in which they have been found to react at rates similar to those of secondary amines of similar basicity.[62] Furthermore, the difference in reactivity between nitronate and enolate ions of similar p$K_a$ toward the NO group is abnormally low compared to that observed in other chemical reactions. This nonanomalous behavior of carbanions in nitrosation reactions was attributed to the high intrinsic barriers to NO transfer, with bond formation and cleavage providing the dominant energetic contribution to these barriers. This raises the question of whether the observed similarities between proton and halogen transfer reactions are due to bonding changes making only a minor contribution to the intrinsic barriers for halogen transfer as it is believed to occur for proton transfer reactions.

Kresge explored the possibility that delocalization of the lone pair on nitrogen would make protonation of this atom slow and found that the extensive delocalization of the nitrogen electron pair in an amide does not cause a big decrease in the rate of protonation.[63] The apparent intrinsic barrier for the reversible transfer of a chlorine atom from *N*-chlorosuccinimide to dimethylamine, $\Delta G_0^{\ddagger} = 7.6$ kcal/mol, estimated from reported rate and equilibrium data on this reaction,[64] is similar to the apparent intrinsic barrier $\Delta G_0^{\ddagger} = 6.9$ kcal/mol reported here for chlorine transfer between amines. It seems therefore that as has been shown to occur for proton transfer, delocalization of charge into the carbonyl groups of succinimide does not lead to a significant increase in the intrinsic barrier for chlorine transfer.

To summarize, halogen transfer reactions seem to share some of the unique features of proton transfer: (1) There is only a small intrinsic barrier to chlorine transfer between amines in aqueous solution, and we would expect this barrier to be lower for the analogous bromine transfer reaction. (2) Intrinsic barriers for halogen transfer at carbon are larger than for the corresponding transfer between electronegative atoms. (3) The well-known nitro anomaly is also present in halogen transfer reactions.

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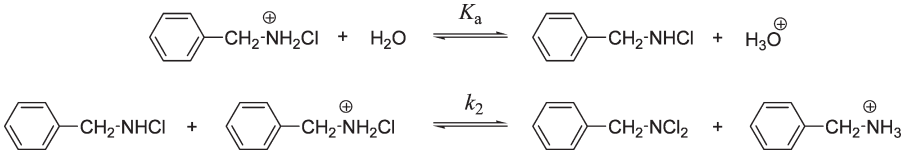
**SCHEME 8**



## Experimental Section

**Materials.** The sodium salt of *N*-chlorotaurine 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.

**General Methods.** Phosphate buffers were prepared by mixing stock solutions of $NaH_2PO_4$ and $Na_2HPO_4$ in $H_2O$ at $I = 0.5$ ($NaClO_4$) to give the desired acid/base ratio. Solution pH was maintained by use of 0.03−0.15 M phosphate buffer (pH 5.8−7.1). Measurements of pH at 25 °C were obtained using a radiometer PHM82 pH-meter equipped with a GK3401C combined glass electrode. Values of pD were calculated by adding 0.4 to the observed reading of the pH meter. An apparent p$K_a$ of p$K_{BH}$ = 9.48 ± 0.04 for benzylamine in $H_2O$ at 25 °C and $I = 0.5$ ($NaClO_4$) was determined by potentiometric titration of a 10 mM solution of the amine with $HClO_4$.

**Kinetic Studies.** All kinetic studies were carried out in $H_2O$ at 25 °C with the ionic strength maintained at $I = 0.5$ ($NaClO_4$). Kinetic experiments always employed at least a 10-fold molar excess of both taurine and amine over *N*-chlorotaurine to ensure pseudo-first-order conditions for both the forward and the reverse reactions. Reactions were initiated by making a 100-fold dilution of an aqueous solution of chloramine into the reaction mixture to give a final substrate concentration of 0.3−3 mM. The chlorine transfer from *N*-chlorotaurine to amines was followed by conventional UV spectrometry by monitoring the change in absorbance at the following wavelengths: benzylamine, 230 nm; dimethylamine, 280 nm. Observed first-order rate constants, $k_{obsd}$ ($s^{-1}$), were determined from the fit of the absorbance−time data to a single exponential function and were reproducible to ± 5%.

**p$K_a$ of Protonated *N*-Chlorobenzylamine.** The p$K_a$ of the conjugate acid of *N*-chlorobenzylamine at 25 °C and $I = 0.5$ ($NaClO_4$) was determined from a kinetic study of the disproportionation of this *N*-chloramine carried out following procedures described previously.[26] A 5 mM solution of *N*-chlorobenzylamine was prepared by adding the appropriate amount of 0.027 M NaOCl to a 7.5 mM solution of the amine at pH 8−9. The kinetics of disproportionation of *N*-chlorobenzylamine to give *N*,*N*-dichlorobenzylamine were initiated by adding a volume of the basic solution of *N*-chloro compound to a solution of perchloric acid (0.01−0.5 M) to give a reaction mixture containing 0.3 mM substrate. The reactions were monitored by following the increase in absorbance at 245 nm using a conventional UV spectrophotometer. Second-order rate constants, $(k_2)_{obsd}$ ($M^{-1}$ $s^{-1}$), were calculated from the nonlinear least-squares fit of the data to the integrated second-order rate equation, eq 12.

$$A = A_\infty - \frac{(A_\infty - A_0)}{1 + 2[\mathrm{BzNHCl}]_0(k_2)_{obsd}t} \qquad (12)$$

Figure S1 of Supporting Information shows the dependence of $(k_2)_{obsd}$ for the disproportionation of *N*-chlorobenzylamine in water at 25 °C and $I = 0.5$ ($NaClO_4$) on the concentration of hydronium ion. The observed nonlinear dependence is consistent with the mechanism proposed in previous work for the disproportionation of *N*-chlorotaurine (Scheme 8), which involves the transfer of a chlorine atom from a protonated to a neutral chloramine molecule to form the dichloramine.

The solid line in Figure S1 shows the nonlinear least-squares fit of the experimental data to eq 13, derived for Scheme 8, which gave $k_2 = 47.8 \pm 0.5$ $M^{-1}$ $s^{-1}$ for the second-order rate constant for disproportionation of *N*-chlorobenzylamine and $K_a = 0.149 \pm 0.004$ M for the acidity constant of the conjugate acid of this chloramine.

$$(k_2)_{obsd} = \frac{k_2K_a[H_3O^+]}{(K_a + [H_3O^+])^2} \qquad (13)$$

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**Supporting Information Available:** Table S1 of the observed second-order rate constants for the reversible reaction of *N*-chlorotaurine with benzylamine in aqueous solution at pH 5.8−7.1 (buffered by phosphate) at 25 °C and $I = 0.5$ ($NaClO_4$). Figure S1 showing the dependence of the observed second-order rate constants $(k_2)_{obsd}$ for disproportionation of *N*-chlorobenzylamine on the concentration of hydronium ion. This material is available free of charge via the Internet at http://pubs.acs.org.