Acid-catalysed chlorine transfer from *N*-chloramines to iodide ion: experimental evidence for a predicted change in mechanism†

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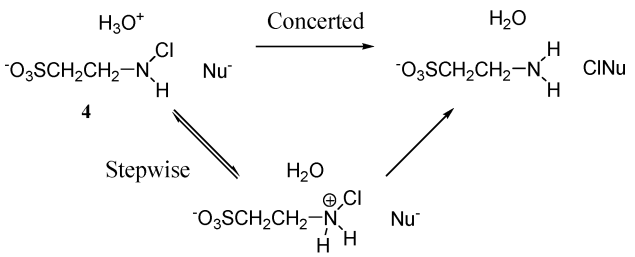
Rate constants for acid catalysis of the reactions of *N*-chlorodimethylamine (**1**), *N*-chloro-2,2,2-trifluoroethylamine (**2**) and *N*,*N*-dichlorotaurine (**3**) with iodide ion were determined in H_2O at 25 °C and $I = 0.5$ ($NaClO_4$). The failure to detect significant catalysis by general acids of chlorine transfer from **1** to the nucleophile, together with the observed inverse solvent deuterium isotope effect on the hydronium ion-catalysed reaction ($k_H/k_D = 0.37$), indicates that this process occurs by protonation of **1** in a fast equilibrium step, followed by rate determining chlorine transfer to iodide ion. The appearance of general acid catalysis for the reactions of **2** and **3** shows that increasing the leaving group ability leads to a change to a concerted mechanism, which is suggested to be enforced by the absence of a significant lifetime of the protonated chloramine intermediate in the presence of iodide ion.

Introduction

The amino groups in amino acids and in protein side chains are believed to be potential targets for electrophilic halogenating compounds generated as microbiocidal agents at the active site of heme-dependent peroxidases present in phagocytic cells.[1–3] The *N*-haloamines formed as a result of these reactions retain a significant oxidizing activity, being able to transfer the halogen to a wide range of nucleophilic groups present in biological systems. A lysine chloramine intermediate has also been postulated as the chlorinating agent in the formation of 7-chlorotryptophan catalysed by a flavin-dependent halogenase.[4,5] The important role played by chloramines in the human immune defense system,[6] together with their proposed involvement as intermediates in biological pathways to chlorinated molecules,[7] shows the need for a detailed understanding of their chemical reactivity, which is the basis for their biological activity.

The chemistry of *N*-chloramines in aqueous solution has been explored extensively,[8] but comprehensive mechanistic studies of their chlorine transfer reactions are scarce. It has been shown, mainly through the work of Margerum *et al.*,[9–11] that chlorine transfer from chloramines to electron rich substrates is subject to acid catalysis, and this reflects the fact that protonation at nitrogen before or during the rate determining step is required to avoid the formation of an unstable amine anion. However, there is currently no clear understanding of the mechanism, stepwise or concerted, by which assistance to leaving group departure occurs in each case and the conditions that determine a change from one mechanism to the other.

We are interested in characterizing the mechanisms of chlorine transfer from *N*-chloramines to nucleophilic reagents[12–14] and have recently reported that the acid-catalyzed reaction of *N*-chlorotaurine (**4**) with iodide ion and less reactive nucleophiles proceeds by a stepwise mechanism, with proton transfer to the leaving nitrogen atom taking place in an initial equilibrium step (Scheme 1).[13] However, chlorination of highly reactive nucleophiles, such as the anion of 2-mercaptoethanol, undergoes a concerted mechanism of general acid catalysis. This shows that increasing the reactivity of the nucleophile results in a change from a two step mechanism, that proceeds through a *N*-protonated chloramine intermediate, to a concerted mechanism involving protonation of the chloramine at nitrogen and chlorine transfer in a single step (Scheme 1). The observed change in mechanism appears to be enforced by the lack of a significant lifetime for the intermediate in the presence of very reactive nucleophilic species.



Scheme 1

We suggest here that it should be possible to find experimental evidence for a similar change in mechanism for chlorine transfer to iodide ion on moving from the chloramines of basic amines to less stable chloramines bearing electron-withdrawing substituents. This is because a decrease in the basicity of the leaving amine will result in an increasing destabilisation of the protonated chloramine, which should favour reaction through a concerted mechanism that avoids its formation. In earlier studies of this reaction, the observation of weak buffer catalysis for chloramines with poor amine leaving groups led to the conclusion that simultaneous chlorine and proton transfer occur in the rate determining step.[10,15,16] In contrast to these results, we were unable to detect general acid catalysis of the reaction of **4** with iodide ion.[13]

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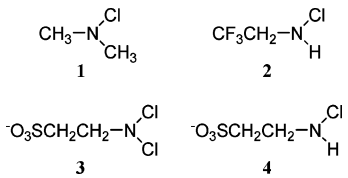
† Electronic supplementary information (ESI) available: Tables S1–S3: Second-order rate constants for chlorine transfer from the *N*-chloramines **1**, **2** and **3** to iodide ion in the presence of buffer solutions in H_2O. See DOI: 10.1039/c004976j

We describe here a study of chlorine transfer to iodide ion from *N*-chlorodimethylamine (**1**), *N*-chloro-2,2,2-trifluoroethylamine (**2**) and *N*,*N*-dichlorotaurine (**3**) (Scheme 2) in H_2O at 25 °C and I = 0.5 ($NaClO_4$). These experiments were carried out for the purpose of examining possible changes in mechanism brought about by changes in leaving group ability.



Scheme 2

Results and discussion

Observed second-order rate constants, $(k_2)_{obsd}$ (M^{-1} s^{-1}), for the reaction of I^- with **1**, **2** and **3**, in aqueous perchloric acid solutions or in the presence of buffers at 25 °C and I = 0.5 ($NaClO_4$), were determined as the slopes of linear plots of k_{obsd} (s^{-1}) against the concentration of iodide ion (not shown) or as $(k_2)_{obsd} = k_{obsd}/[I^-]$. Table S1 of the ESI† shows the dependence of $(k_2)_{obsd}$ for chlorine transfer from **1** to iodide ion on the concentration of acetate (pH = 4.5 or 5.1), phosphate (pH = 5.5 or 6.5) or borate (pH = 8.3) buffers. No general acid catalysis of this reaction was observed in 0.02–0.2 M acetate and 0.01–0.1 M phosphate or borate buffers. Small changes in the observed rate constants with increasing the buffer concentration were accounted for by parallel small changes in solution pH. The second-order rate constants $(k_2)_{obsd}$ (M^{-1} s^{-1}) are therefore equal to the rate constants $(k_2)_o$ for catalysis of this reaction by solvent species only. Fig. 1 (●) shows the pH-rate profile of $(k_2)_o$ for the reaction of iodide ion with **1**, where $(k_2)_o = k_H[H_3O^+]$ and k_H (M^{-2} s^{-1}) is the third-order rate constant for the chlorine transfer reaction catalysed by hydronium ion. The solid line shows the fit of the data to eqn (1) (L = H), which gives k_H = (2.69 ± 0.08) × 10^{10} M^{-2} s^{-1} for the acid-catalysed reaction of I^- with **1** (Table 1). This value agrees, to within 24%, with a value reported in earlier work.[16]

$$\log(k_2)_o = \log k_L - pL \quad (1)$$

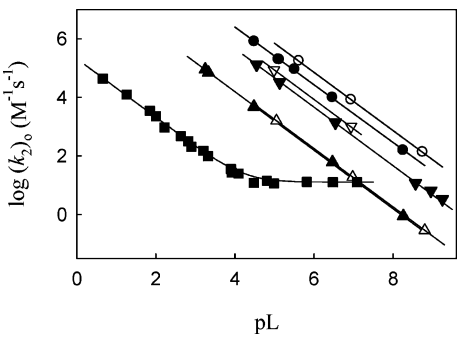


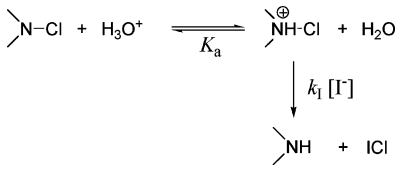
Fig. 1 pL-rate profiles of $(k_2)_o$ (M^{-1} s^{-1}) for the reaction of iodide ion with *N*-chloramines at 25 °C and I = 0.5 ($NaClO_4$). The solid symbols show data for **1** (●), **2** (▲), **3** (■) and **4** (▼, data from ref. 13) in H_2O. The open symbols show data for **1** (○), **2** (△) and **4** (▽, data from ref. 13) in D_2O. The solid lines through the data show the fits to eqn (1) for **1**, **2** and **4**, and to eqn (4) for **3** (see text).

Table 1 Third-order rate constants for the acid-catalyzed reaction of iodide ion with the *N*-chloramines **1–4** in water[a]

Acid catalyst	pK_a[b]	Chloramine	k_H or k_{AH}/M^{-2} s^{-1}	
H_3O^+	–1.7	**1**	(2.69 ± 0.08) × 10^{10}	
			(7.24 ± 0.12) × 10^{10}	(D_2O)
		2	(1.52 ± 0.07) × 10^8	
			(1.795 ± 0.013) × 10^8	(D_2O)
		3	(2.05 ± 0.10) × 10^5	
		4	(4.6 ± 0.1) × 10^9 [c]	
			(8.5 ± 0.2) × 10^9 [c]	(D_2O)
$Cl_2CHCOOH$	1.1	**3**	(5.32 ± 0.13) × 10^4	
$ClCH_2COOH$	2.6	**3**	(3.54 ± 0.05) × 10^3	
CH_3OCH_2COOH	3.4	**3**	(1.79 ± 0.04) × 10^3	
CH_3COOH	4.6	**3**	(3.58 ± 0.04) × 10^2	
$H_2PO_4^-$	6.5	**2**	(3.8 ± 0.2) × 10^2	
		3	(1.21 ± 0.02) × 10^2	
H_2O	15.7	**3**	(2.27 ± 0.14) × 10^{-1}	

[a] At 25 °C and I = 0.5 ($NaClO_4$). [b] Apparent pK_a of the acid catalyst in H_2O at 25 °C. [c] Data from ref. 13

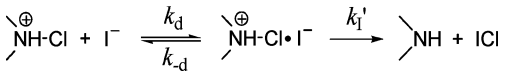
Fig. 1 (○) also shows the pD-rate profile for the reaction of iodide ion with **1** in D_2O at 25 °C and I = 0.5 ($NaClO_4$). The solid line through the data shows the fit to eqn (1) (L = D), which gives k_D = (7.24 ± 0.12) × 10^{10} M^{-2} s^{-1} for the acid-catalysed reaction of I^- with **1** in D_2O (Table 1). Combination of the two rate constants gives a solvent deuterium isotope effect on the hydronium ion-catalysed reaction of k_H/k_D = (0.37 ± 0.01). The absence of detectable catalysis by general acids, together with the inverse nature of this isotope effect, indicates that chlorine transfer to iodide ion occurs through a mechanism involving pre-equilibrium protonation of **1** followed by the reaction of the protonated chloramine with the nucleophile (Scheme 3). The observed isotope effect is the consequence of a large inverse solvent isotope effect on the pre-equilibrium combined with a small isotope effect on the rate determining chlorine transfer.[17] A second-order rate constant, k_I = 5.4 × 10^9 M^{-1} s^{-1}, for the reaction of I^- with protonated *N*-chlorodimethylamine (**1-H**) was determined from the relationship $k_H = k_I/K_a$, derived for Scheme 3, using the observed value of k_H and K_a = 0.2 M[18,19] for ionization of **1-H**.



Scheme 3

We have recently reported that the reaction of *N*-chlorotaurine (**4**) with iodide ion proceeds by a stepwise mechanism through a *N*-protonated chloramine intermediate (**4-H**) (Scheme 3), which is consistent with the inverse solvent deuterium isotope effect k_H/k_D = 0.54 observed for this reaction.[13] Catalysis by H_3O^+ of chlorine transfer from **4** to iodide ion must correspond to specific acid catalysis because proton transfer from the catalyst to the chloramine nitrogen atom is thermodynamically favourable.[20,21] A change in the leaving group from taurine to the more basic dimethylamine results in a larger stability of the protonated chloramine that will favour the reaction through a stepwise mechanism. We suggest that the reaction of iodide ion with

chloramines of amines more basic than taurine must involve specific acid catalysis, because the pK_a of the protonated chloramine intermediate is larger than pK_a = –1.7 for H_3O^+. The experimental data reported here for *N*-chlorodimethylamine are consistent with this conclusion. The reactions of **1-H** and **4-H** with I^- are diffusion limited, with $k_I \approx 5 \times 10^9$ M^{-1} s^{-1}. An estimate of the rate constant for the reaction of protonated chlorodimethylamine with iodide ion in an encounter complex, k_I', can be made from an association constant $K_{ass} \leq 1$ M^{-1} for formation of the ion pair,[22] which gives $k_{-d} \geq 5 \times 10^9$ s^{-1} and, therefore, $k_I' \geq 10^{11}$ s^{-1} for the reaction to be diffusion limited (Scheme 4). This suggests that decreasing the basicity of the leaving amine could make this rate constant larger than 10^{13} s^{-1} for a bond vibration. In this situation, the ion pair has no lifetime and the reaction must proceed through a pre-association concerted mechanism.[23] We predict a change in mechanism from stepwise to concerted on going from *N*-chlorotaurine to chloramines with less basic leaving groups.

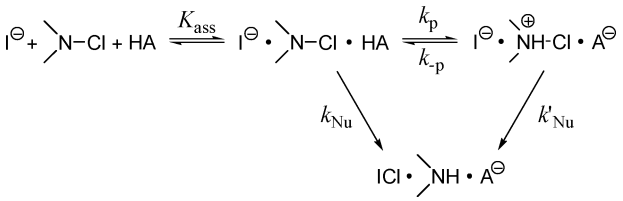


Scheme 4

Table S2 of the ESI† gives values of $(k_2)_{obsd}$ (M^{-1} s^{-1}) for chlorine transfer from **2** to iodide ion in the presence of chloroacetate (pH 3.2), methoxyacetate (pH 3.3), acetate (pH 4.5), phosphate (pH 6.5) and borate (pH 8.3) buffers at 25 °C and $I = 0.5$ ($NaClO_4$). The values of $(k_2)_{obsd}$ for the reaction in the presence of 0.01 M buffer are essentially equal to the rate constants $(k_2)_o$ for the reaction catalysed by solvent species only, because there is no significant general acid catalysis of chlorine transfer at this low buffer concentration ($(k_2)_o \gg k_{HA}$[HA], eqn (2)). Fig. 1 (▲) shows that $(k_2)_o$ increases with increasing $[H_3O^+]$ due to the acid-catalysed nature of the chlorine transfer reaction. A value of $k_H = (1.52 \pm 0.07) \times 10^8$ M^{-2} s^{-1} for the acid-catalysed reaction of iodide ion with **2** was calculated from the fit of the data to eqn (1) (L = H), which is shown as a solid line through the data in Fig. 1. Similarly, a value of $k_D = (1.795 \pm 0.013) \times 10^8$ M^{-2} s^{-1} for this acid-catalysed reaction in D_2O was determined from the fit of the data in this solvent (Fig. 1, △) to eqn (1) (L = D).

$$(k_2)_{obsd} = (k_2)_o + k_{HA}[HA] \quad (2)$$

The acidity constant of protonated **2** is not known, but there is good evidence that the introduction of a chlorine atom at the nitrogen of an amine lowers its pK_a by *ca.* 9–10 units.[24] A combination of the observed rate constant $k_H = 1.52 \times 10^8$ M^{-2} s^{-1} for the hydronium ion-catalysed reaction of **2** with an estimated pK_a of –3 for **2-H**[25] leads to $k_I \approx 10^{11}$ M^{-1} s^{-1} for chlorine transfer from **2-H** to iodide ion (Scheme 3), which is an order of magnitude above the experimentally observed value of 5×10^9 M^{-1} s^{-1} for the encounter-limited reactions of **1-H** and **4-H** with this nucleophile. This shows that **2-H** is not involved as a free solvent-equilibrated intermediate in the acid-catalysed reaction of this chloramine and it suggests that the reaction is forced to proceed through a mechanism involving an initial association of the reactants and catalyst into a ternary encounter complex (K_{ass}, Scheme 5). This pre-association mechanism may be stepwise (through k_p and k'_{Nu}) or concerted (through k_{Nu}) depending on the lifetime of the triple ion complex [$I^- \cdot \rangle NHCl^+ \cdot A^-$].[21,23]



Scheme 5

Table S2 of the ESI† gives the dependence of $(k_2)_{obsd}$ for the reaction of **2** with iodide ion on the concentration of buffers. An increase in the total concentration of buffer from 0.01 to 0.1 M results in small changes in solution pH (ΔpH ≤ 0.08) which complicate the detection of weak general acid catalysis. After correction of the observed rate constants for these changes in pH, small catalytic effects of up to 9% over the background hydronium ion-catalysed reaction were found in the presence of substituted acetic acids in the concentration range 0.01–0.1 M. The observed rate enhancements were too small to obtain reliable values of the catalytic rate constants, k_{HA} (M^{-2} s^{-1}), for these acids. A somewhat larger effect was observed for the weaker catalyst, phosphate monoanion (*ca.* 40% in 0.01–0.1 M buffers, 50% acid). Fig. 2 (●) shows a plot of the normalised rate constant $k_{rel} = (k_2)_{obsd}/k_H[H_3O^+]$ for the reaction of **2** with iodide ion against $[H_2PO_4^-]/[H_3O^+]$ according to eqn (3). A value of $k_{HA} = (3.8 \pm 0.2) \times 10^2$ M^{-2} s^{-1} for general acid catalysis of this reaction by phosphate monoanion was determined from the slope of this plot and the value of k_H given in Table 1.

$$k_{rel} = \frac{(k_2)_{obsd}}{k_H[H_3O^+]} = 1 + \frac{k_{HA}}{k_H}\frac{[HA]}{[H_3O^+]} \quad (3)$$

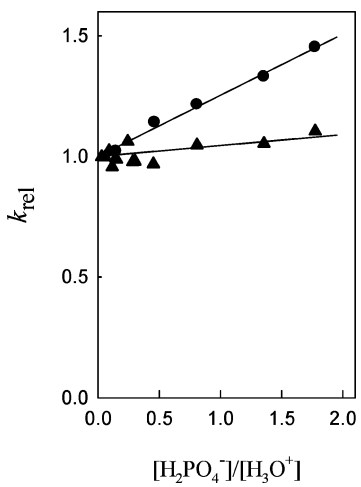


Fig. 2 Dependence of the normalised rate constant $k_{rel} = (k_2)_{obsd}/k_H[H_3O^+]$ for chlorine transfer to iodide ion on $[H_2PO_4^-]/[H_3O^+]$ in phosphate buffers at 25 °C and $I = 0.5$ ($NaClO_4$). (▲) Reaction of **1** at pH 5.6–6.5. (●) Reaction of **2** at pH 6.5.

The lack of significant general acid catalysis of chlorine transfer from **1** to iodide ion (see data for phosphate monoanion in Fig. 2, ▲) is consistent with a stepwise pathway through the protonated intermediate **1-H** (Scheme 3). The detection of weak general acid catalysis for the reaction of **2** provides evidence for a change to a mechanism in which proton transfer occurs in the

rate determining step. These results show that the acid-catalysed transfer of chlorine from **2** to iodide ion proceeds through either a stepwise pre-association mechanism, with protonation at nitrogen (k_p, Scheme 5) rate limiting, or a concerted mechanism (k_{Nu}, Scheme 5). The observed weak catalytic effect suggests that proton transfer is well advanced in the transition state. A lower limit of the Brønsted coefficient $\alpha \geq 0.72$ was calculated as the slope of a Brønsted line through the statistically corrected data for H_3O^+ and $H_2PO_4^-$. However, the nitrogen atom of the chloramine is likely to take on a partial positive charge in the transition state. This would result in significant electrostatic interactions between the developing positive charge at nitrogen and the charges on these catalysts in the transition state, leading to a negative deviation of k_H and a positive deviation of $k_{H_2PO_4^-}$ from the Brønsted correlation for protonation of the chloramine by neutral acids. Therefore, the α value for neutral catalysts may be significantly larger than the estimated value of 0.72.

Additional evidence for a change in mechanism comes from the observed increase in solvent deuterium isotope effect from $k_H/k_D = 0.37$ and 0.54 for the reactions of **1** and **4**, respectively, to $k_H/k_D = (0.85 \pm 0.04)$ for the reaction of **2**. The latter is larger than the isotope effect in the range 0.3–0.5 that would be expected if protonation of the substrate occurs in a fast equilibrium preceding the rate determining step.[26,27] The value of $k_H/k_D = 0.85$ is in accord with a mechanism involving rate determining proton transfer from the hydronium ion to the nitrogen atom of the chloramine. The inverse nature of this isotope effect comes from the combination of a weak primary isotope effect in the normal direction for a product-like transition state with a large inverse secondary component due to the tightening of the two non-reacting bonds in L_3O^+ on moving to a late transition state.[17]

Table S3 in the ESI† shows that the second-order rate constants, $(k_2)_{obsd}$ (M^{-1} s^{-1}), for the reaction of iodide ion with **3** increase with increasing the concentration of substituted acetate or phosphate buffers in the range 0.04–0.4 M and 0.02–0.15 M, respectively. Fig. 1 (■) gives the dependence on pH of the second-order rate constants for the solvent-catalysed reaction, $(k_2)_o$ ($M^{-1}s^{-1}$), obtained as the intercepts of linear plots of $(k_2)_{obsd}$ ($M^{-1}s^{-1}$) against the total buffer concentration (not shown). The pH-rate profile shows a region of slope −1.0 at pH < 3.5 which corresponds to the hydronium ion-catalysed chlorine transfer to iodide ion. A value of the third-order rate constant for catalysis by H_3O^+ of the reaction of iodide ion with **3**, $k_H = (2.05 \pm 0.10) \times 10^5$ M^{-2} s^{-1} (Table 1), was determined from the fit of the data at pH < 3.5 to eqn (1) (L = H). At higher pH, chlorine transfer proceeds by a pH-independent pathway and the average value of $(k_2)_o$ at pH > 4.5 gives $k_o = (12.6 \pm 0.8)$ M^{-1} s^{-1} as the second-order rate constant for the solvent-catalysed reaction. The solid line through the data in Fig. 1 shows the fit to the logarithmic form of eqn (4) using the k_H and k_o values given above.

$$(k_2)_0 = k_0 + k_H[H_3O^+] \quad (4)$$

Fig. 3 shows plots of $(k_2)_{obsd} - (k_2)_o$ against the concentration of the acid form of substituted acetate buffers, according to eqn (2). The data obtained at different buffer ratios fall on the same correlation line, which shows that there is no significant catalysis of this reaction by the basic form of the buffer. Table 1 gives third-order rate constants k_{AH} (M^{-2} s^{-1}) for general acid catalysis of the addition reaction by substituted acetic acids, determined as

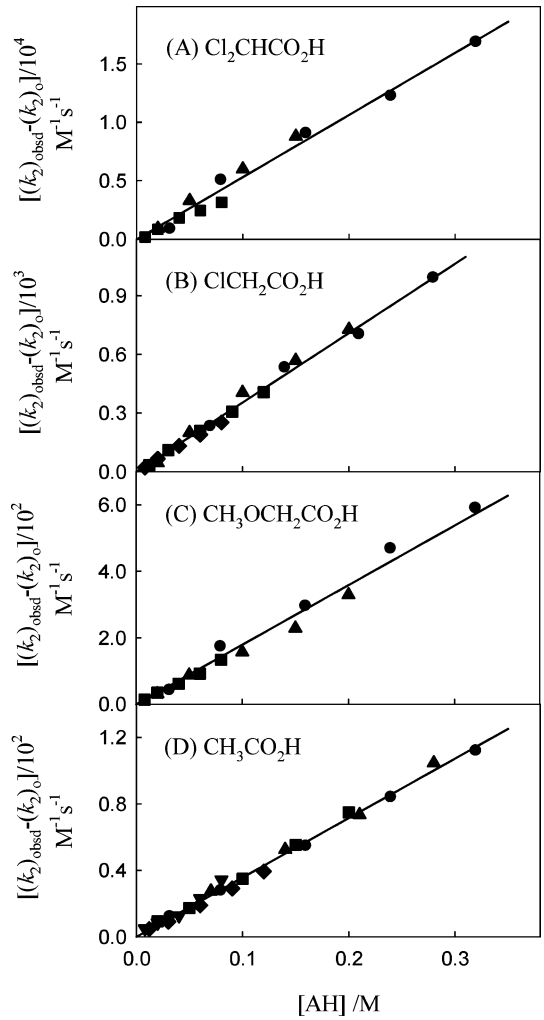


Fig. 3 General acid catalysis by substituted acetic acids of the reaction of iodide ion with **3** at 25 °C and $I = 0.5$ ($NaClO_4$). (A) Catalysis by Cl_2CHCO_2H. Fraction of buffer acid, $f_{AH} = 0.8$ (●), 0.5 (▲), 0.2 (■). (B) Catalysis by $ClCH_2CO_2H$. $f_{AH} = 0.7$ (●), 0.5 (▲), 0.3 (■), 0.2 (◆). (C) Catalysis by $CH_3OCH_2CO_2H$. $f_{AH} = 0.8$ (●), 0.5 (▲), 0.2 (■). (D) Catalysis by CH_3CO_2H. $f_{AH} = 0.8$ (●), 0.7 (▲), 0.5 (■), 0.3 (◆), 0.2 (▼).

the slopes of the linear plots in Fig. 3. This set of rate constants follows a Brønsted plot with $\alpha = 0.61$, as shown in Fig. 4. A similar treatment of the data for catalysis by phosphate buffers gives $k_{HA} = (1.21 \pm 0.02) \times 10^2$ M^{-2} s^{-1} (Table 1) for phosphate monoanion. This catalytic rate constant and that for H_3O^+ show significant deviations from the Brønsted correlation defined by the neutral substituted acetic acids, which can be attributed to electrostatic interactions between these charged catalysts and the developing positive charge on nitrogen in the transition state.

A $pK_a \approx -7$ for **3-H** can be estimated by assuming that the effect of a second chlorine for hydrogen substitution on the acidity of **4-H** ($pK_a = -0.1$)[12] is ≈ 80%[28] of the 9 unit effect of the first chlorine for hydrogen substitution on the pK_a of the parent amine taurine ($pK_a = 9.0$).[12] The value of $k_H = 2.05 \times 10^5$ M^{-2} s^{-1} for the hydronium ion-catalysed reaction of **3**, combined with $pK_a = -7$ for **3-H**, gives a value of $k_I = 2 \times 10^{12}$ M^{-1} s^{-1} for chlorine transfer from **3-H** to iodide ion (Scheme 3). This is much larger than the value of 5×10^9 M^{-1} s^{-1} for the encounter-controlled reactions of **1-H** and **4-H**,

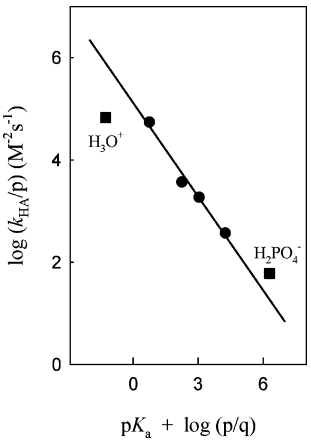
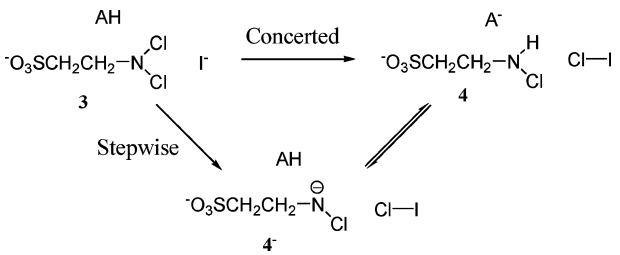


Fig. 4 Statistically corrected Brønsted correlation for general acid catalysis of chlorine transfer from **3** to iodide ion, where p and q are equal to the number of chemically equivalent acidic hydrogens in the acid and equivalent basic sites in the conjugate base, respectively.

so that **3-H** cannot form as a reaction intermediate. The observed general acid catalysis of the reaction of **3** supports a concerted mechanism of catalysis in which the acid assists chlorine transfer to iodide ion by partial protonation at nitrogen (Scheme 5). Protonation of **3** by H_3O^+ or substituted acetic acids is expected to be thermodynamically unfavourable due to the strong electron-withdrawing character of chlorine. Therefore, this reaction meets the requirements for concerted general acid catalysis, which avoids the formation of the highly unstable protonated intermediate **3-H**.

There is a positive deviation of ~10^3-fold of the rate constant for H_2O from the extrapolated Brønsted line for substituted acetic acids, which suggests that this reaction follows a different mechanism. Although the pK_a for ionization of **4** to give an amine anion is not known, the introduction of a chlorine atom at nitrogen is expected to bring the pK_a of the amine down by *ca.* 9–10 units, so that the pK_a of **4** is probably not very much larger than pK_a = +15.7 for H_2O. A small ΔpK_a would make concerted protonation by water insignificant,[30] so that the uncatalysed reaction is likely to proceed through a stepwise mechanism involving nucleophilic attack of iodide ion at **3** and expulsion of the chloramine anion $\mathbf{4}^-$ in the slow step (Scheme 6). The failure of water to act as a general acid catalyst through the concerted mechanism provides a plausible explanation for the observed large deviation of the water point from the Brønsted plot.



Scheme 6

In summary, the results described here show that there is a transition from specific acid catalysis to general acid catalysis of chlorine transfer to iodide ion as the amine leaving group becomes more acidic. The reaction of basic chloramines proceeds through a protonated chloramine intermediate, with therefore full protonation at nitrogen in the transition state (α = 1). The protonated intermediate reacts with iodide ion at the diffusion limit, which means that chlorine transfer within the ion pair is faster than diffusional separation and therefore occurs with a rate constant ≥10^{11} s^{-1} (Scheme 4). When electron-withdrawing substituents are introduced in the leaving amine, a point is reached at which the protonated intermediate becomes so reactive that it no longer has a significant lifetime when it is in contact with iodide ion. When this occurs, the reaction mechanism is forced to become concerted and the reaction is subject to general acid catalysis. There is a progressive decrease in the amount of proton transfer to nitrogen, and consequently in the Brønsted α value, with decreasing the base strength of the amine, which reflects an increasingly smaller requirement for assistance to leaving group expulsion by protonation.

Conclusions

N-Protonated chloramines derived from basic amines have pK_a's in water in the range 0–2 and therefore are sufficiently basic to exist as free solvent-equilibrated intermediates in aqueous solution. These chloramines transfer the chlorine atom to weak nucleophiles through a stepwise mechanism involving protonation at nitrogen in an initial equilibrium step. As the leaving amine is made more acidic or the nucleophile stronger, a change to a concerted mechanism of catalysis is observed which appears to be enforced by the absence of a significant lifetime of the protonated chloramine in the presence of the nucleophilic reagent.

Experimental

The sodium salt of *N*-chlorotaurine (**4**) was prepared by reaction of taurine with chloramine-T in ethanol. *N*-Chlorodimethylamine (**1**) was synthesized by treating the amine with a basic solution of sodium hypochlorite. The chloramine separated as an organic phase, which was isolated and dried over sodium sulfate. Deuterium oxide (99.9% D) and deuterium chloride (35% w/w, 99.5% D) were purchased from Aldrich. Commercially available inorganic salts and organic chemicals were reagent grade or better and were used without further purification.

Solutions of *N*-chloro-2,2,2-trifluoroethylamine (**2**) were prepared daily by mixing aqueous solutions of NaOCl and the amine to give a 2×10^{-3} M solution of **2** at pH 6–6.5. Solutions of *N*,*N*-dichlorotaurine (**3**) were prepared by disproportionation of **4** at pH 2–2.5 and used immediately after preparation. The concentration of **3** was determined spectrophotometrically at 302 nm using a molar absorption coefficient of 332.9 M^{-1} cm^{-1}.[31]

Buffer solutions and pH measurements

The following buffers were used to maintain constant pH in studies of the reaction of **1**, **2** and **3** with iodide ion: dichloroacetate, pH < 2; chloroacetate, pH 2.2–3.3; methoxyacetate, pH 2.8–4.0; acetate, pH 3.9–5.1; phosphate, pH 5.5–7.1; borate, pH 8.3. With dichloroacetate buffers, the required hydronium ion concentration was comparable to the concentration of the acid component of the buffer and an appropriate amount of $HClO_4$ was added to each solution to ensure constant pH. Solution pH was measured at

25 °C using a Radiometer PHM82 pH-meter equipped with a GK3401C combined glass electrode. Values of pD were obtained by adding 0.40 to the observed reading of the pH meter. In reactions monitored by 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 prepared to be identical to the solutions used in the stopped-flow experiments.

Kinetic studies

All reactions were carried out in water at 25 °C and I = 0.5 ($NaClO_4$). Kinetic experiments always employed at least a 10-fold excess of nucleophile over substrate, with iodide ion concentrations in the range 0.5–5 mM. Reactions with half-times 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 2×10^{-5} M substrate. The reactions were monitored by following the increase in absorbance at 287 nm due to the appearance of I_3^-. The slower reactions of **3** were monitored at 270 nm 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 concentration of 2×10^{-5} M. First-order rate constants, k_{obsd} (s^{-1}), were determined from the fit of the absorbance data to a single-exponential function and were reproducible to ±5%.

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