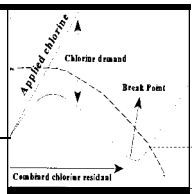
Aqueous chemistry of *N*-halo-compounds



CHEMICAL SOCIETY REVIEWS

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Halogens in aqueous solution are still used world-wide as disinfectants. During the process of halogenation, the substances present in water undergo several chemical processes, yielding relatively unstable intermediate species; their life-times in the medium depend on their structure and on the physico-chemical conditions. Several low molecular weight hydrocarbons are formed during water halogenation, some of them potent mutagens and/or carcinogens. Halogenation also takes place *in vivo* involving the system myeloperoxidase/H_2O_2/halide, which increases the relevance of such reactions and opens new research fields.

1 Introduction.

The general chemistry of aqueous halogen oxidants, X_2 (aq), has long received attention and has been summarized a number of times by different authors in general environmental chemistry textbooks.[1] Of course, there have also been many specialized symposia and publications related, specifically, to the environmental and health problems of water treatment.[2] The chemistry of *N*-halo-amines has also been reviewed in an overall manner, with emphasis on *N*-Cl- and *N*-Br-amines.[3] Recently, the IUPAC has devoted a 'White Book on Chlorine' to a broad review covering, among other topics, industrial, environmental and health aspects of chlorine and organochlorine chemistry.[4]

Even though aqueous halogens and their derivatives are still used world-wide as disinfectants, in the last few years halogen-based water treatment has become more and more unpopular. Most of the developed countries endeavour to apply new water disinfection techniques that avoid the use of halogens. However, the situation is still far from an end and halogen-based water treatment will continue to be unavoidable in the near future.

All these facts give only a vague idea of the enormous importance that aqueous halogen chemistry has reached, both

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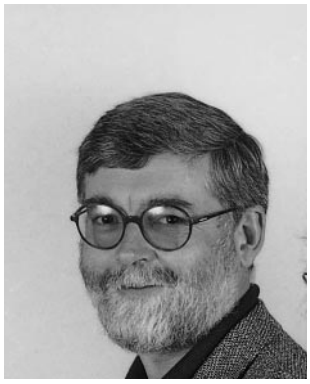

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from the fundamental and industrial point of view. Here, we attempt to present a broad view of the state-of-the-art of the chemistry of *N*-halo-compounds in aqueous solution, their generation, reactivity, and of the renewed interest of these substances in biological systems.

2 Generation of N-halo-compounds.

Aqueous solutions of halogens have a strong oxidizing character. Different species can be responsible for such oxidizing character, depending on the acidity of the medium. Some of the possible equilibria between the oxidizing species are summarized in eqns. (1)–(8), the equilibrium constants are given for a 298 K and are in the order Cl, Br, I.[2,5,6]

$$X_2\,(g) \rightleftharpoons X_2\,(aq)\ K_1 = 0.062,\ 0.21,\ 0.0013 \quad (1)$$

$$X_2\,(aq) + 2\,H_2O\,(l) \rightleftharpoons HOX\,(aq) + H_3O^+\,(aq) + X^-\,(aq)$$
$$K_2 = 4.2 \times 10^{-4},\ 7.2 \times 10^{-9},\ 2.0 \times 10^{-13} \quad (2)$$

$$X_2\,(aq) + 2\,OH^-\,(aq) \rightleftharpoons XO^-\,(aq) + X^-\,(aq) + H_2O\,(l)$$
$$K_3 = 7.5 \times 10^{15},\ 2 \times 10^8,\ 30 \quad (3)$$

$$X_2\,(aq) \rightleftharpoons X^+\,(aq) + X^-\,(aq)$$
$$K_4 \sim 10^{-40},\ 10^{-30},\ 10^{-21} \quad (4)$$

$$X_2\,(aq) + H_2O\,(l) \rightleftharpoons H_2OX^+\,(aq) + X^-\,(aq)$$
$$K_5 \sim 10^{-30},\ 10^{-20},\ 10^{-10} \quad (5)$$

$$HOX\,(aq) + H_2O\,(l) \rightleftharpoons XO^-\,(aq) + H_3O^+\,(aq)$$
$$K_6 = 3.4 \times 10^{-8},\ 2 \times 10^{-9},\ 2 \times 10^{-11} \quad (6)$$

$$3\,XO^-\,(aq) \rightleftharpoons 2\,X^-\,(aq) + XO_3^-\,(aq)$$
$$K_7 = 10^{27},\ 10^{15},\ 10^{20} \quad (7)$$

$$X_2\,(aq) + X^-\,(aq) \rightleftharpoons X_3^-\,(aq)\ K_8 = 0.18,\ 15.9,\ 698 \quad (8)$$

These oxidant species react readily with N-compounds to give the corresponding *N*-halo-derivatives. The oxidation products depend on the ratio $[X_2\,(aq)]/[\text{N-compounds}]$, and on the acidity of the medium. Such dependence is usually known as 'breakpoint', and is illustrated in Fig. 1 for a general case in

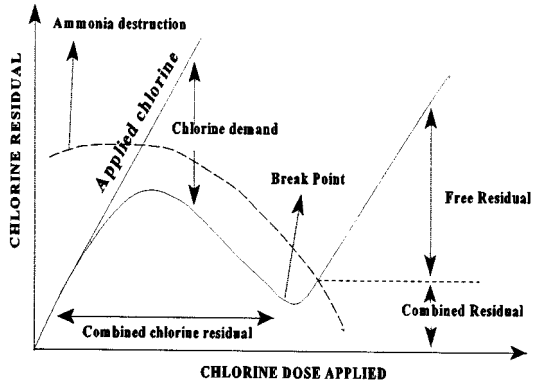


Fig. 1 General scheme of the breakpoint chlorination of a sample of natural water

which a sample of natural water is chlorinated.[1]

'Free chlorine' is the content of Cl_2, HOCl and ClO^-; 'combined chlorine' is the total concentration of chloramines (NR_2Cl + $NRCl_2$ + NCl_3) and their sum (free chlorine + combined chlorine) is called 'total chlorine'. The dose of chlorine is the analytical concentration of chlorine dissolved in water and the difference between this and the residual chlorine reflects the demand of chlorine, that is, how much chlorine is consumed to oxidize the pollutants (organic and inorganic) contained in the sample.

As a consequence of the world-wide use of chlorination in water and wastewater treatment, studies regarding the halogenation of N-compounds have been mostly restricted to the use of chlorine and bromine derivatives. The relevance of bromine for water treatment comes mainly from the relative abundance of bromide in natural waters, mainly in seawater; in the presence of the bromide ion, the following fast process given in eqn. (9) takes place.[2]

$$HOCl(aq) + Br^-\,(aq) \rightarrow HOBr\,(aq) + Cl^-\,(aq)$$
$$k = 2.95 \times 10^3\ mol^{-1}\ dm^3\ s^{-1}\ (T = 298\ K) \quad (9)$$

i.e., when $[Br^-]$ is relatively high, chlorination is effectively equivalent to bromination. An analogous process is observed with I^-, but at the same time fast disproportionation reactions occur,[5] which seriously complicate kinetic studies. Interest in the application of I-derivatives to water disinfection comes from their use on board the Shuttle Orbiter and, in the near future, in the International Space Station Alpha.[7] Fluorine is extremely reactive and oxidation products are usually obtained, rather than the *N*-fluoroamines.

2.1 Monohalogenated amino compounds

When the ratio of the amino compound concentration to the halogen concentration is 1 : 1 or higher, the monohalogenated compound is formed.[8] The mechanism of halogenation by molecular halogens $[X_2\,(aq)]$[9,10] involves the fast bimolecular halogen transfer to the unprotonated nitrogen, formally as X^+, with release of halide ion, [eqn. (10)].

$$R_2NH\,(aq) + X_2\,(aq) \rightarrow R_2NXH^+\,(aq) + X^-\,(aq) \quad (10)$$

Bimolecular rate constants for these reactions are collected in Fig. 2, the values being very high, *i.e.*, at or close to the diffusion control limit. When pH > 5, $[X_2\,(aq)]$ is so small that the previously mentioned pathway is no longer significant, HOX and/or XO^- becoming the active species. The generation of *N*-Cl-compounds follows a second order rate law, first order in both the nitrogenated compound and the halogenating agent. A bell-shaped dependence of the rate constant with the acidity is observed (shown in Fig. 3 for the case of amino acids), according to eqn. (11), where *a*, *b* and *c* are empirical parameters.

$$k_{obs} = a\frac{\left[H_3O^+\right]}{\left(b + \left[H_3O^+\right]\right)\left(c + \left[H_3O^+\right]\right)} \quad (11)$$

The observed behaviour is adequately explained by assuming a reaction between the halogenating agent and the nitrogenated compound. However, identifying the nature of the rate determining step is not straightforward. Considering the major species present under the experimental conditions (HOX **1**, XO^- $\mathbf{1}^-$, R_2NH **2** and $R_2NH_2^+$ $\mathbf{2H}^+$), four elementary steps are possible in the case of amines. If more than one acid–base equilibrium takes place for the nitrogenated compound, the number of possible elementary steps increases. The experimental evidence is consistent with both HOX **1** + R_2NH **2** ('molecular pathway') and XO^- $\mathbf{1}^-$ + $R_2NH_2^+$ $\mathbf{2H}^+$ ('ionic pathway'), two kinetically indistinguishable processes. A detailed study of the structure–activity effects, and the comparison with analogous processes allowed identification of the 'molecular pathway' as the one taking place.[11] An expression like eqn. (11) is deduced for the pH dependence of k_{obs} with $a = k \times Ka_2$, $b = Ka_2$ and $c = K_5$ where *k* is the second order rate constant for the chlorination reaction and Ka_2 and K_5 are, respectively, the equilibrium constants for deprotonation of the ammonium cation and of HOCl. Thus the maximum lies at the average of the pK_a's of HOCl **1** (pK_6) and $R_2NH_2^+$ $\mathbf{2H}^+$ (pKa_2).

Fig. 2 broadly sketches the typical order of magnitude of *k* measured for the chlorination of different amino compounds **2** with HOCl. They are of the same order of magnitude (10^7–10^8 $mol^{-1}\ dm^3\ s^{-1}$) for all the amines with conjugate acids of $pK_a > 9$. Such similarity, together with the very low activation enthalpies, points to a nearly diffusion controlled bimolecular process. However, this is not in agreement with the observed $k \sim 10^8\ mol^{-1}\ dm^3\ s^{-1}$ for HOCl and $k > 10^9\ mol^{-1}\ dm^3\ s^{-1}$ for Cl_2 (aq).[12] A cyclic structure for the transition state **3**, implying

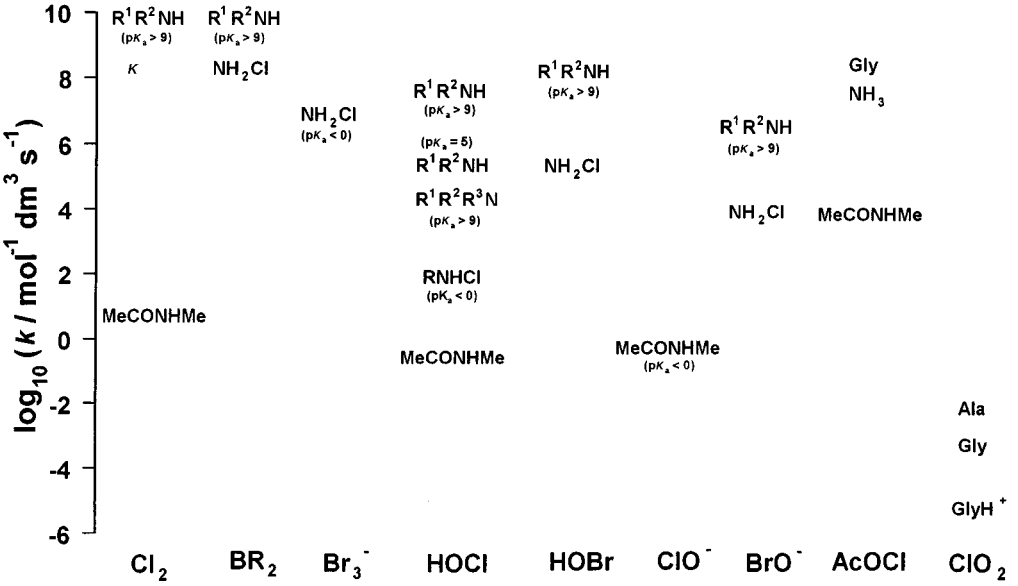


Fig. 2 Bimolecular rate constants for halogenating agents

a number of hydrogen-bonded solvent molecules (Scheme 1), could account for the activation parameters.

For less basic N-compounds, a curved dependence of the second order rate constant for chlorination with the basicity of the amino group has been found (Fig. 4). The analysis of the curvature in terms of Marcus' theory[13] (using the More O'Ferrall–Lewis approach) gives an intrinsic barrier $\Delta^{\ddagger}G_0^0 \approx 15$ kJ mol^{-1} for the chlorine transfer between the HOCl and the unprotonated nitrogen. The lack of measurements of the Gibbs free energy for the reaction does not allow estimation of the work terms.

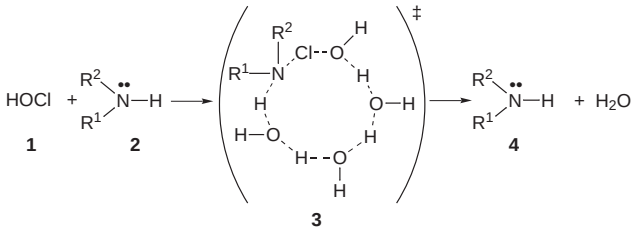
Chlorination of tertiary amines is a much slower reaction, the rate equation being consistent with reaction of HOCl and the unprotonated amine ('molecular' pathway). Second order rate constants are some three orders of magnitude lower than those for primary or secondary amines of similar base strength. The fact that these substrates are incapable of hydrogen bonding to the solvent at the transition state may explain such rate differences and reinforces the suggestion of the involvement of water molecules at the transition state (TS) in the chlorination of primary and secondary aliphatic amines.

A comparison of the substituent effects for the chlorination of primary/secondary and tertiary amines shows opposite slopes in the Taft plots. This is interpreted in terms of a development of positive charge ($\rho < 0$) on the nitrogen for tertiary amines and of negative charge ($\rho > 0$) for primary/secondary amines.

In the presence of acetic/acetate buffer CH_3COOCl is formed according to eqn. (12).[14]

$$CH_3COOH\ (aq) + HOCl\ (aq) \rightleftharpoons CH_3COOCl\ (aq) + H_2O\ (l) \qquad K_9 = 2.5 \times 10^{-3}\ (298.0\ K) \qquad (12)$$

This species is even more powerful as a chlorinating agent than Cl_2 (aq) itself. In the chlorination of *N*-methylacetamide,[15] the corresponding second order rate constant is 100 times higher than that of Cl_2 (aq). It is noticeable that chlorination by ClO^- also takes place, which is not observable in the chlorination of amines or α-amino acids. The following sequence holds for the reactivity of the different aqueous chlorinating agents mentioned: HOCl < ClO^- < Cl_2 < AcOCl.



Scheme 1

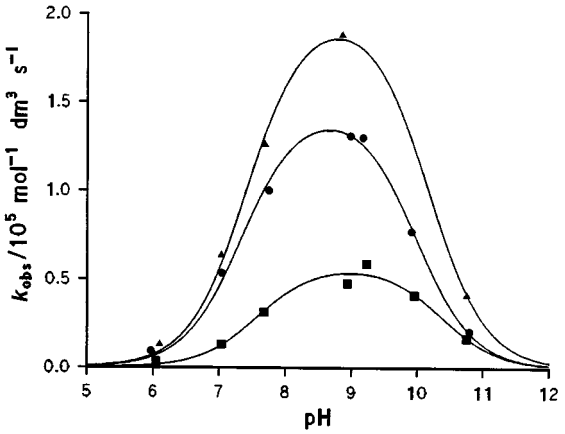


Fig. 3 pH-dependence of the rate of chlorination of α-amino acids by HOCl; (▲) glycine, (●) isoleucine, (■) amino isobutiric acid

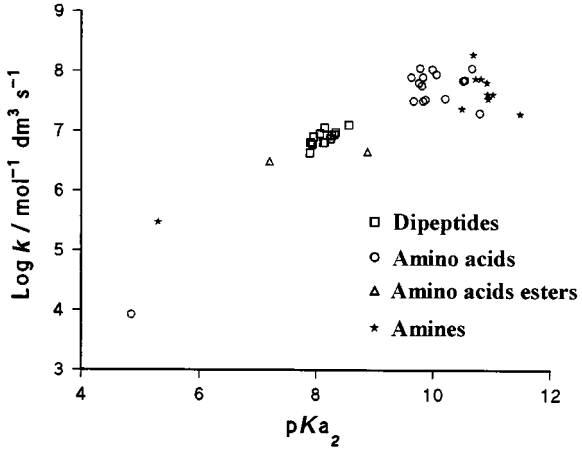


Fig. 4 Rate-equilibrium plot in the chlorination of N-compounds by HOCl

Halogenation of nitrogenated compounds can also be achieved with other *N*-halo-compounds. In fact, some of them have been used in water treatment in order to minimize the formation of trihalomethanes and other halogenated by-products.[2] *N*-Cl- and *N*-Br-succinimide readily halogenate amines by direct halogen transfer between the N atoms.[16] Several other *N*-halo-compounds, *e.g.*, *N*-Cl-toluene-*p*-sulfonamide, *N*-Cl-saccharine, *etc.*, have been used for this purpose but it is unclear if direct halogenation takes place or whether the *N*-halo-compound first undergoes hydrolysis to the corresponding HOX, which is then responsible for the halogenation. Although bromination by HOBr/BrO^- would be expected to be very similar to chlorination by HOCl/ClO^-, it has been proposed that bromination also takes place *via* a reaction between the unprotonated amine and BrO^-.[17]

ClO_2 is frequently used in water treatment and is sometimes preferred to aqueous chlorine since it leads to fewer chlorinated by-products, and no $CHCl_3$. The reaction is first order in both ClO_2 and the N-compound. The observed rate constant shows a marked dependence on the pH of the medium.[18] Both the free and the protonated amines yield the corresponding *N*-Cl-derivatives. The protonated form is *ca*. four orders of magnitude less reactive toward chlorine dioxide than the free form, the chlorination of the latter by ClO_2 being much slower than by HOCl/OCl^- (see Fig. 2).

2.2 Dihalogenated amino compounds

Dihalogenated compounds are formed when the concentration of the halogenating agent is higher than that of the N-compound. If this ratio is two or higher, the dihalogenated compound is the main product.[8]

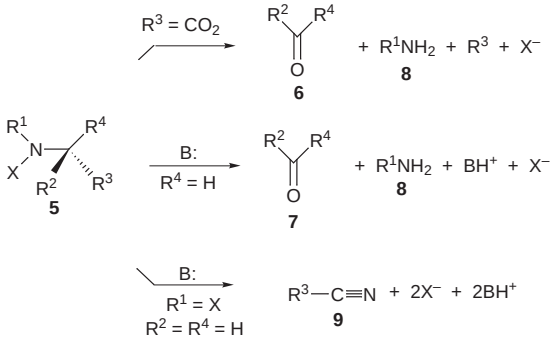
The reactions suffered by monohalogenated compounds following their formation complicate the study of the generation of the dihalogenated ones. It would be expected that dihalogenation, taking place by reaction between the monohalogenated substrate and a halogenating agent, follows a mechanism similar to that previously described for the initial halogenation. As shown in Fig. 2, the reaction is much slower due to the remarkably lower basicity of the N-halo-substituted amino group relative to amines (about 8 pK_a units).

Mixed dihalo-amines,[10] *i.e.*, (*N*-Br, *N*-Cl)-methylamine, have been observed when *N*-Cl-amines react with HOBr. The mechanism is expected to be similar to that previously mentioned (*vide supra*). Often dihalo-compounds are generated by disproportionation of two monohalamines, [eqn. (13)].[19] The observed rate constants for such reactions vary with the acidity of the medium, the maximum of the bell shaped pH-dependence giving an estimation of the pK_a of the protonated *N*-halo-amine. The rate determining step for these processes seems to be the first step in eqn. (13), *i.e.*, the direct halogen transfer between *N*-halo-amines, followed by fast deprotonation of the dihalo-amine.

$$RNXH_2^+ (aq) + RNXH(aq) \rightarrow RNX_2H^+(aq) + RNH_2(aq) \rightarrow RNX_2 (aq) + RNH_3^+ (aq) \qquad (13)$$

3 Decomposition of *N*-halo-compounds

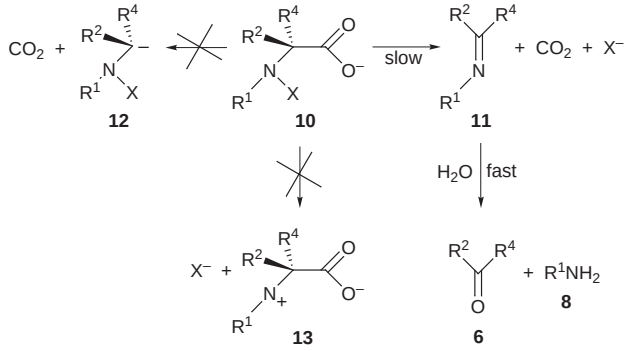
The main efforts in this field have been devoted to the decomposition of *N*-Cl and *N*-Br-compounds. *N*-I-compounds have received much less attention due to the difficulty of their direct generation, together with their expected higher instability. Once formed, *N*-halo-compounds **5** can undergo several processes, depending on the conditions of the medium (Scheme 2). Generally speaking, the products of such reactions are carbonyl compounds **6**, **7**, halide ions $\mathbf{X}^-$, and ammonia/amines **8** and/or cyano derivatives **9**. Here, we classify the possible processes in terms of types of reactions rather than considering their products.



Scheme 2

3.1 Grob fragmentation

Most studies[20] have concentrated on the decomposition of *N*-halo-α-amino acids, due to their environmental relevance, in near-neutral conditions where the anionic form **10** is the main species. As shown in Scheme 3, the Grob fragmentation yields



Scheme 3

an aldehyde or ketone **6** with one carbon fewer than the parent amino acid, carbon dioxide, ammonia or primary amines **8** and halide ions (Strecker degradation). The decomposition takes place in two consecutive steps. First, a unimolecular rate-determining fragmentation of the *N*-halo-amino acid **10** to halide, CO_2 and an imine **11** takes place, followed by a fast hydrolysis of the latter to the corresponding amine **8** and carbonyl compound **6**.

The process is first order in the N-halo-amino acid **10**, independent of the ionic strength and pH, and faster as the solvent polarity decreases. Analysis of the effect of alkyl substituents both on the C_α and on the N, and a comparison of the behaviour of *N*-Cl- and *N*-Br-α-amino acids, allow the structure of the transition state to be described,[21] using a More O'Ferrall diagram.[13]

As shown in Fig. 5, the Grob fragmentation is a nearly synchronous concerted D_ED_N process, with a product-like transition state (shaded zone). This is supported by the observation of a bigger inductive effect for the alkyl substituents on the C_α than for the nucleofuge in the N. In the transition state, the electrofuge and the nucleofuge (CO_2 and X^-) adopt an antiperiplanar configuration, and the C_α–CO_2^- bond breaking is slightly ahead of the N–X bond breaking.

The simplicity of the mechanism involved in the decarboxylation of *N*-Cl-α-amino acids has been used to test the phenomenological theory of solvent effects on chemical reaction rates.[22] At lower pH values, *N*-halo-α-amino acids can also occur in three protonation states, other than the anionic. Grob fragmentation is observed for such species if they are derived from secondary amino acids, in which case the disproportionation (Section 2.2) becomes rather slow. If pH < 5 the carboxylate is protonated, and the same is true for the amino group when $[H^+] > 1.0$ mol dm^{-3}. The neutral form of *N*-Cl-α-amino acids is favoured relative to the zwitterionic form by a factor of *ca*. 10^5, contrary to the case of α-amino acids.

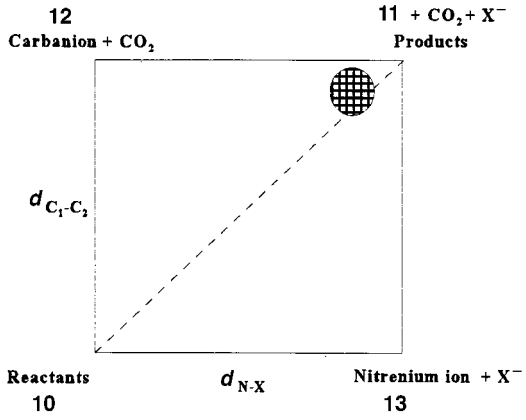
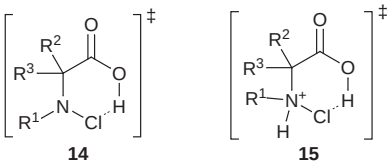
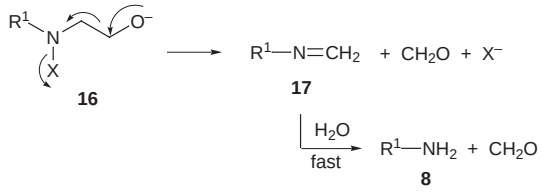


Fig. 5 More O'Ferrall plot for the Grob fragmentation of *N*-halo-α-amino acids

Under acidic conditions all four protonation states undergo fragmentation.[23] As expected, the decomposition of the zwitterion is faster, and for the neutral **14** and the protonated species **15**



a cyclic transition state has been proposed. *N*-Halo-amino alcohols **16** also undergo fragmentation,[24] the electrofuge and nucleofuge being, respectively, formaldehyde and halide, as shown in Scheme 4. The −OH group is only significantly



Scheme 4

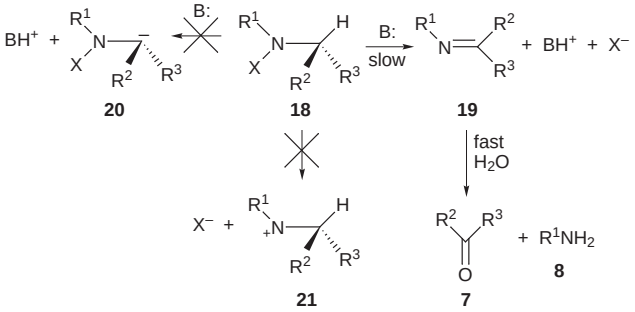
deprotonated in strongly alkaline medium. Under such conditions, an imine **17** is formed, which then quickly hydrolyses to the final products. The lack of precise pK_a measurements for the hydroxylammonium ions prevents good estimations of the first order rate constants. Nevertheless, considering the values available in the literature, this fragmentation is some three orders of magnitude faster for *N*-Cl-alcoholamines than for similar *N*-Cl-α-amino acids.

3.2 Elimination

In the presence of bases, *N*-halo-amines **18** undergo an elimination process, according to Scheme 2. The reaction products are similar to those obtained in the Grob fragmentation. Two different elimination processes have been identified in the decomposition of *N*-halo-amines: an intermolecular elimination (well known), and an intramolecular one (recently proposed).

3.2.1 Intermolecular elimination in halo-amines

The reaction follows a second order kinetic law, first order in both the *N*-halo-compound **18** and the base.[25] It shows general base catalysis and a marked effect of the ionic strength which, in some cases, has led to misinterpretations of the kinetic data. Scheme 5 displays the detailed mechanism: a first step involves



Scheme 5

proton abstraction from the C_α to the N, and expulsion of X^-, an imine **19** being formed. In a subsequent step the imine **19** undergoes a fast hydrolysis to ammonia/amine **8** and to the corresponding carbonyl compound **7** (an α-keto acid in the case of *N*-halo-α-amino acids).

The base-promoted generation of imines has been extensively studied[26] for many substrates and leaving groups, even in the case of *N*-Cl-amines.[27] Most of the available studies have been carried out in mixed and non-aqueous media. Such studies stress the effect of steric hindrance on the reactivity and support an $A_{xh}D_HD_N$ concerted mechanism (E2 according to the Ingold nomenclature). The studies in aqueous solution are also in agreement with such behaviour. In the case of *N*-halo-α-amino acids, studies of the Brønsted and pseudo-Brønsted plots (β, β_{lg}),[13] kinetic isotope effects, crossed-interaction parameters, *etc.*, allow the process to be identified as an asynchronous concerted $A_{xh}D_HD_N$ elimination.[25] The N–X bond breaking is generally ahead of the C–H bond breaking. The process shows an important Thornton (perpendicular) effect,[13] shown in Fig. 6, more important as the alkyl substituent on the C_α gets bulkier. Parallel to this effect, the TS **22** changes its structure from slightly carbanion-like to nitrenium-like.

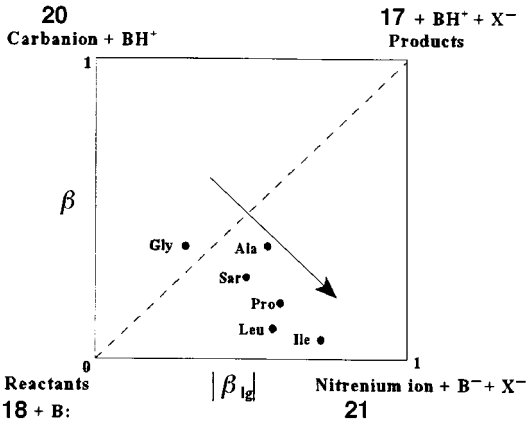
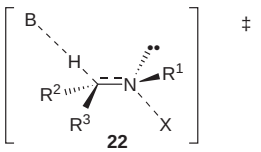


Fig. 6 More O'Ferrall–Albery–Jencks plot for the base promoted elimination of *N*-halo-α-amino acids



The decomposition of *N*-halo-dipeptides follows the same general pattern already described. However, some relevant differences are observed. Using NH_3 (g) and Cl^- selective electrodes, the formation of the imine **19** and its decomposition becomes evident, as shown in Fig. 7. NH_3 production does not start until the concentration of Cl^- is close to its maximum.

As with other *N*-halo-amines, the first step in the base-promoted decomposition of *N*-halo-dipeptides (Scheme 5) is an

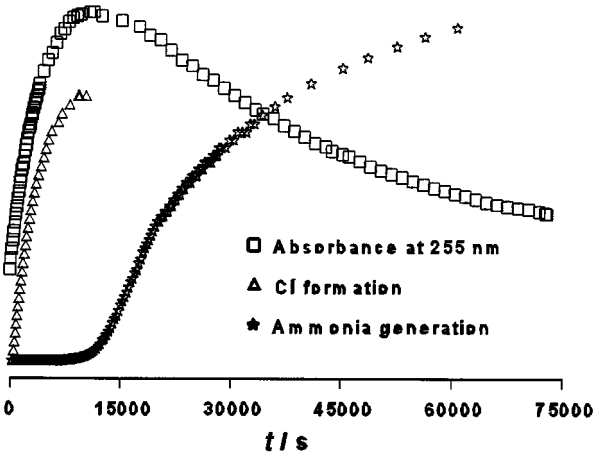
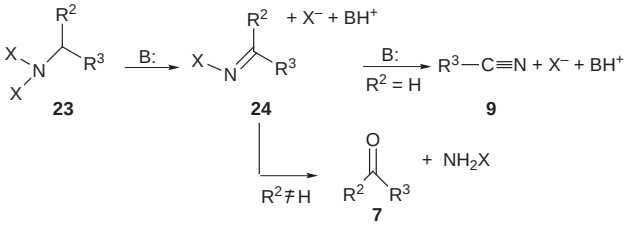


Fig. 7 Spectrophotometric, Cl^-, NH_3 kinetic profiles in the base promoted decomposition of *N*-Cl-Ala-Gly

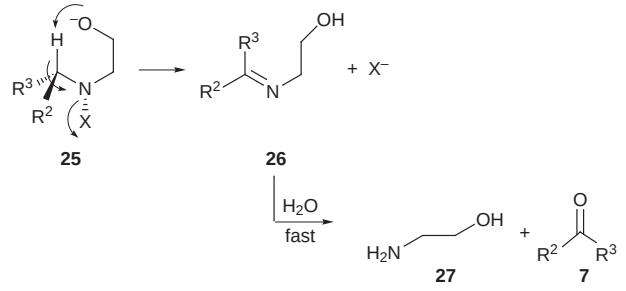
$A_{xh}D_HD_N$ process, in this case with a reactant-like transition state,[28] and the second step, the hydrolysis of the imine **19**, is slower than for *N*-halo-amines and *N*-halo-amino acids. No detailed mechanistic studies are available for the decomposition of (*N*,*N*)-dihalo-amines **23**. In the simpler cases, the experimental evidence suggests the existence of two consecutive dehydrohalogenation processes, yielding eventually the corresponding cyano derivative **9**, as shown in Scheme 6. The intermediacy of an *N*-halo-imine **24** has been clearly demonstrated.[8] Although detailed kinetic and mechanistic studies on this process would be desirable, two concerted base-promoted eliminations are likely to be involved in the mechanism. If a second dehydrohalogenation is not possible, the hydrolysis of the *N*-halo-imine **24** yields the corresponding carbonyl compound **7** and NH_2X, a very active halogenating species.[2]



Scheme 6

3.2.2 Intramolecular elimination

An intramolecular elimination process has been observed[24] in the decomposition of *N*-Cl-amino alcohols **25**, a process illustrated in Scheme 7. Following the deprotonation of the OH group, an intramolecular proton transfer from the C_α to the oxygen takes place. In this process an imine **26** is formed that quickly hydrolyzes.

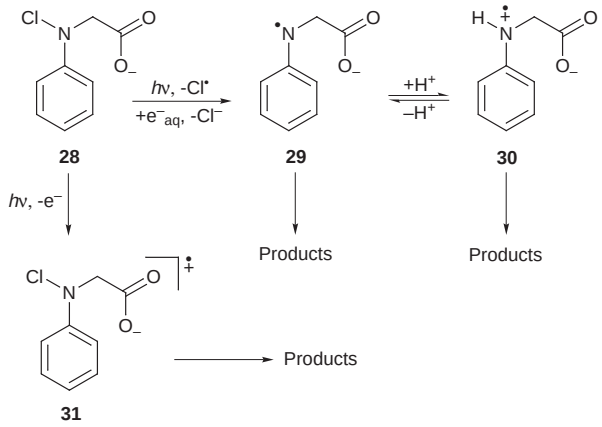


Scheme 7

Comparison of the reaction rate for this process with that observed for similar compounds lacking the OH allows an estimation of the effectiveness of the intramolecular pathway. A value of 10^6 mol dm^{-3} has been measured for the effective molarity,[13] an unexpectedly high value for such a process which may be due to the uncertainty in the pK_a of the OH of the amino alcohol.

5 Photolysis and radiolysis

Some work has been done on the applications of N-centered radicals: aminyl radicals and the corresponding protonated species, aminium radicals. The latter are much more electrophilic and reactive than the former.[29] The implication of aminium radicals in the Hoffman–Löffler–Freytag pyrrolidine synthesis (cyclization of *N*-halogenated amines), as well as in the chlorination of hydrocarbons and other organic compounds by chloramines, was proposed long ago. Aminyl and aminium radicals can be generated in several ways, *i.e.*, electrochemistry, pulse radiolysis,[30] and photolysis. In the laser flash photolysis (LFP) and pulse radiolysis (PR) studies of (*N*-Cl,*N*-phenyl)-glycine **28**,[31] photohomolysis and reductive homolysis (shown in Scheme 8) were observed. The corresponding aminyl radical (a γ-distonic radical anion) **29** and aminium radical (a γ-distonic radical zwitterion) **30** are generated.



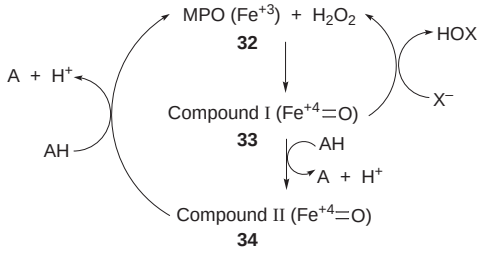
Scheme 8

The photoionization process is monophotonic when the excitation is performed with 193, 248 and 266 nm light, and biphotonic if 308 nm radiation is used. The photoionization and photohomolysis quantum yields decrease with increasing excitation wavelengths. These results have shown that N-centered radicals are generated from *N*-halo-compounds during UV-based water treatment. Despite the increasing interest in the synthetic use of aminium and aminyl radicals, and of their possible environmental and health implications, there is a lack of detailed mechanistic and kinetic studies of their behaviour.

6 *In vivo N*-halogenation

There has been much controversy about the benefits and risks of halogen-based water treatment to human health. In fact, several countries are looking for safer and cheap water treatment methods. For a long time there has been speculation about the carcinogenic and/or mutagenic activity of chloramines or HOCl itself. Studies on the mutagenic activity of chloramines suggest that chloramines are unlikely to penetrate the skin and mucous membranes.[32] Furthermore, the high SCN^- content in human saliva acts as a reducing agent toward ingested chloramines. HOCl and chloramines are also generated *in vivo*. When infection or tissue injury takes place, phagocytic leukocytes release certain compounds with antimicrobial and antitumor activity. Although such substances are able to fight against infection and tumor growth, at the same time they provoke

inflammatory tissue destruction and (maybe) carcinogenesis in other tissues. The *in vivo* production of HOCl involves the enzyme myeloperoxidase (MPO), which is secreted by neutrophiles (neutrophilic polymorphonuclear leukocytes, PMN). In the presence of H_2O_2, myeloperoxidase **32** catalyzes the oxidation of Cl^- to HOCl (Scheme 9), which rapidly oxidizes



Scheme 9

other substances present in the medium. HOCl is membrane permeable but has lower or no mutagenic activity, it is very reactive (see Section 2) and the carcinogenic/mutagenic activity could be related to the chloramines so generated.

It has long been known that even partial chlorination of DNA bases interferes with vital biological functions of the DNA. The reaction of HOCl with DNA is slow and chlorination of the amino groups of DNA bases causes its inactivation.[33] The hydrogen bonding is lost and consequently the double strand dissociates into single strands. Reaction with NH_4^+ rapidly produces NH_2Cl, which is highly toxic and also membrane permeable. In fact it modifies isolated DNA and it has been shown to be mutagenic for *Bacillus Subtilus*. The mutagenic activity shown by lipophilic chloramines, like monochlorohistamine, is rather higher than for hydrophilic chloramines, such as monochlorotaurine. Histamine facilitates the entry of leukocytes into the inflammatory site. Hence, as a result of its action, HOCl is generated, and consequently chlorohistamine formed, which could be responsible for chronic inflammation and eventually carcinogenesis. The formation of chlorotaurine is enzyme-catalyzed by myeloperoxidase rather than being formed by direct reaction with HOCl.[34] Presumably this essentially inert chloramine exerts a protective effect against HOCl/OCl^- damage.

In vitro experiences show that dichloramines have higher mutagenic activity than chloramines.[32] As stated in Section 2.2, these are formed from chloramines at low pH values and high Cl^- concentration or at high HOCl : amine ratios. There is indirect evidence of small amounts of dichloramines being generated by stimulated neutrophiles, but their role *in vivo* is still unclear. There are many other examples of *in vivo* oxidative damage by chloramines. Amongst them, it is worth mentioning that collagen displays greatly increased proteolytic susceptibility following chloramine and HOCl/OCl^- treatment.[35] Collagen degradation by collagenase is increased three-fold after exposure to chloramines, with the exception of chlorotaurine which has no effect. Hypohalous acids and haloamines, produced as a consequence of leukocyte action, show unequivocally an inactivating effect on the antiproteolytic effect of human α_2-macroglobulin. Oxidation of Br^- by myeloperoxidase has also been observed. In the presence of amines, bromamines are generated which, in contrast to chloramines, react with the H_2O_2 present in the medium. As for Cl^- and Br^-, peroxidases enzymatically oxidize I^- to I_2 and, for example, tyrosine is iodinated, but it remains unclear whether the iodinating species is HOI or I_2 itself.

The mutagenic and/or carcinogenic effect of haloamines could also be due to the effect of secondary mutagens, *i.e.*, to the by-products. For example, the decomposition of *N*-halo-α-amino acids yields aldehydes or ketones (Section 3) which show mutagenic and/or carcinogenic activity. Research in the field of *in vivo* halogenation is growing, offering an extremely interesting field of investigation from the basic, applied and theoretical chemical and biological points of view.

7 Theoretical studies

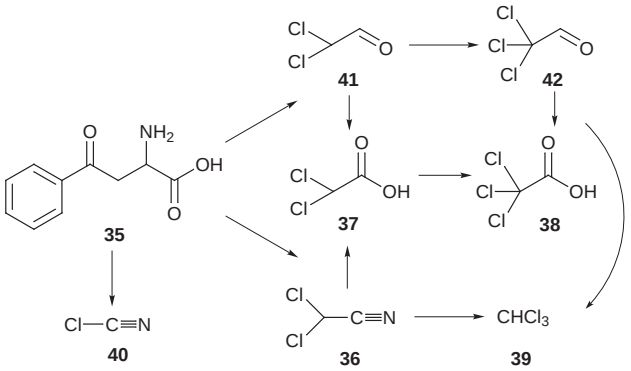
All the computational studies on the reactivity of *N*-halo-compounds are quite recent, all of them referring to the Grob fragmentation mechanism (Section 3.1). The unimolecular decomposition of the anionic form of *N*-Cl-glycine **10** (R2 = R4 = H) was studied[36] using analytical gradients and AM1 and PM3 semiempirical procedures, and the *ab initio* RHF and UHF methods at the 4-31G, 6-31G* and 6-311+G* basis set levels. Correlation effects were also analyzed at the MP2/6-31G* basis set level. Although the results are for the gas phase, the overall picture agrees with the experimentally observed behaviour in solution. The possible intermediates, a carbanion **12** and a nitrenium ion **13**, are not stationary points on the potential energy surface. In agreement with experiment, calculations point to a concerted and slightly asynchronous process, starting from the antiperiplanar form, the N–Cl bond breaking being ahead of the C_α–CO_2^- bond breaking, with a product-like transition state. An analysis of the substituent effects on the transition stucture has also been carried out, concluding that the size of the substituent relates to Thornton effects, while their type and number relate to Hammond effects.[37]

8 Final comments

Rather than summarizing the material presented in previous sections, we highlight here the aspects that merit further careful examination. A lot of analytical work has been done on the identification, detection and quantitative determination of the chlorination by-products but the picture is still far from complete. For simple substances like proline, chlorination yields more than 10 products, some of which are still not unambiguously identified.[2] Some of these substances come partly from the chlorination of the initial decomposition products, and partly from subsequent reactions of the main proline chlorination products.

Halogenation of more complex substrates, like humic acids, produces a broad spectrum of organochlorine derivatives, including the nitrogenated ones, which should be identified. The same is true for the chlorination by-products of other nitrogen-based common pollutants of water, like pesticides, herbicides, *etc.* Reliable analytical identifications are also needed for the products generated after UV-irradiation of *N*-halo-compounds, and to the chemicals involved in *in vivo* halogenation. These analytical studies are needed for a better understanding of the reaction mechanisms, for which a lot of kinetic research is still needed. Simple processes like the decomposition of (*N*,*N*)-dihalo-amines, the halogenation of ureas or carbamates, and the fate of the products so-generated are not known in detail or at all. A challenge for those looking for more complex mechanistic puzzles is, for instance, a complete description of the chlorination of humic and fulvic acids. The chlorination of some model compounds has been analysed, like kynurenine **35**,[38] a urinary tryptophan metabolite that yields chloroform **39**, chloroacetonitriles **36**, **40** and chloroacetic acids **37**, **38** (Scheme 10), all of them potentially dangerous. Although an approximate explanation for each pathway could be given, the detailed mechanism of some steps remains unclear. Generally speaking, the pathways from haloamines to potentially toxic compounds, like trihalomethanes, haloacetonitriles or haloacetic acids, have no detailed mechanistic explanation.

Not much attention has been paid to the reactions involving heavy metals and haloamines. A wide variety of such processes is to be expected, some of which could be of great environmental concern. Radiolysis and photolysis of haloamines offer an interesting and fruitful field. The study of the reactions taking place after UV-irradiation of haloamines has just started. The increasing availability of laser flash photolysis instrumentation for the study of transient species is an opportunity for those



Scheme 10

willing to enter the fascinating world of short-lived intermediates. Such species are extremely interesting both from the basic and applied chemical point of view. Apart from the understanding of the reactivity of N-centered radicals, they have interesting applications, for example, in organic synthesis. The environmental aspect should be kept in mind, considering the recent trend to combine UV-irradiation and chlorination in water treatment. The corresponding by-products must be identified, their reaction mechanisms explained and especially toxicological activity determined. Moreover, some of the processes involved in radiolysis and photolysis could be used to model the damage to DNA induced by irradiation or by the N-centered radicals themselves. Another highly attractive developing field is the study of *in vivo* halogenation and effects of halogenation by-products. Some of the enzymatic and non-enzymatic mechanisms involving haloamines have been related to carcinogenesis.

As already stated, the study of the iodination of N-compounds has been a tough problem. A good possibility for such study is the use of the system {peroxidase/H_2O_2/I^-}. The reactivity of haloamines with sulfur compounds deserves careful study, provided mutagenic *N*-halo-compounds are rapidly inactivated in the presence of certain sulfur compounds. On the chemical–biological side, an explanation is lacking for the protection mechanism exhibited by microorganisms like *Escherichia coli*, which shows negative chemotaxis in gradients of different substances, like for example *N*-chlorotaurine.[39]

Computational studies are at their very beginning. Only the Strecker degradation of *N*-Cl-α-amino acids in the gas phase has been analyzed. More complex processes like the generation of *N*-halo-compounds, their base-promoted elimination, the structure and reactivity of aminium and aminyl radicals and, of course, the *in vivo* reactions would merit further theoretical study.

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