Pergamon

Tetrahedron 54 (1998) 521–530

TETRAHEDRON

Oxidation of Aliphatic Amines by Aqueous Chlorine

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Received 21 March 1997; revised 4 November 1997; accepted 6 November 1997

Abstract: The oxidation of aliphatic amines by aqueous chlorine has been studied. The kinetic behaviour is similar for primary, secondary and tertiary aliphatic amines, the elementary step being the transfer of chlorine from the hypochlorous acid molecule to the nitrogen of the free amino group. Chlorination of aliphatic primary and secondary amines involves some water molecules in the transition state. Inductive effects are also discussed.

Introduction.

Water chlorination is nowadays the most widely used method for water disinfection and for the control of water-transmited diseases.[1,2] It is well known that during potabilization the chlorinating agents react with organic matter to yield different byproducts, some of which are toxic.[3,4,5] For this reason, it is important to understand the different reaction mechanisms implied in these processes, specially when the increasingly higher amount of organic materials found in natural waters is considered.

It has already been established that aqueous chlorine reacts readily with different nitrogenated compounds,[6,7,8,9] yielding the corresponding *N*-Cl-compounds, that are unstable and subsequently react through different pathways depending on the compound and on the reaction conditions.[6,10,11]

Due to their biochemical relevance, we have previously concentrated on the reactivity of aminoacids[6] and peptides[7] toward aqueous chlorine, as well as on the reactivity of their *N*-Cl derivatives. In this paper we present a mechanistic study of the chlorination of secondary aliphatic amines and the comparison with the behaviour of primary and tertiary aliphatic amines.

Experimental.

Sodium hypochlorite solutions were prepared by bubbling Cl_2 (g) through a NaOH solution. The so-obtained NaOCl solution was stored in an opaque flask at pH>12 and low temperature, and its concentration spectrophotometrically determined daily (λ_{max}=292 nm, ε=350 $dm^3 \cdot mol^{-1} \cdot cm^{-1}$). All other chemicals were Merck® or Aldrich® *p.a.* products. Millipore-Milli Q® water was used to make up the solutions.

Buffer solutions of $H_2PO_4^- / HPO_4^{-2}$ and HCO_3^- / CO_3^{-2} were used, their total concentration being kept to 0.01 $mol \cdot dm^{-3}$. pH measurements were carried out with an adequately calibrated combined glass electrode. The ionic strength was maintained constant using $NaClO_4$.

The pK_a values of the aliphatic secondary amines and the pK_a of the HOCl were taken from the literature.[12]

PII: S0040-4020(97)10312-X

The *N*-Cl-amines were generated by mixing equal volumes of solutions of the chlorinating agent and of the amine, both equally buffered and with the same ionic strength.

The reactions were followed with a single-mixing SF-61 Hi-Tech Scientific® stopped-flow spectrophotometer, thermostatted by water flow to within 0.1 K. The increase in the absorbance of the maximum at 262 nm was measured. The rate constants were thus obtained by fitting the adequate kinetic equation to the experimental data, using a modification of the DSC algorithm.[13] All reported rate constants are average values obtained from at least four experiments, their reproducibility being within 5%.

Results and Discussion

The reaction follows an overall second order rate law, first order relative to the amine and first order relative to the chlorinating agent:

$$r = k_{obs} \cdot [chlorinating\ agent] \cdot [amine] \qquad [1]$$

The dependence of the observed rate constant with the pH goes through a maximum, as shown in Figure 1.

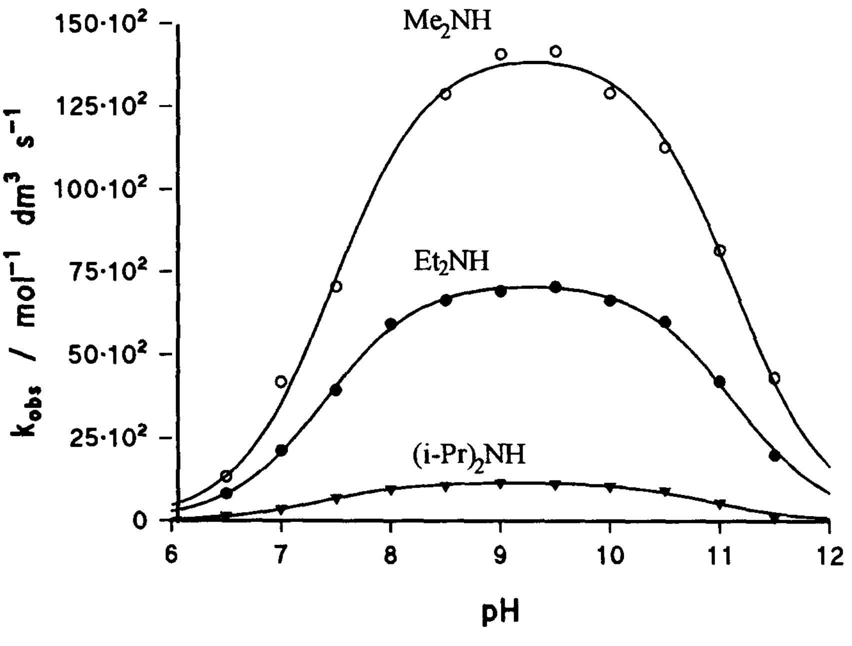


Figure 1. Influence of pH on the chlorination rate constant (T = 298 K). [Amine] = [Chlorinating agent] = $2.3 \cdot 10^{-3}$ mol·dm^{-3}; I(NaClO) = 0.3 mol·dm^{-3}

Equation [2] adequately fits the pH dependence of the observed rate constant:

$$k_{obs}=a\cdot\left(\frac{[H^+]}{(b+[H^+])\cdot(c+[H^+])}\right) \qquad [2]$$

where a, b, c are parameters to be optimized.

Two equilibria are involved in the process:

$$HClO + H_2O \rightleftharpoons ClO^- + H_3O^+ \qquad (1)$$

$$R_2NH_2^+ + H_2O \rightleftharpoons R_2NH + H_3O^+ \qquad (2)$$

Taking into account the four possible species, the following rate determining steps can be considered:

$$R_2NH + HClO \xrightarrow{k_1} R_2NCl + H_2O \qquad (3)$$

$$R_2NH_2^+ + ClO^- \xrightarrow{k_2} R_2NCl + H_2O \qquad (4)$$

$$R_2NH + ClO^- \xrightarrow{k_3} R_2NCl + OH^- \qquad (5)$$

$$R_2NH_2^+ + HClO \xrightarrow{k_4} R_2NCl + H_3O^+ \qquad (6)$$

Processes (5) and (6) would show a dependence k_{obs} *vs.* pH different to that observed (eq. [2]), which allows rejection of these processes. The remaining processes (3),"molecular" and (4), "ionic", are kinetically indistinguishable, and the following theoretical rate equation can be deduced for them:

$$r=k\cdot K\cdot\left(\frac{[H^+]}{(K_a+[H^+])\cdot(K_c+[H^+])}\right)\cdot[amine]\cdot[chlorinating\ agent] \qquad [3]$$

where k is the bimolecular rate constant, K can be either the ionization constant of the amine or that of HOCl and K_a and K_c are the protonation constants of the amine and HOCl, respectively.

The fact that equation [3] coincides with the empirical equation [2] suggests that the elementary reaction taking place corresponds to either (3) or (4). From this equation, it follows that the maxima in Figure 1 correspond to the arithmetical average of the pK_a values of the amine and of HOCl, *i.e.*: $pH_{max}=(pK_a+pK_c)/2$.

From the kinetic data is not possible to decide whether the process takes place *via* the " molecular" or the "ionic" elementary step. However, this can be solved on the basis of some reasonable statements:

i) Protonated amines cannot act as nucleophiles. On the other hand, an electrophilic behaviour of ClO^- would be very unfavourable, leading to an extremely improbable O^{-2} anion. Therefore, the "ionic" process should be rejected.

ii) The chlorination rate constants for amine[14] and amides[15] using Cl_2(aq.) as chlorinating agent are faster than using HOCl, and the rate of chlorination by HOCl for similar compounds increases with the basicity of the amino group[16]. This suggests the reaction takes place between the molecular species.

iii) The possibility exists that a H^+ transfer from the amine to the ClO^- takes place into the encounter pair in the reaction between ionic species prior to a nucleophilic attack of the amine to the HOCl, so that the actual rate determining step would be the reaction between molecular species.

Bearing in mind the previous considerations, the reaction *via* charged species can be rejected, and the only remaining possible process is the one taking place between molecular species.

Table 1 shows the bimolecular rate constant values for the chlorination of the secondary aliphatic amines used in this study accepting the reaction takes place between the neutral species, *i.e.*, the elementary step (3).

Table 1. Bimolecular rate constants and pK_a values for aliphatic secondary amines. $I(NaClO_4)= 0.3\ mol\cdot dm^{-3}$.

	$k\cdot10^{-7}$ / $mol^{-1}\cdot dm^3\cdot s^{-1}$						
T / K	**Me_2NH**	**MeEtNH**	**Et_2NH**	**Pr_2NH**	**iPr_2NH**	**iBu_2NH**	**IDPN***
293	---	5.16	3.71	3.04	1.36	---	0.026
298	6.05	6.45	4.14	3.81	1.80	2.20	0.029
303	---	---	4.64	4.46	1.94	---	0.035
308	---	7.00	6.46	4.53	2.70	---	0.037
	pK_a [12]						
298	10.72	10.92	11.02	10.94	11.48	---	5.30

* IDPN= 3,3'-iminodipropionitrile= bis-(2-cyanoethyl)-amine

Although the magnitude of the bimolecular rate constants is below the commonly accepted limit for diffusion-controlled reactions, the constancy of those bimolecular rate constants for the more basic amines could suggest that diffusion control is playing a role. The low $\Delta H^{\ddagger}$ values (Table 2) are also in support of this idea.

Table 2. Activation parameters for the chlorination of aliphatic amines. I($NaClO_4$)=0.3 mol·dm^{-3}.

Amine	**$\Delta H^{\ddagger}$ / kJ·mol^{-1}**	**$\Delta S^{\ddagger}$ / J·mol^{-1}·K^{-1}**
Methylethylamine	12 ± 3	-57 ± 6
Diethylamine	24 ± 4	-18 ± 2
Dipropylamine	18 ± 2	-40 ± 5
Diisopropylamine	30 ± 5	-8 ± 1
bis-(2-cyanoethyl)-amine	16 ± 2	-86 ± 8
***Ethylamine**[25]	9	-55
***Propylamine**[25]	1	-102
***Isopropylamine**[25]	1	-84
***Methyldiethanolamine**[17]	32 ± 2	-61 ± 4

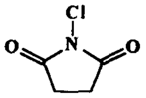
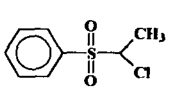
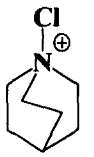
* Experimental data taken from the cited reference and fitted to our mechanistic model

However, this idea can be rejected on the basis of the following considerations:

i) The higher k values obtained are lower than those generally accepted for diffusion-controlled processes.

ii) When the chlorination by different agents is considered[14,15,18] it is found that the reactivity follows the sequence: k(AcOCl) > k(Cl_2) > k(HOCl), which would not be expected for a diffusion-controlled process. In addition, Table 3 shows there is no relation between the rate constants obtained for the chlorination of Me_2NH by different chlorinating agents and the size of the chlorinating agent.

Table 3. Rate constants for the chlorination of Me_2NH by different agents (T=298.0K).

Chlorinating agent	**k / mol^{-1}·dm^3· s^{-1}**	**Reference**
HOCl	$6.1\cdot10^7$	This work
NH_2Cl	$80\cdot10^7$	19
Cl_2	$160\cdot10^7$	20
	$1.5\cdot10^7$	21
	$0.02\cdot10^7$	21
	$2.0\cdot10^7$	21

iii) The bimolecular rate constants for the more basic amines are well correlated in a Taft's plot ($\rho = 1.2\pm0.1$, $r=0.95$) as shown in the Figure 2.

The previous statements allow rejection of the diffusion control idea, so that the process must be chemically controlled.

The same conclusion comes from the observed behaviour of other amino compounds like primary aliphatic amines[25], α-amino acids[6] and dipeptides[7]. In all those cases the reaction is second order, one both in the amine concentration and in the chlorinating agent concentration; the pH dependence of the observed rate constant is bell-shaped similar to that shown in Figure 1.

Chlorination bimolecular rate constants of primary amines, α-amino acids and dipeptides are collected in Table 4. These rate constants were calculated from the data in the corresponding reference and fitted to the mechanism proposed in this work, *i.e.*, the reaction between the free amino group and the hypochlorous acid molecule.

Comparison of Table 1 with Table 4 shows similar bimolecular rate constants for the chlorination of the amino compounds with analogous pKa value for the amino group. Within each group the bimolecular rate constant increases with the basicity of the amino group and levels off for the more basic amines.

Table 4: Bimolecular rate constants for the chlorination of amino compounds (T=298.0 K).

Compound	**pK_a [22]**	**$k\cdot10^{-7}$ / $mol^{-1}\cdot dm^{3}\cdot s^{-1}$**
NH_3 [23]	9.25	36.31
$MeNH_2$ [24]	10.66	19.00
$EtNH_2$ [25]	10.81	19.78
$PrNH_2$ [25]	10.56	18.30
$BuNH_2$ [25]	10.49	16.27
$iPrNH_2$ [25]	10.67	18.80
$iBuNH_2$ [25]	10.49	15.72
$sBuNH_2$ [25]	10.56	8.90
$tBuNH_2$ [25]	10.69	5.44
Glycine [26]	9.87	11.3
Sarcosine [26]	8.25	10.08
Alanine [26]	9.75	3.4
Glycyl-Glycine [7]	9.82	0.9

Aliphatic primary and secondary amines lie well in the same line in a Taft's plot (see the Figure 2), suggesting the chlorination process is similar in both cases.

The behaviour observed for aliphatic tertiary amines is formally similar to other amino compounds, *i.e.*, overall second order, one in amine and one in chlorinating agent; the pH dependence of the observed rate constant is similar to that shown in Figure 1.

Table 5 collects the bimolecular rate constants for the chlorination of tertiary amines assuming the same mechanism as that of primary and secondary amines.

Table 5. Bimolecular rate constants for chlorination of aliphatic tertiary amines (T=298.0 K).

Amine	pK_a [22]	$k \cdot 10^{-7}$ / $mol^{-1} \cdot dm^3 \cdot s^{-1}$
(N-Me)-Piperidine[27]	10.08[28]	0.008
(N,N)-di-Me-Glycine[27]	9.94[29]	0.005
*Trimethylamine[17]	9.75	0.005
*Diethylethanolamine[17]	9.82	0.014
*Dimethylethanolamine[17]	9.26	0.003
*Methyldiethanolamine[17]	8.52	0.00064
*Ethyldiethanolamine[17]	8.92	0.0016
*Triethanolamine[17]	7.98	0.00012

* Experimental data taken from the cited reference and fitted to our mechanistic model.

These values are at least 2 orders of magnitude less than the bimolecular rate constants of primary and secondary amines; another difference being the sign of the Taft's plot slope (ρ = -2.5±0.4, r = 0.95), as shown in Figure 2.

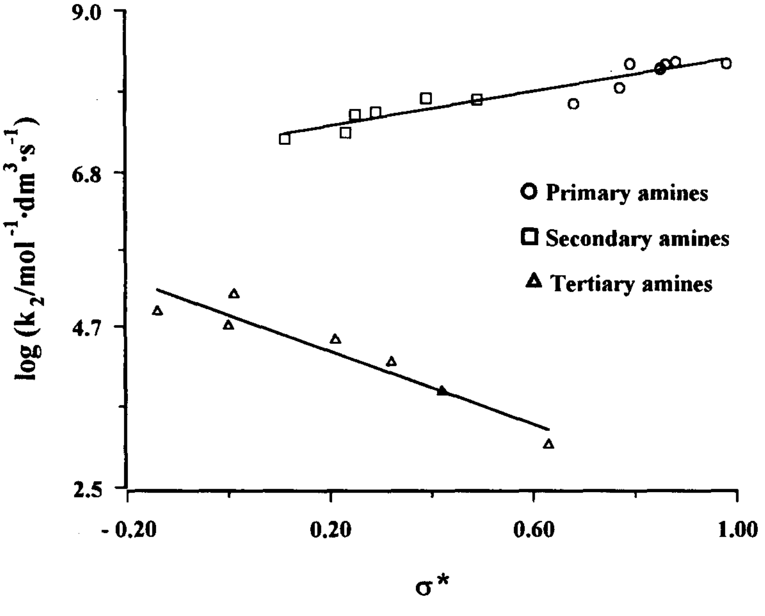
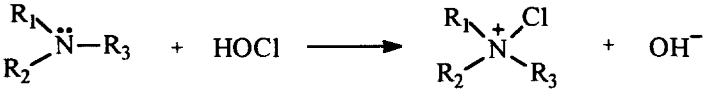


Figure 2. Taft's plot for the chlorination of aliphatic amines. (T = 298 K)

The pattern using Charton's steric parameters[30] is not clear, a negative correlation is always observed ($|r| < 0.80$), when this steric dependence is considered the correlation with σ^* is similar to that found previously. A third feature is the linear relationship between the bimolecular rate constant and the pK_a values of the tertiary amines.

The slope of the Taft's plot for tertiary amines is consistent with an elementary step in which positive charge is developed in the nitrogen atom as shown in Scheme 1.



Scheme 1

The ρ value for primary and secondary amines could tentatively be ascribed to a negative charge development at the transition state, which is hard to understand thinking in terms of Scheme 1. This implies some differences between tertiary amines and primary and secondary amines in the detailed chemical events of the chlorination process.

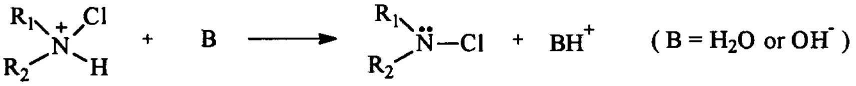
The high bimolecular rate constants obtained for primary and secondary amines indicate a low free energy barrier ($\Delta G^{\ddagger} \approx 30$ kJ·mol^{-1} at 298K -calculated from Table 2-) in the chlorination of the more basic amines. This agrees with the very similar gas-phase dissociation energies reported for the O-Cl and N-Cl bonds:[31]

$$D^0_{298}(\text{Cl-O}) = 272 \pm 4 \text{ kJ·mol}^{-1}$$

$$D^0_{298}(\text{Cl-N}) = 334 \pm 10 \text{ kJ·mol}^{-1}$$

Although it would be necessary to account for the solvation effects, the fact that $D^0_{298}(\text{Cl-O}) < D^0_{298}(\text{Cl-N})$ seems to suggest that the process may begin with the Cl-O bond breaking. This would give rise to charge-separated species in the encounter complex, which is disfavoured. Moreover, one of these species would be a chlorinium ion (Cl^+), highly improbable on thermodynamic basis.[32] A possible initial protonation of the HOCl to hypochlorous acidium ion (H_2OCl^+) must also be discarded, provided that this would imply a k_{obs} *vs.* pH dependence different from that observed and a negative ρ value in the Taft's plot.

One possibility to account for the observed ρ value and the constancy of bimolecular rate contants for primary and secondary amines is to consider the process shown in Scheme 2 as rate determining step.

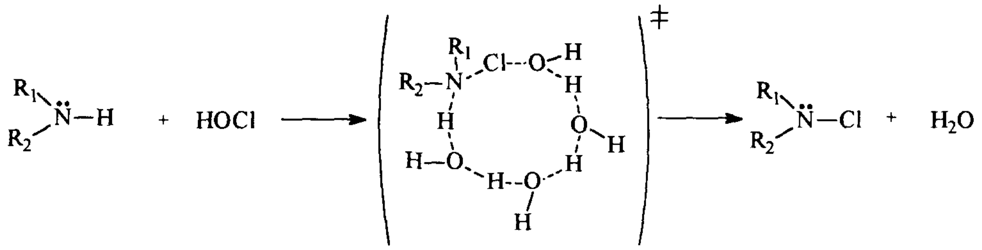


Scheme 2

In that case the chemical event depicted in Scheme 1 should be faster than the proton transfer between the charged nitrogen atom and the solvent, which seems unreasonable considering the values of the bimolecular rate constants estimated for tertiary amines where the process shown in Scheme 1 takes place.

To understand what happens in the chlorination of primary and secondary amines three points should be jointly considered: i) the high and nearly constant bimolecular rate constant for the more basic amines (Tables 1 and

4), ii) the low activation enthalpy (Table 2) and, iii) the negative values of the entropy of activation (Table 2). On this basis, a highly ordered transition state (TS), in which at least a water molecule is implied, seems highly probable. Scheme 3 depicts an example of such TS for the case in which three water molecules are involved.



Scheme 3

The water molecules are hydrogen-bonded to both the HOCl and the nitrogen, the transfer of the chlorine atom is coupled with the proton transfer from the nitrogen to the water avoiding the charge-separated species. The TS would comprise an interaction formally similar to H_2OCl^+, but avoiding this long-time controversial species.[33]

On the other hand, the hydrogen bonds in the transition state could explain the low values of the enthalpy of activation and the negative values of the activation entropy.

The participation of only one water molecule in the transition state could be proposed but would imply bonding angle strain and, more relevant, an unfavourable bent proton transfer. In this sense, a ten-membered ring is more feasible, with three water molecules (Scheme 3), which is closer to the typical hydration number of water.[34,35]

The sign of the ρ parameter for primary and secondary amines implies an asychronous process in which the proton transfer from the nitrogen to the water is ahead of the transfer of the chlorine from the HOCl molecule to the amine. The major contribution to the free energy barrier comes from the Cl-O bond breaking, which explains the constancy of the bimolecular rate constants for the more basic amines.

Conclusion.

The oxidation of amines by aqueous chlorine takes place *via* chlorine transfer from the HOCl to the nitrogen of the amine. For primary and secondary amines, the reaction begins with the proton transfer from the nitrogen to the water coupled with the bond breaking of the O-Cl bond and subsequent N-Cl bond making; the available data point to the participation of several water molecules in the transition state. For tertiary amines the process is the attack of the lone pair of the nitrogen on the HOCl molecule, with generation of charged species.

Acknowledgments.

The authors thank the Xunta de Galicia (project XUGA 10307B95) and the Universidade da Coruña for financial support.

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