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Chlorine Transfer Reactions between Chloramine and 1-Piperidine: Kinetic Reactivity and Characterization in a Raschig Medium

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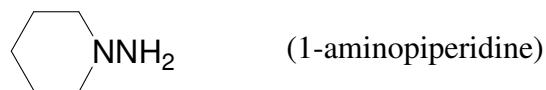
* Corresponding author

Abstract

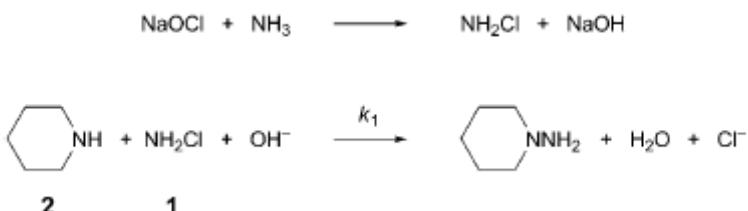
The kinetics of the chlorine transfer reaction between chloramine and 1-piperidine in a Raschig medium ($8 < \text{pH} < 9$) was studied at various temperatures, with variable concentrations of the two reactants. The influence of the pH on the interaction chloramine/piperidine was examined at a pH ranging between 8.25 and 12.89. The chlorine transfer reaction resulted in the formation of 1-chloropiperidine, which, in the presence of sodium hydroxide, underwent a dehydrohalogenation leading to an imine derivative: 2,3,4,5-tetrahydropyridine. The kinetics of dehydrohalogenation was also studied at different temperatures, with variable concentrations of 1-chloropiperidine and sodium hydroxide. Kinetic and thermodynamic parameters were determined for the chlorine transfer and dehydrohalogenation reactions. Both 1-chloropiperidine and 2,3,4,5-tetrahydropyridine were prepared according to efficient synthetic routes; they have been isolated and purified, then characterized by elemental analysis, IR, $^1\text{H}/^{13}\text{C}$ -NMR and MS. Their thermal stabilities were evaluated by using DSC, and their absorption coefficients at various wavelenghts were determined experimentally by UV spectrophotometry.

Introduction

This work comes as a part of a complete study involving the preparation of an unsymmetrical substituted hydrazine – 1-aminopiperidine – in an ammoniacal hypochlorite (“Raschig”) medium, which is used in the pharmaceutical industry as a precursor of medicinal drugs.

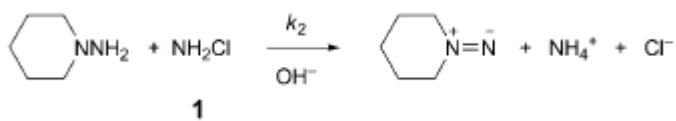


For the hydrazine preparation, Raschig synthesis [1-4] can be considered the most environmentally friendly route among the various syntheses described in the literature [5-25]. It is also the most suitable synthetic route for a large scale preparation. In the case of 1-aminopiperidine, Raschig synthesis can be schematized by the two following reactions (Scheme 1):



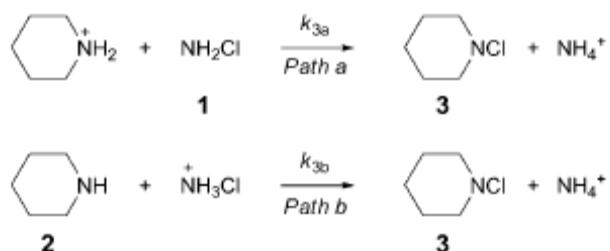
Scheme 1

However, it presents the major drawback of leading to numerous by-products. This behaviour is particularly due to the pH dependent reactivity of NH₂Cl, which may exhibit, depending on the pH value, an aminating (see Scheme 1), oxidizing (Scheme 2) [26] or even chlorinating character (see Scheme 3).



Scheme 2

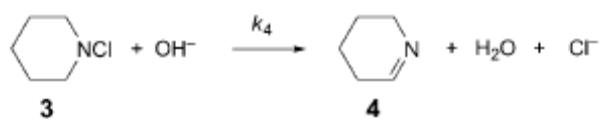
In particular, the chlorine transfer reaction (Scheme 3) between chloramine (**1**, NH₂Cl) and piperidine (**2**, C₅H₁₀NH) is one of the principal side reactions observed during the synthesis of 1-aminopiperidine in the Raschig process [27]. A change of orientation in the NH₂Cl/C₅H₁₀NH interaction is observed with the acidification of the reaction medium, involving the protonation of either piperidine or chloramine:



Scheme 3

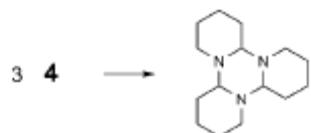
In a slightly alkaline medium, the amount of 1-aminopiperidine decreases in 1-chloropiperidine's favor. The latter (**3**, C₅H₁₀NCI) preponderates at pH ≈ 8. Therefore, an accidental lack in the sodium hydroxide supply of our pilot plant resulted in the formation of **3**.

In an alkaline medium, 1-chloropiperidine (**3**) undergoes a dehydrohalogenation, leading to the formation of an imine derivative: 2,3,4,5-tetrahydropyridine (**4**, C₅H₉N), according to Scheme 4:



Scheme 4

2,3,4,5-Tetrahydropyridine (**4**) is likely to precipitate in monomeric or polymeric form as shown in Scheme 5:



Scheme 5

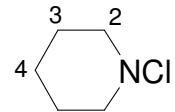
Hence, when 1-chloropiperidine molecules are surrounded by sodium hydroxide molecules, they are immediately converted into imine derivatives, which, at high concentrations, precipitate and block up the inlets of the pilot plant unit.

Since these reactions limit the yield and lead to the precipitation of by-products, which are difficult to separate during the continuous extraction of 1-aminopiperidine [27], it is necessary to create a kinetic model quantifying the contribution of main and side-reactions involved in the Raschig medium. Therefore, we have to investigate the kinetics of each of these reactions separately. Herein, we report on the kinetics of chlorine transfer (Scheme 3) and dehydrohalogenation (Scheme 4) as well as on the efficient syntheses of **3** and **4** and their characterization by several analytical and thermochemical techniques.

Results and Discussion

Characterization

Characterization of 1-chloropiperidine (3, C₅H₁₀NCl)



EA (calc. /found, mass %): C 50.21 / 50.17, H 8.43 / 8.38, N 11.71 / 11.84, Cl 29.64 / 29.51. These results corroborate the purity grade determined by DSC (see below).

IR Δv / cm⁻¹ (KBr, rel. int.): The absorptions corresponding to the various bonds can be assigned as follows: C-H (2940(s) 2830(s) 1471(s) 1452(s) 1359(s)), C-N (1273(s) 1215(s)), C-C (1086(m) 1056(m) 1031(m)), N-Cl (881(w) 864(w) 823(w) 679(s) 513(m)).

MS (EI, 70 eV) m/z (abundance %): 118 (100), 55 (80.2), 42 (75.8), 28 (72.4), 119 (51.4), 84 (37.1), 120 (34.8), 83 (31.8), 78 (23.4), 56 (18.3), 36 (18.2), 121 (16.8), 39 (16.7), 54 (15.6), 29 (15.1), 82 (12.0).

The two intense peaks 118 and 120 are related to the chlorine isotopes ³⁵Cl and ³⁷Cl.

¹H-NMR (DMSO-d₆, 400.18 MHz, 25°C, TMS) δ/ppm: 3.40 (4H, m, H-C(2)), 1.67 (4H, m, H-C(3)), 1.40 (2H, m, H-C(4)); *¹³C{¹H}-NMR (DMSO-d₆, 100.63 MHz, 25°C, TMS) δ/ppm:* 63.7 (2C, C(2)), 27.4 (2C, C(3)), 22.7 (1C, C(4)). Many ¹H/¹H couplings were observed, however, it was not possible to determine the corresponding coupling constants.

DSC (5°C/min, °): -59 (m.p.), ~125 (decomposition).

The molar purity and the melting parameters of **3** were determined in a first experiment by cooling a sample of freshly distilled chloropiperidine from 0 to -100°C (cooling rate = 5°C/min).

$$\text{Purity} = 98.95 \pm 403.74 \times 10^{-6} \text{ mol\% or } 99.84\%$$

$$\text{m.p.} = -59.03^\circ, \quad \Delta H \text{ (melting)} = 8.68 \text{ kJ/mol}$$

A second experiment was carried out in order to determine the thermal stability of the compound: **3** was heated from -30 up to 250°C with a heating rate of 5°C/min. The decomposition started around 125°C, became more and more violent and reached its apogee around 140°C. The heat of decomposition released ΔH (decomposition) was evaluated around 31.55 kJ/mol.

UV: The absorption parameters of **3** ($\epsilon = f(\lambda)$) were determined by calibration, using a series of solutions of several concentrations (1×10^{-3} , 2×10^{-3} , 4×10^{-3} and 6×10^{-3} M) prepared from freshly distilled chloropiperidine diluted in water. The solutions were titrated by iodometry [28]. Figure 1 shows a superposition of the UV spectra of **1** and **3**. Another series of solutions was prepared at pH = 13 by adding a suitable amount of sodium hydroxide, the absorption parameters obtained were identical to those determined in water.

(λ (nm); ϵ ($M^{-1} \cdot cm^{-1}$)): (295;112) (290;150) (285;193) (280;239) (275;281) (270;317) (265;341) (261;348) (260;347) (255;331) (250;294) (245;245) (243;224) (240;192) (235;149) (230;118).

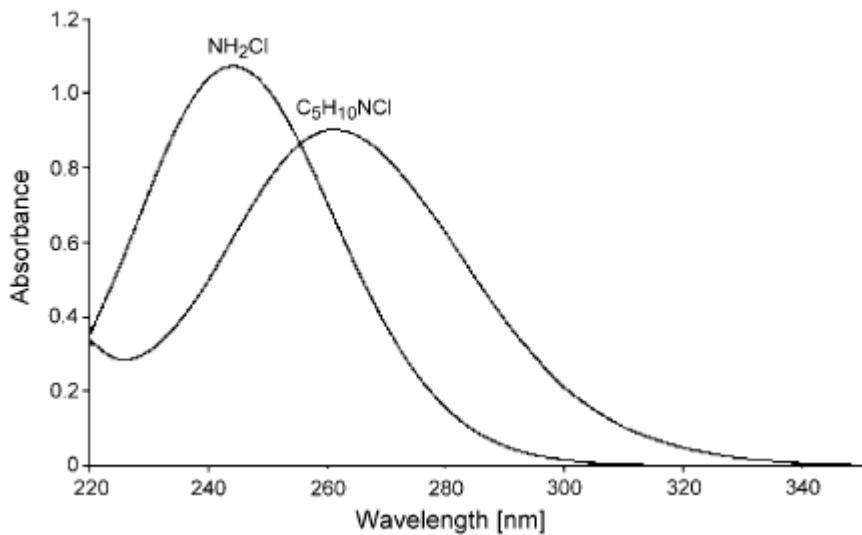
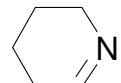


Figure 1

*Characterization of 2,3,4,5-tetrahydropyridine (**4**, C₅H₉N)*



EA (calc. / found, mass %): C 72.24 / 71.03, H 10.91 / 10.52, N 16.85 / 17.48.

IR Δν / cm⁻¹ (KBr, rel. int.): Similar bands to those observed for **3** are found, the C=N group has a weak absorption at 1653 cm⁻¹, C-H (2958(s) 2923(s) 2846(m) 2807(m)) C=N 1653 (w) C-N 1372(s) 1303(m) 1238(m) C-C 1108(m) 1022(m) 1031(m) 667(m) 507(m).

MS (EI, 70 eV) m/z (abundance %): 166 (100), 55 (98.6), 84 (76.8), 83 (73.0), 82 (60.9), 137 (53.4), 138 (40.5), 41 (30.3), 56 (28.4), 42 (25.1), 85 (24.2), 54 (22.5), 167 (19.2), 123 (18.3), 96 (17.9), 68 (17.3), 81 (14.5), 124 (13.5), 57 (12.9), 39 (12.8), 165 (12.0), 122 (8.3), 249 (4.1).

This result shows that **4** may exist in its dimer (166) or even trimer (249) forms (see Scheme 5), which explains the weak absorption at 1653 cm^{-1} corresponding to the imino-group. Moreover, after a short time, the solid obtained seems to be converted into its polymerized form and that, once dissolved in water, it is hydrolyzed into its monomer form.

$^1\text{H-NMR}$ (DMSO-d_6 , 400.18 MHz , 25°C , TMS): mixture of multiplets, no possible assignment; $^{13}\text{C}\{^1\text{H}\}$ - NMR (DMSO-d_6 , 100.63 MHz , 25°C , TMS): many peaks were detected.

Due to equilibrium between monomer, dimer and trimer forms of **4**, the ^1H and ^{13}C NMR spectra were quite complex and it was not possible to assign the various peaks and determine coupling constants. Several measurements, at different temperatures, in DMSO-d_6 and CDCl_3 were conducted, however, no improvement was observed. D_2O was tested as well, but due to the low solubility of **4** in water, the concentration was too low to detect peaks.

DSC (5°C/min , °): 60 (m.p.), ~120 (decomposition).

4 was prepared according to the procedure described later (see Experimental). By heating a sample of 6.06 mg between -20 and 250°C (heating rate = 5°C/min), a sharp peak was observed around 60°C , which corresponds to the melting point of **4**, followed by a decomposition starting around 120°C and reaching its highest stage at 167°C .

From the melting phase, it was possible to determine the molar purity and melting parameters of **4**:

Purity = $98.19 \pm 26.29 \times 10^{-3}$ mol% or 99.60%

m.p. = 60.50° , ΔH (melting) = 7.07 kJ/mol

UV: Imino-groups have UV absorption maxima around 225 nm (Figure 2), absorption parameters of **4** ($\epsilon = f(\lambda)$) were determined by calibration, using a series of solutions of different concentrations (1×10^{-3} , 2×10^{-3} , 3×10^{-3} and 4×10^{-3} M) prepared by dissolving a small amount of **4** in 2 ml of ether and diluting in 100 ml of water. The UV reference cell contained 2 ml ether diluted in 100 ml water.

(λ (nm); ϵ ($M^{-1} \cdot cm^{-1}$)): (295;0) (290;0) (285;0) (280;1.5) (275;6) (270;12.5)
(265;23.5) (260;37.5) (255;57) (250;85) (245;116.5) (240;146) (235;165.5)
(230;174) (227.59;175) (225;173) (220;165.5).

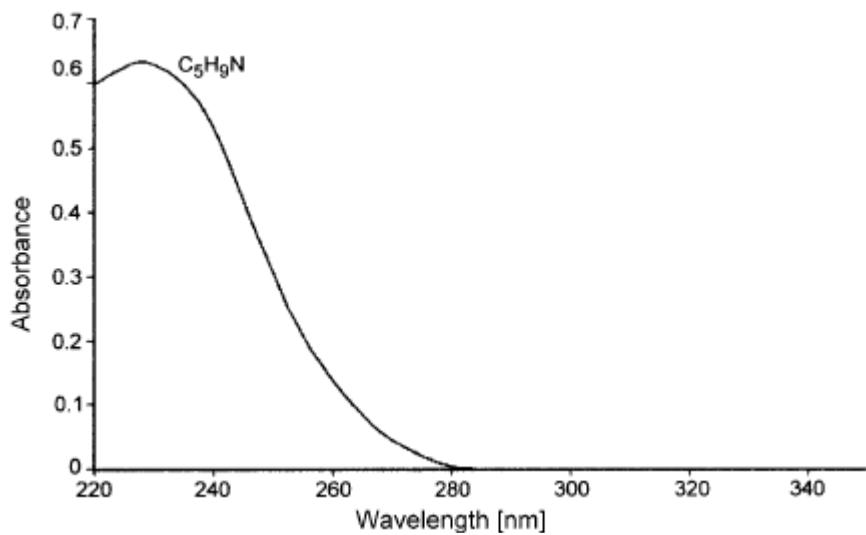


Figure 2

Kinetics of the chlorine transfer reaction between chloramine and 1-piperidine

Reaction order and stoichiometry

At $8 < \text{pH} < 9$, **3** becomes the exclusive product of the $\text{C}_5\text{H}_{10}\text{NH}/\text{NH}_2\text{Cl}$ interaction.

Therefore, in order to measure the rate constant with the utmost precision, experiments were conducted at 25°C and $\text{pH} \approx 8$. Figure 3 shows the UV spectrophotometric evolution of a chloramine/piperidine aqueous mixture at different times of the reaction ($[\text{C}_5\text{H}_{10}\text{NH}]_0 = 10 \times 10^{-3} \text{ M}$, $[\text{NH}_2\text{Cl}]_0 = 2 \times 10^{-3} \text{ M}$, $\text{pH} = 8.20$ and $T = 25^\circ\text{C}$). While the UV absorption of chloramine decreased at 243 nm, the one of chloropiperidine increased simultaneously creating an isobestic point at 257 nm, which can be expressed by the following equation:

$$[\text{NH}_2\text{Cl}]_0 - [\text{NH}_2\text{Cl}] = [\text{C}_5\text{H}_{10}\text{NCl}]$$

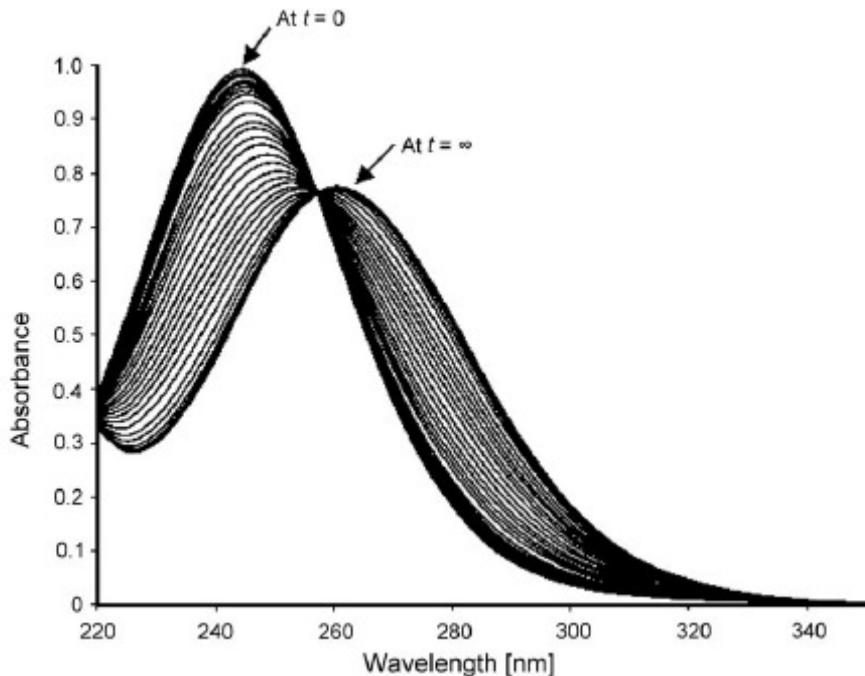


Figure 3

Since an overlap between UV absorption spectra of chloramine (**1**) and chloropiperidine (**3**) is observed (see Figure 1), we chose to work at two wavelengths ($\lambda_1 = 243$ nm and $\lambda_2 = 280$ nm), at which absorbencies can be expressed as follows ($l = 1.00$ cm):

$$D(\lambda_1) = \varepsilon_{\text{NH}_2\text{Cl}}^{\lambda_1} [\text{NH}_2\text{Cl}] + \varepsilon_{\text{C}_5\text{H}_{10}\text{NCl}}^{\lambda_1} [\text{C}_5\text{H}_{10}\text{NCl}]$$

$$D(\lambda_2) = \varepsilon_{\text{NH}_2\text{Cl}}^{\lambda_2} [\text{NH}_2\text{Cl}] + \varepsilon_{\text{C}_5\text{H}_{10}\text{NCl}}^{\lambda_2} [\text{C}_5\text{H}_{10}\text{NCl}]$$

Instantaneous concentrations of **1** and **3** (Figure 4) become:

$$[\text{NH}_2\text{Cl}] = \frac{[\varepsilon_{\text{C}_5\text{H}_{10}\text{NCl}}^{\lambda_2} D(\lambda_1, t) - \varepsilon_{\text{C}_5\text{H}_{10}\text{NCl}}^{\lambda_1} D(\lambda_2, t)]}{\varepsilon_{\text{NH}_2\text{Cl}}^{\lambda_1} \varepsilon_{\text{C}_5\text{H}_{10}\text{NCl}}^{\lambda_2} - \varepsilon_{\text{NH}_2\text{Cl}}^{\lambda_2} \varepsilon_{\text{C}_5\text{H}_{10}\text{NCl}}^{\lambda_1}}$$

$$[\text{C}_5\text{H}_{10}\text{NCl}] = \frac{[\varepsilon_{\text{NH}_2\text{Cl}}^{\lambda_1} D(\lambda_2, t) - \varepsilon_{\text{NH}_2\text{Cl}}^{\lambda_2} D(\lambda_1, t)]}{\varepsilon_{\text{NH}_2\text{Cl}}^{\lambda_1} \varepsilon_{\text{C}_5\text{H}_{10}\text{NCl}}^{\lambda_2} - \varepsilon_{\text{NH}_2\text{Cl}}^{\lambda_2} \varepsilon_{\text{C}_5\text{H}_{10}\text{NCl}}^{\lambda_1}}$$

with: $\varepsilon_{\text{NH}_2\text{Cl}}^{\lambda_1=243} = 458 \text{ M}^{-1} \text{ cm}^{-1}$; $\varepsilon_{\text{C}_5\text{H}_{10}\text{NCl}}^{\lambda_1=243} = 224 \text{ M}^{-1} \text{ cm}^{-1}$

$\varepsilon_{\text{NH}_2\text{Cl}}^{\lambda_2=280} = 62 \text{ M}^{-1} \text{ cm}^{-1}$; $\varepsilon_{\text{C}_5\text{H}_{10}\text{NCl}}^{\lambda_2=280} = 239 \text{ M}^{-1} \text{ cm}^{-1}$

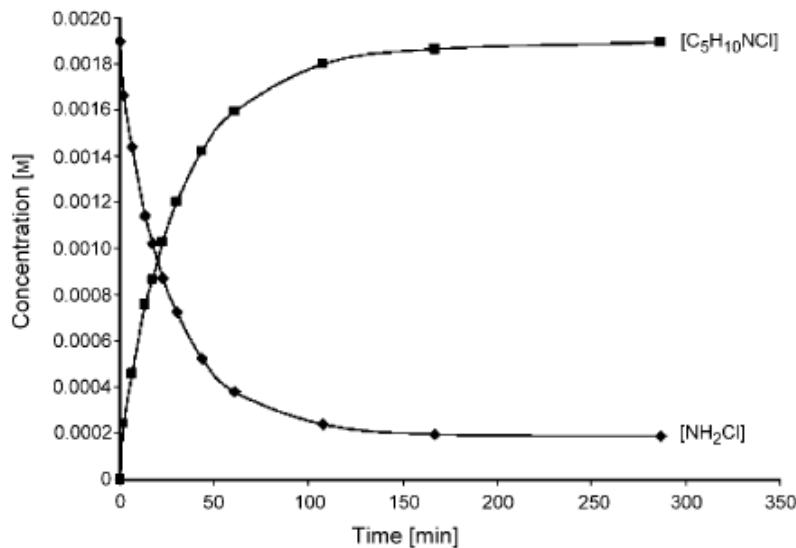


Figure 4

To represent chlorine transfer in the C₅H₁₀NH/NH₂Cl interaction, two reactional schemes are plausible (see Schemes 3a and 3b). The rate law can be expressed by the equation below:

$$r = d[C_5H_{10}NCl]/dt = k_{3a} [NH_2Cl]^\alpha [C_5H_{10}NH_2^+]^\beta = k_{3b} [NH_3Cl^+]^\alpha [C_5H_{10}NH]^\beta$$

with k_{3a} (or k_{3b}), α and β, respectively, are the rate constant and partial orders of the reaction.

Taking acid-dissociation equilibrium of **1** and **2** into account, it leads to the following:

$$[NH_2Cl] = x_1 [NH_2Cl]_{all} \quad [NH_3Cl^+] = y_1 [NH_2Cl]_{all}$$

$$[C_5H_{10}NH] = x_2 [C_5H_{10}NH]_{all} \quad [C_5H_{10}NH_2^+] = y_2 [C_5H_{10}NH]_{all}$$

With:

$$[NH_2Cl]_{all} = [NH_2Cl] + [NH_3Cl^+]; \quad [C_5H_{10}NH]_{all} = [C_5H_{10}NH] + [C_5H_{10}NH_2^+]$$

$$x_1 = \frac{k_a^{NH_3Cl^+}}{[H^+] + k_a^{NH_3Cl^+}}; \quad y_1 = 1 - x_1; \quad x_2 = \frac{k_a^{C_5H_{10}NH_2^+}}{[H^+] + k_a^{C_5H_{10}NH_2^+}}; \quad y_2 = 1 - x_2$$

Hence:

$$r = k_{3a} [NH_2Cl]^\alpha [C_5H_{10}NH_2^+]^\beta = k_{3b} [NH_3Cl^+]^\alpha [C_5H_{10}NH]^\beta = \chi [NH_2Cl]_{all}^\alpha [C_5H_{10}NH]_{all}^\beta$$

$$[C_5H_{10}NH]_{all}^\beta$$

$$\text{with } \chi = k_{3a} x_1 y_2 = k_{3b} x_2 y_1 \quad \text{and } k_{3b} = k_{3a} \frac{K_a^{NH_3Cl^+}}{K_a^{C_5H_{10}NH_2^+}}$$

Furthermore, according to the acid-ionization constant K_a values of the two reactants

($K_a^{\text{NH}_3\text{Cl}^+} = 3.41 \times 10^{-2}$ M [29], $K_a^{\text{C}_5\text{H}_{10}\text{NH}_2^+} = 7.53 \times 10^{-12}$ M [30]) at pH = 8.20,

neutral and protonated species of **1** and **2** have the following percentages:

1

$\approx 100\%$ NH₂Cl

2

99.88 % C₅H₁₀NH₂⁺

$0.18 \times 10^{-4}\%$ NH₃Cl⁺

0.12 % C₅H₁₀NH

Therefore, at this pH value, (3a) is the overriding reactional scheme. As the kinetic parameters were determined by the Ostwald method, the corresponding rate law becomes:

$$r = k_{3a} [\text{NH}_2\text{Cl}]^\alpha [\text{C}_5\text{H}_{10}\text{NH}]_0^\beta \quad ([\text{C}_5\text{H}_{10}\text{NH}_2^+]_0 \approx [\text{C}_5\text{H}_{10}\text{NH}]_{0\text{all}}).$$

To evaluate α , a series of three measurements was carried out, using a constant concentration of **2** (20×10^{-3} M) and chloramine concentrations ranging from 1×10^{-3} to 4×10^{-3} M (pH = 8.20, T = 25°C). The curves $\text{Log}([\text{NH}_2\text{Cl}]_0/[\text{NH}_2\text{Cl}]) = f(t)$ came up to be straight lines with the slope $\psi = k_{3a} [\text{C}_5\text{H}_{10}\text{NH}]_0^\beta$, indicating that $\alpha = 1$. Similarly, β was determined by the same method and under the same conditions by maintaining the concentration of **1** constant (2×10^{-3} M) and varying the concentration of **2** (10×10^{-3} to 60×10^{-3} M). The curve $\text{Log } \psi = f(\text{Log} [\text{C}_5\text{H}_{10}\text{NH}]_{0\text{all}})$ is a straight line with the slope $\beta = 1.00$ and a Y intercept = $\text{Log } k_{3a}$ ($r^2 = 0.997$). Results are shown in Table 1.

$[\text{NH}_2\text{Cl}]_0 \text{ [M]}$	$[\text{C}_5\text{H}_{10}\text{NH}]_{\text{all}} \text{ [M]}$	$\psi \text{ [s}^{-1}\text{]}$	$k_{3a} \text{ [M}^{-1} \text{ s}^{-1}\text{]}$
$2 \cdot 10^{-3}$	$10 \cdot 10^{-3}$	$5.13 \cdot 10^{-4}$	$51.3 \cdot 10^{-3}$
$2 \cdot 10^{-3}$	$20 \cdot 10^{-3}$	$1.13 \cdot 10^{-3}$	$56.6 \cdot 10^{-3}$
$2 \cdot 10^{-3}$	$30 \cdot 10^{-3}$	$1.66 \cdot 10^{-3}$	$55.5 \cdot 10^{-3}$
$2 \cdot 10^{-3}$	$40 \cdot 10^{-3}$	$2.24 \cdot 10^{-3}$	$55.9 \cdot 10^{-3}$
$2 \cdot 10^{-3}$	$60 \cdot 10^{-3}$	$3.20 \cdot 10^{-3}$	$53.3 \cdot 10^{-3}$
$1 \cdot 10^{-3}$	$20 \cdot 10^{-3}$	$1.10 \cdot 10^{-3}$	$54.2 \cdot 10^{-3}$
$3 \cdot 10^{-3}$	$20 \cdot 10^{-3}$	$1.10 \cdot 10^{-3}$	$54.7 \cdot 10^{-3}$
$4 \cdot 10^{-3}$	$20 \cdot 10^{-3}$	$1.14 \cdot 10^{-3}$	$56.8 \cdot 10^{-3}$

Table 1

The plot $\Delta[\text{NH}_2\text{Cl}] = f([\text{C}_5\text{H}_{10}\text{NCl}])$ (Figure 5) shows that the amounts ratio of chloramine consumed and chloropiperidine formed is linear and ≈ 1 , which proves that the stoichiometry of the reaction is 1:1.

Consequently, the second order rate constant, at $\text{pH} = 8.20$ and $T = 25^\circ\text{C}$, was found to be equal to $k_{3a} = 54.8 \times 10^{-3} \pm 1.84 \times 10^{-3} \text{ M}^{-1} \text{ s}^{-1}$ ($k_{3b} = 24.8 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$).

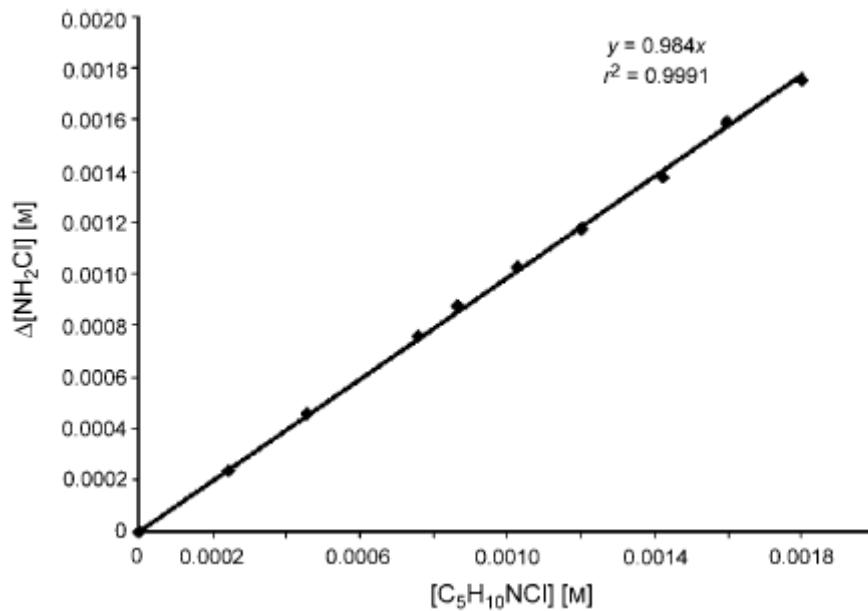


Figure 5

Influence of pH

In order to study the pH effect on the chloramine/piperidine interaction, another series of measurements was performed by using constant concentrations of **1** and **2** titrating 2×10^{-3} M and 20×10^{-3} M, respectively, and varying the pH value between 8.20 and 12.89. The observed rate constant k_{obs} corresponds to the disappearance of chloramine (**1**) against the concurrent formations of 1-chloropiperidine (**3**) by chlorine transfer and of 1-aminopiperidine by amination of 1-piperidine (**2**). The values of the observed rate constant were determined from the slopes r_0 of the curves $[\text{NH}_2\text{Cl}] = f(t)$, at $t = 0$:

$$k_{\text{obs}} = -\frac{r_0}{[\text{C}_5\text{H}_{10}\text{NH}]_{\text{all}} [\text{NH}_2\text{Cl}]_0}$$

The values of k_{obs} with respect to the pH values are summarized in Table 2.

pH	8.20	9.30	10.50	11.50	12.00	12.70	12.89
$k_{\text{obs}} [\text{M}^{-1} \text{s}^{-1}] \cdot 10^3$	54.8	55.6	57.3	59.9	60.8	61.4	61.1

Table 2

Under these conditions, the rate of the interaction of chloramine/piperidine can be expressed by the following equation:

$$-\frac{d[\text{NH}_2\text{Cl}]}{dt} = [x_2 k_{1a} + y_2 k_{3a}] [\text{NH}_2\text{Cl}] [\text{C}_5\text{H}_{10}\text{NH}]_{\text{all}}$$

where k_{1a} is the rate constant of 1-aminopiperidine formation and x_2 and y_2 are the neutral and protonated fractions of piperidine, respectively.

Hence at $t = 0$: $k_{\text{obs}} = (1-y_2) k_{1a} + y_2 k_{3a}$

Therefore, at pH = 8.20 ($y_2 \approx 1$), k_{obs} becomes identical to k_{3a} , whereas at pH = 12.89 ($y_2 \approx 0$), k_{obs} corresponds to the formation of 1-aminopiperidine (k_{1a}).

The plot $k_{\text{obs}} = f(\text{pH})$ can be determined as well from the aforementioned equation.

Influence of temperature

The temperature effect was studied at pH = 8.20 between 15 and 45°C.

Concentrations used for **1** and **2** were equal to 2×10^{-3} M and 10×10^{-3} M, respectively. The variation of k_{3a} with temperature was found to comply with the Arrhenius law. The curve $\text{Log } k_{3a} = f(1/T)$ is a straight line of slope = $-E_{3a}/R$ and Y intercept = $\text{Log } A_{3a}$ ($r^2 = 0.999$). A_{3a} and E_{3a}/R represent the Arrhenius factor and activation energy, respectively.

$$k_{3a} = 2.38 \cdot 10^9 \exp(-60.69/RT) \quad (\text{E}_{3a} \text{ in kJ mol}^{-1})$$

The enthalpy and entropy of activation can be deduced from the following formulae:

$$\Delta H_{3a}^{\circ \neq} = E_{3a} - RT \quad \Delta S_{3a}^{\circ \neq} = \text{Log}(A_{3a} h)/(e k_B T)$$

where k_B is Boltzmann's constant and h is Planck's constant ($k_B = 1.38033 \times 10^{-23}$ J K $^{-1}$, $h = 6.623 \times 10^{-34}$ J s).

The calculated values are:

$$\Delta H_{3a}^{\circ \neq} = 58.22 \text{ kJ mol}^{-1} \quad \Delta S_{3a}^{\circ \neq} = -73.59 \text{ J mol}^{-1} \text{ K}^{-1}$$

Kinetics of the dehydrohalogenation of 1-chloropiperidine in alkaline media

Reaction order and influence of temperature

Figure 6 shows the UV spectrophotometric evolution of a chloropiperidine/sodium hydroxide aqueous mixture at different times of the reaction ($[C_5H_{10}NCl]_0 = 2 \times 10^{-3}$ M, $[NaOH]_0 = 0.1$ M, $T = 25^\circ C$): a decrease in the intensity of chloropiperidine's UV absorption is occurring simultaneously to an absorption's shift to the shorter wavelengths; the isobestic point observed at 238 nm indicates that **3** and the product of its dehydrohalogenation are stoichiometrically proportional. The UV absorption spectrum registered at the end of the reaction, with a maximum at 227 nm, shows that **3** has been completely consumed. In order to identify the product resulting from the dehydrohalogenation of **3**, further experiments were carried out (see synthesis and characterization of **4**). It was proven that, in alkaline medium, **3** is converted into **4**.

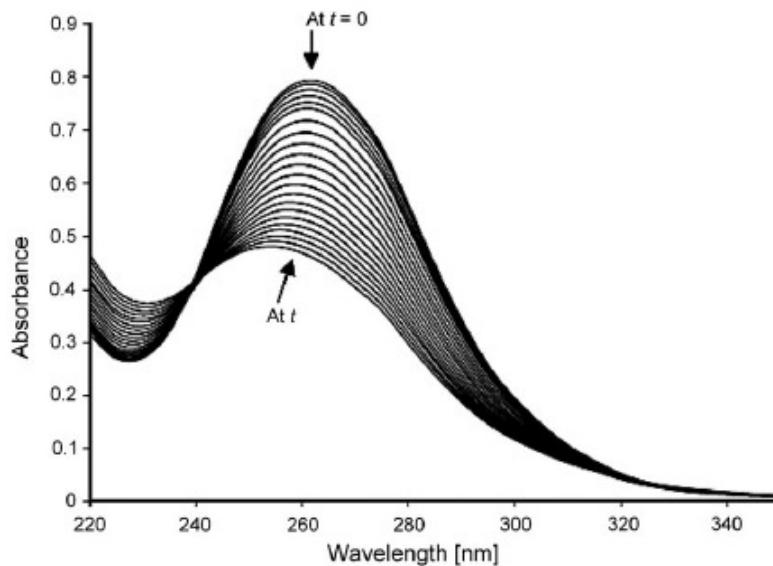


Figure 6

Experiments were conducted at 25°C with concentrations of sodium hydroxide and chloropiperidine ranging from 0.1 to 1 M and from 1×10^{-3} to 4×10^{-3} M, respectively. The kinetic parameters were determined by the Ostwald method, and the rate law can be expressed as follows:

$$r = -d[C_5H_{10}NCl]/dt = k_4 [C_5H_{10}NCl]^\alpha [OH^-]_0^\beta$$

with k_4 , α and β , respectively, are the rate constant and partial orders of the reaction.

A first series of measurements was carried out, using a constant concentration of sodium hydroxide (0.1 M) and variable concentrations of **3** ranging from 1×10^{-3} to 4×10^{-3} M (T = 25°C). The curves $\text{Log } ([C_5H_{10}NCl]_0/[C_5H_{10}NCl]) = f(t)$ came up to be straight lines with the slope $\varphi = k_4 [OH^-]_0^\beta$, indicating that $\alpha = 1$. A second series of measurements was performed at the same temperature by maintaining the concentration of **3** constant (4×10^{-3} M) and varying the concentration of sodium hydroxide from 0.1 to 1 M. The curves $\text{Log } \varphi = f(\text{Log } [OH^-]_0)$ showed to be straight lines with the slope $\beta = 1.00$ ($r^2 = 0.999$) and Y intercept = $\text{Log } k_4$. All results are summarized in Table 3.

In consequence, the rate constant of chloropiperidine's dehydrohalogenation at T = 25°C, can be expressed by the equation:

$$k_4 = \frac{-d[C_5H_{10}NCl]/dt}{[C_5H_{10}NCl][OH^-]} = 34.2 \times 10^{-6} \pm 0.64 \times 10^{-6} \text{ M}^{-1} \text{ s}^{-1}$$

$[C_5H_{10}NCl]_0 [M]$	$[NaOH]_0 [M]$	$\varphi [s^{-1}]$	$k_4 [M^{-1} s^{-1}]$
$4 \cdot 10^{-3}$	0.10	$3.37 \cdot 10^{-6}$	$33.7 \cdot 10^{-6}$
$3 \cdot 10^{-3}$	0.10	$3.42 \cdot 10^{-6}$	$34.2 \cdot 10^{-6}$
$2 \cdot 10^{-3}$	0.10	$3.51 \cdot 10^{-6}$	$35.1 \cdot 10^{-6}$
$1 \cdot 10^{-3}$	0.10	$3.45 \cdot 10^{-6}$	$34.5 \cdot 10^{-6}$
$4 \cdot 10^{-3}$	1.00	$33.7 \cdot 10^{-6}$	$33.7 \cdot 10^{-6}$
$4 \cdot 10^{-3}$	0.75	$24.97 \cdot 10^{-6}$	$33.3 \cdot 10^{-6}$
$4 \cdot 10^{-3}$	0.50	$17.50 \cdot 10^{-6}$	$35.0 \cdot 10^{-6}$
$4 \cdot 10^{-3}$	0.25	$8.52 \cdot 10^{-6}$	$34.1 \cdot 10^{-6}$

Table 3

The influence of temperature was studied between 15 and 45°C; with concentrations of **3** and NaOH equal to 2×10^{-3} M and 0.1 M, respectively. Figure 7 shows that Log $k_4 = f(1/T)$ is a straight line of slope = $-E_4/R$ and Y intercept = Log A_4 ($r^2 = 0.995$). A_4 and E_4/R represent the Arrhenius factor and activation energy of the reaction, respectively (E_4 in kJ mol⁻¹).

One deduces the following equation for the rate constant:

$$k_4 = 1.02 \cdot 10^{12} \exp(-93.45/RT) M^{-1} s^{-1}$$

and the following values for enthalpy and entropy of activation (see formulae in influence of temperature for chlorine transfer):

$$\Delta H_4^\circ \neq = 90.98 \text{ kJ mol}^{-1} \quad \Delta S_4^\circ \neq = -23.29 \text{ J K}^{-1} \text{ mol}^{-1}$$

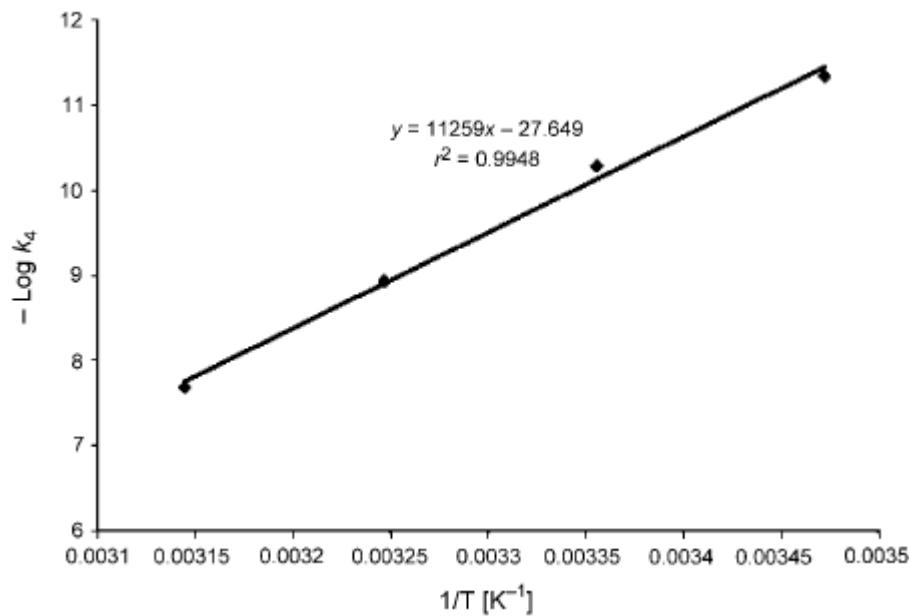
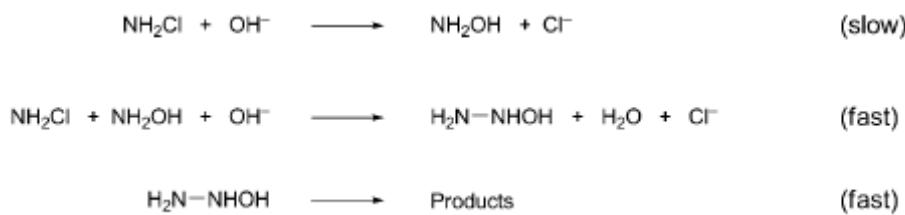


Figure 7

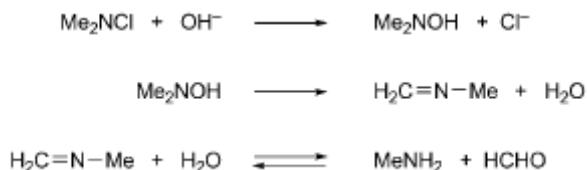
Mechanism

In order to suggest a mechanism for the dehydrohalogenation of chloropiperidine, an overview of similar chloramines' reactivity is worthy of mention. The reactivity of chloramine in alkaline medium has been the subject of previous studies [31-34]. The suggested mechanism involves the formation of hydroxylamine, which reacts with another molecule of chloramine to form an unstable hydroxylhydrazine. The latter might be oxidized into nitrite and peroxonitrite ions with $N_2(g)$ emission.



Scheme 6

As for 1,1-dimethylchloramine, the formation of 1,1-dimethylhydroxylamine may correspond to the first elementary step (S_N2) of the following reactional scheme:

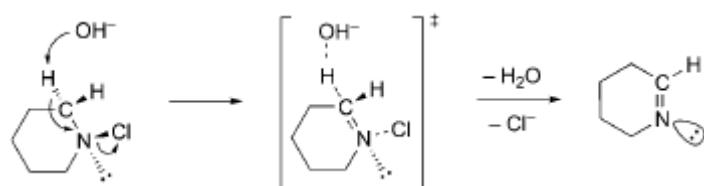


Scheme 7

To confirm the above-mentioned hypothetic scheme, a precise amount of 1,1-dimethylhydroxylamine hydrochloride (99%, Aldrich) was dissolved in alkaline medium (addition of sodium hydroxide) and the solution was analyzed by GC/MS. Neither the corresponding imino derivative nor its hydrolyzed form was detected in the chromatogram [35].

Moreover, by reacting equimolar solutions (10×10^{-3} M) of 1,1-dimethylhydroxylamine and 1,1-dimethylchloramine at $\text{pH} = 12.89$ ($T = 25^\circ\text{C}$), a gas emission was observed and new derivatives, which were not observed in the dehydrohalogenation of 1,1-dimethylchloramine, were detected [35].

These results exclude the hypothetic formation of a substituted hydroxylamine compound. Since hydroxide ions have both basic and nucleophilic properties, there exists a competition between $\text{S}_{\text{N}}2$ and E2. Furthermore, when bulky substituents are present next to the electrophilic site, they create sterical limitations for $\text{S}_{\text{N}}2$ and hence E2 becomes preponderate (Scheme 8):



Scheme 8

Experimental Part

Reagents

All reagents and salts used were reagent grade products from ALDRICH® and PROLABO RP®. Water was passed through an ion-exchange resin, and then distilled twice.

Preparation of chloramine

NH_2Cl is unstable in water, thus it was prepared extemporaneously at -10°C by reacting 25 ml of sodium hypochlorite 2 M and 20 ml of $\text{NH}_3/\text{NH}_4\text{Cl}$ aqueous solution ($[\text{NH}_4\text{Cl}] = 2.3 \text{ M}$, $[\text{NH}_3] = 3.6 \text{ M}$) in the presence of diethyl ether (40 ml). The organic layer (0.8 – 1 M of NH_2Cl) was shaken and washed several times with aliquots of distilled water. Aqueous solution of chloramine was obtained by re-extraction from the ethereal phase. Its concentration was determined by UV spectroscopy at $\lambda = 243 \text{ nm}$ ($\epsilon = 458 \text{ M}^{-1} \text{ cm}^{-1}$) [36].

Preparation of 1-chloropiperidine

1-Chloropiperidine was prepared at 0°C by reaction of 100 ml of an aqueous solution of piperidine (2.4 M) and 100 ml of sodium hypochlorite (2.25 M). The chlorination is instantaneous and gives a mixture of two phases. The upper yellow phase was distilled under 0.05 bar leading to a pure fraction of **3** at 65°C. The purity determined by DSC was of 99.84%.

Preparation of 2,3,4,5-tetrahydropyridine

2,3,4,5-Tetrahydropyridine was obtained by the dehydrohalogenation of 1-chloropiperidine in alkaline methanolic medium. It was prepared at 25°C by reacting 5 g of distilled chloropiperidine with 10 g of potassium hydroxide in 90 g of methanol. The mixture was stirred overnight and a white precipitate of potassium chloride was formed and filtered off. The filtrate was concentrated under reduced pressure then treated with an aqueous solution of hydrochloric acid (0.1 M) which resulted in the precipitation of 1.8 g (52%) of **4** that were filtered off and washed with small amounts of cold water.

Kinetic apparatus

The apparatus consisted of two thermo-stated vessels of borosilicate glass, one on the top of the other and joined by a conical fitting. The lower reactor (200 cm³) had inlets allowing the measurement of pH and temperature, and removal of aliquots for analysis. This set-up allows a quick introduction of the ampoule contents into the reactor, and hence a precise definition of the start of the reaction. A slightly reduced pressure was maintained throughout the reaction mixture, and the reactor temperature was kept constant to ± 0.1°C (thermocouple). A glass electrode (TACUSSEL TB/HS model) and a calomel reference electrode connected to a TACUSSEL ISIS 20000 pH meter were used for pH control.

Procedure and Analysis

For chlorine transfer:

Reactant solutions were prepared at the same pH, **2** was introduced into the lower reactor. The pH value was adjusted by addition of a buffer solution of potassium hydrogenophosphate. As soon as the thermal equilibrium was reached, the aqueous solution of **1** (prepared according to the above-mentioned procedure) of identical pH was added from the upper vessel.

The concentrations of chloramine consumed and chloropiperidine formed were monitored by making use of their ultraviolet absorptions ($\epsilon_{\text{NH}_2\text{Cl}} = 458 \text{ M}^{-1} \text{ cm}^{-1}$ at $\lambda = 243 \text{ nm}$ and $\epsilon_{\text{ClPP}} = 348 \text{ M}^{-1} \text{ cm}^{-1}$ at $\lambda = 261 \text{ nm}$). The reaction mixture was analyzed by UV spectrophotometry using a Cary 1E double-beam spectrophotometer.

For dehydrohalogenation:

The afore-mentioned procedure was used: **3** was introduced into the lower reactor and its disappearance with respect to time was monitored by UV spectrophotometry.

Acknowledgments

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Tables

Table 1

Table 1. Kinetics of chlorine transfer between chloramine and 1-piperidine.

Determination of partial orders and rate constants ($T = 25^\circ\text{C}$, $\text{pH} = 8.20$).

$[\text{NH}_2\text{Cl}]_0$ (M)	$[\text{C}_5\text{H}_{10}\text{NH}]_{0\text{all}}$ (M)	ψ (s $^{-1}$)	k_{3a} (M $^{-1}$ s $^{-1}$)
2×10^{-3}	10×10^{-3}	5.13×10^{-4}	51.3×10^{-3}
2×10^{-3}	20×10^{-3}	1.13×10^{-3}	56.6×10^{-3}
2×10^{-3}	30×10^{-3}	1.66×10^{-3}	55.5×10^{-3}
2×10^{-3}	40×10^{-3}	2.24×10^{-3}	55.9×10^{-3}
2×10^{-3}	60×10^{-3}	3.20×10^{-3}	53.3×10^{-3}
1×10^{-3}	20×10^{-3}	1.10×10^{-3}	54.2×10^{-3}
3×10^{-3}	20×10^{-3}	1.10×10^{-3}	54.7×10^{-3}
4×10^{-3}	20×10^{-3}	1.14×10^{-3}	56.8×10^{-3}

Table 2

Table 2. pH effect on the rate constant of the chloramine/piperidine interaction ($T = 25^\circ\text{C}$).

pH	8.20	9.30	10.50	11.50	12.00	12.70	12.89
$k_{\text{obs}} (\text{M}^{-1} \text{s}^{-1}) \times 10^3$	54.8	55.6	57.3	59.9	60.8	61.4	61.1

Table 3

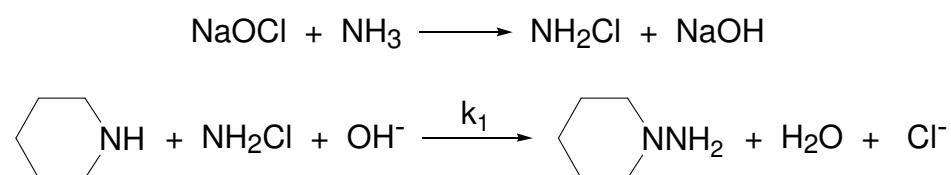
Table 3. Kinetics of dehydrohalogenation of 1-chloropiperidine in alkaline medium.

Determination of partial orders and rate constants ($T = 25^\circ\text{C}$).

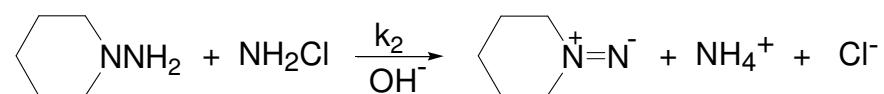
$[\text{C}_5\text{H}_{10}\text{NCl}]_0 (\text{M})$	$[\text{NaOH}]_0 (\text{M})$	$\phi (\text{s}^{-1})$	$k_4 (\text{M}^{-1} \text{s}^{-1})$
4×10^{-3}	0.10	3.37×10^{-6}	33.7×10^{-6}
3×10^{-3}	0.10	3.42×10^{-6}	34.2×10^{-6}
2×10^{-3}	0.10	3.51×10^{-6}	35.1×10^{-6}
1×10^{-3}	0.10	3.45×10^{-6}	34.5×10^{-6}
4×10^{-3}	1.00	33.7×10^{-6}	33.7×10^{-6}
4×10^{-3}	0.75	24.97×10^{-6}	33.3×10^{-6}
4×10^{-3}	0.50	17.50×10^{-6}	35.0×10^{-6}
4×10^{-3}	0.25	8.52×10^{-6}	34.1×10^{-6}

Schemes

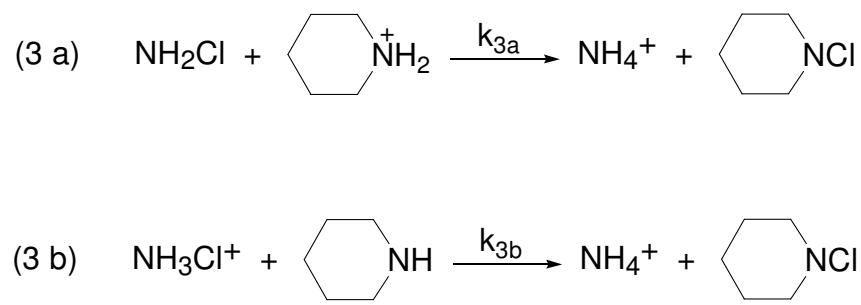
Scheme 1



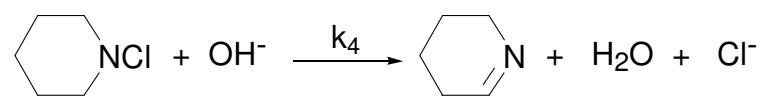
Scheme 2



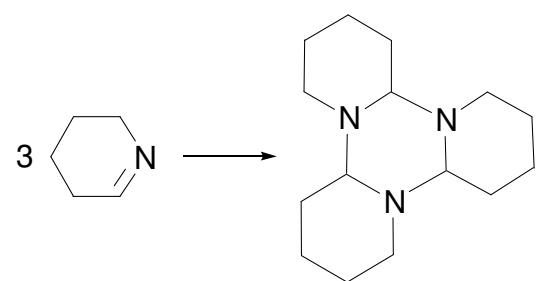
Scheme 3



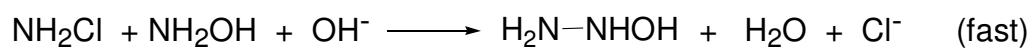
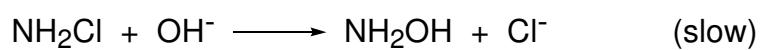
Scheme 4



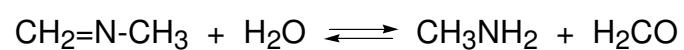
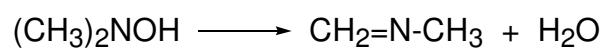
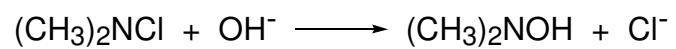
Scheme 5



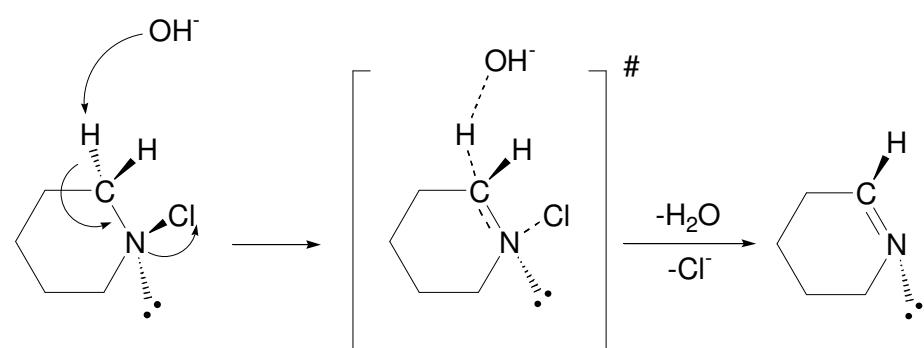
Scheme 6



Scheme 7



Scheme 8



Figures

Figure 1

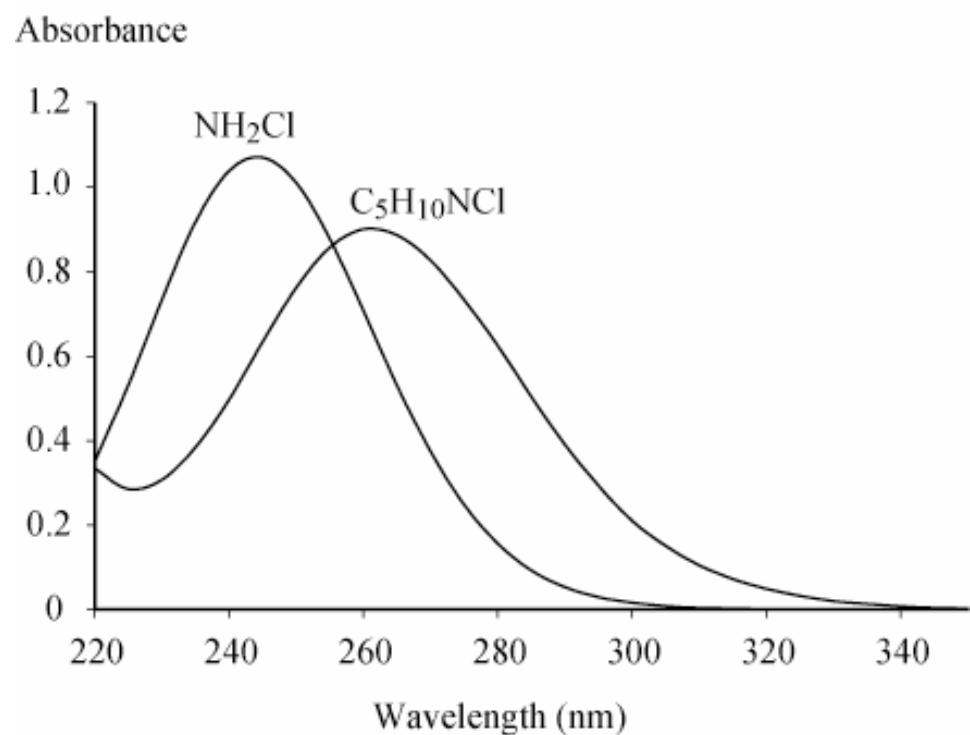


Figure 1. Superposition of UV absorption spectra of chloramine and 1-chloropiperidine in aqueous solutions ($[\text{NH}_2\text{Cl}] = 2.34 \times 10^{-3} \text{ M}$; $[\text{C}_5\text{H}_{10}\text{NCl}] = 2.60 \times 10^{-3} \text{ M}$).

Figure 2

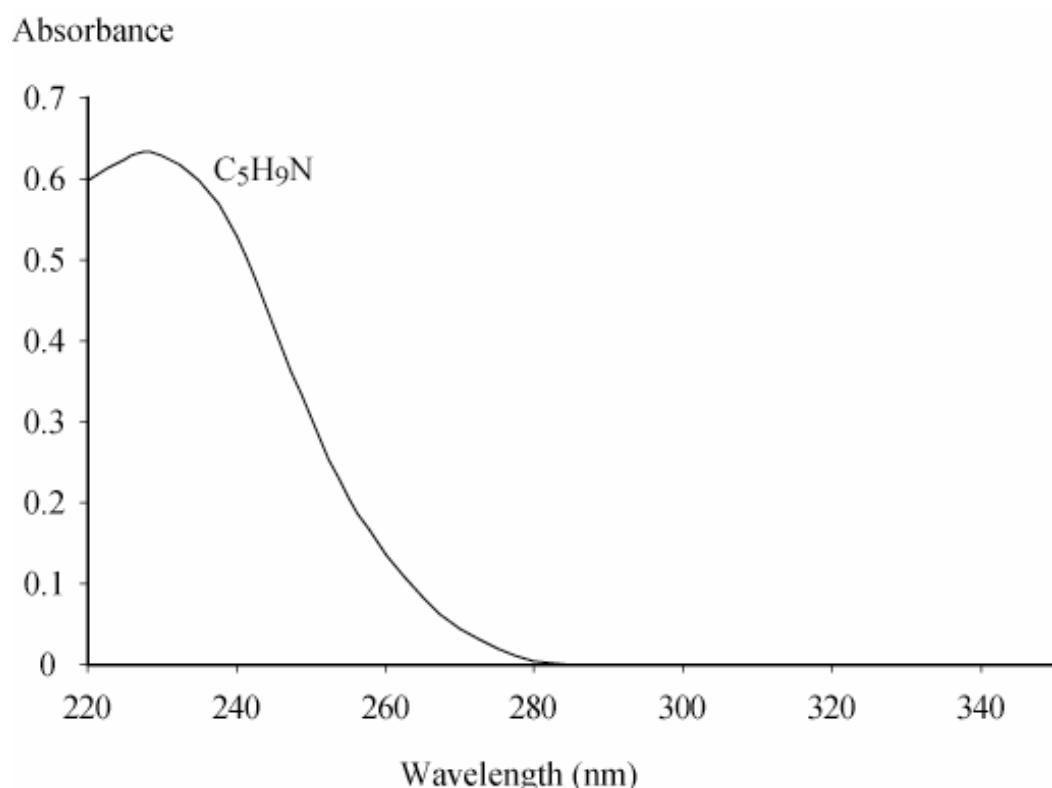


Figure 2. UV absorption spectrum of an aqueous solution of 2,3,4,5-tetrahydropyridine ($[C_5H_9N] = 3.61 \times 10^{-3}$ M).

Figure 3

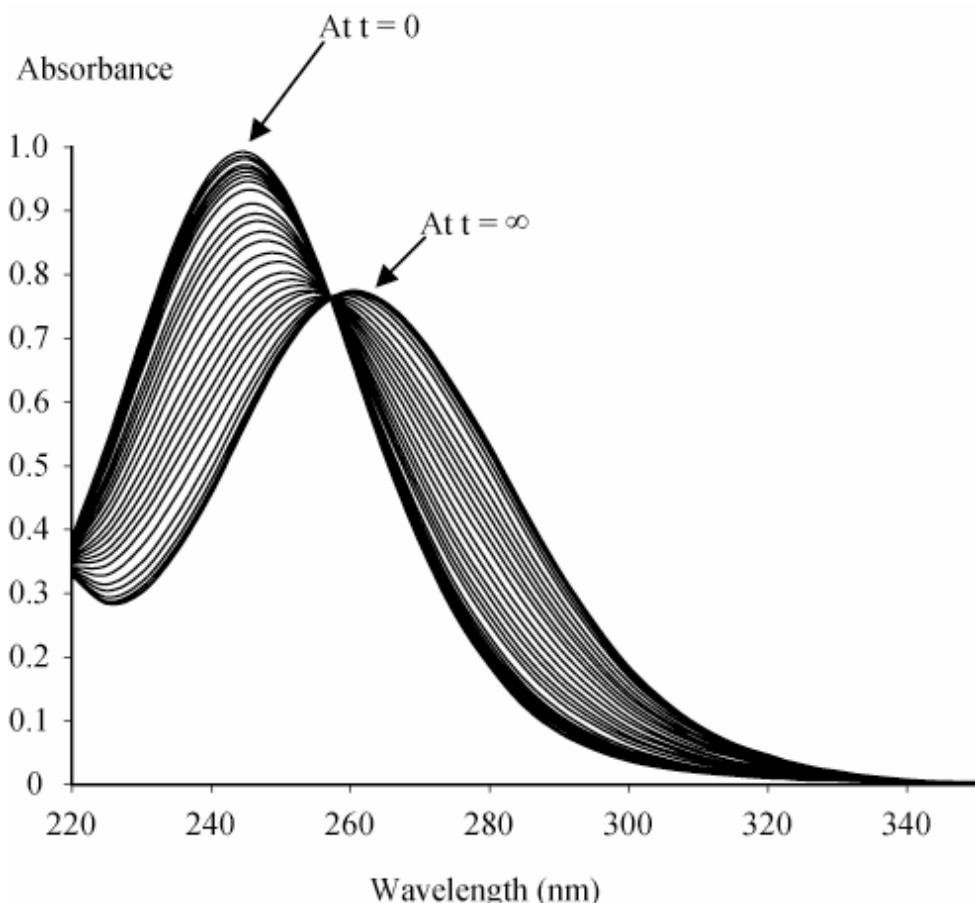


Figure 3. Kinetics of chlorine transfer: UV spectrophotometric evolution of the reaction mixture ($[C_5H_{10}NH]_0 = 10 \times 10^{-3}$ M, $[NH_2Cl]_0 = 2 \times 10^{-3}$ M, pH = 8.20, T = 25°C).

Figure 4

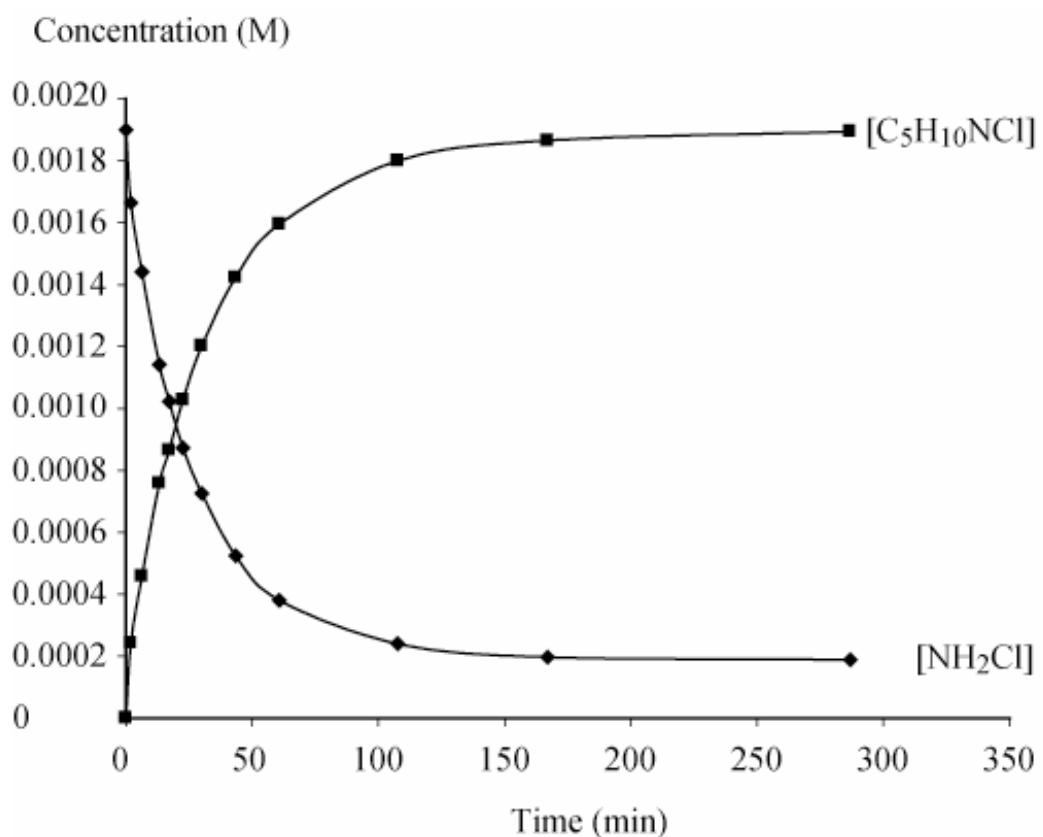


Figure 4. Evolution of the concentrations of **1** and **3** with the reaction time (initial conditions: $[C_5H_{10}NH_2^+]_0 = 10 \times 10^{-3}$ M, $[NH_2Cl]_0 = 2 \times 10^{-3}$ M, $T = 25^\circ C$, $pH = 8.25$).

Figure 5

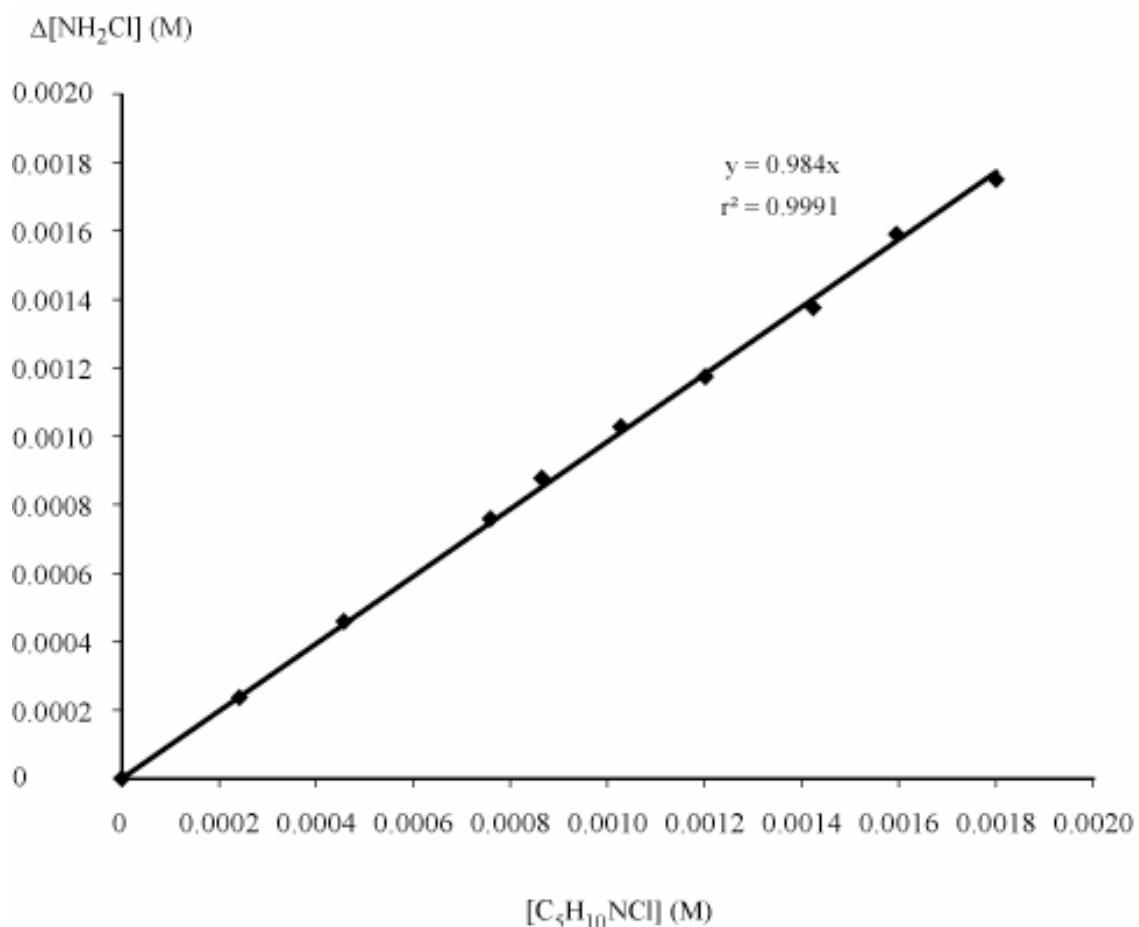


Figure 5. $\Delta[\text{NH}_2\text{Cl}] = [\text{C}_5\text{H}_{10}\text{NCl}]$ plot (experimental conditions at $t = 0$: $[\text{C}_5\text{H}_{10}\text{NH}_2^+]_0 = 10 \times 10^{-3} \text{ M}$, $[\text{NH}_2\text{Cl}]_0 = 2 \times 10^{-3} \text{ M}$, $T = 25^\circ\text{C}$, $\text{pH} = 8.25$).

Figure 6

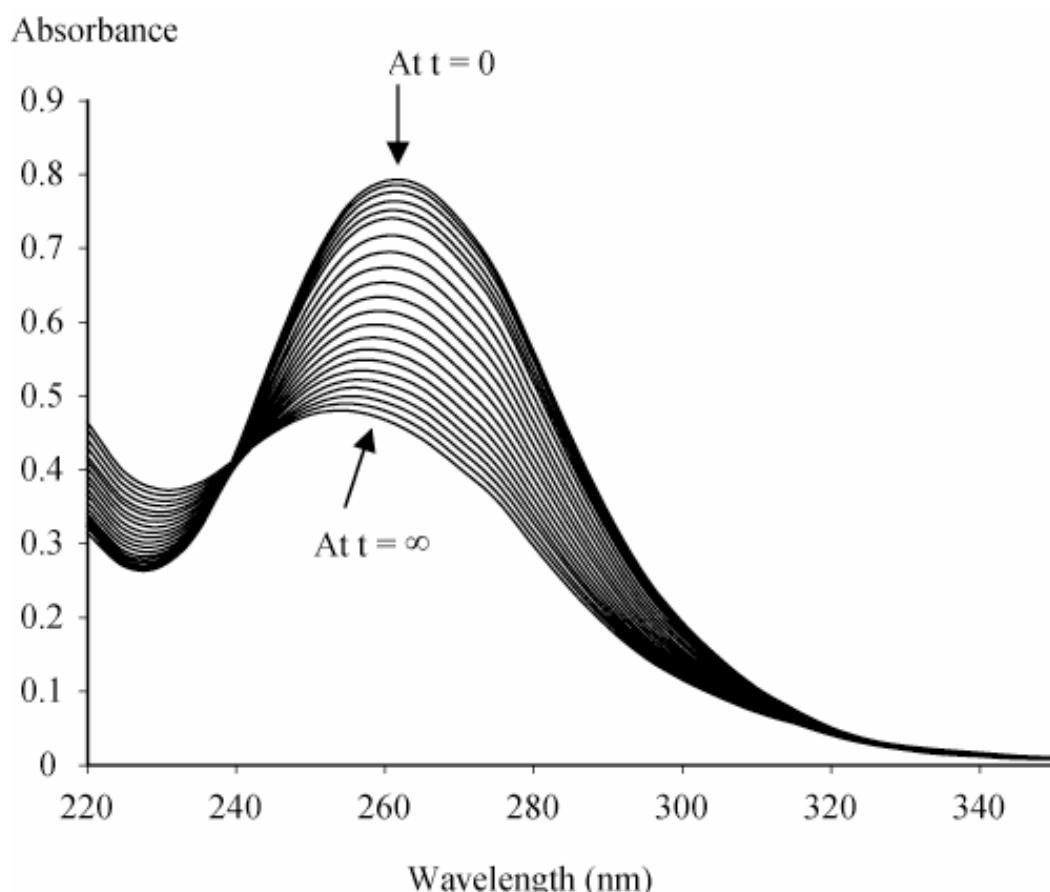


Figure 6. Kinetics of dehydrohalogenation of 1-chloropiperidine: UV spectrophotometric evolution of the reaction mixture ($[C_5H_{10}NCl]_0 = 2 \times 10^{-3}$ M, $[NaOH]_0 = 0.1$ M, $T = 25^\circ C$).

Figure 7

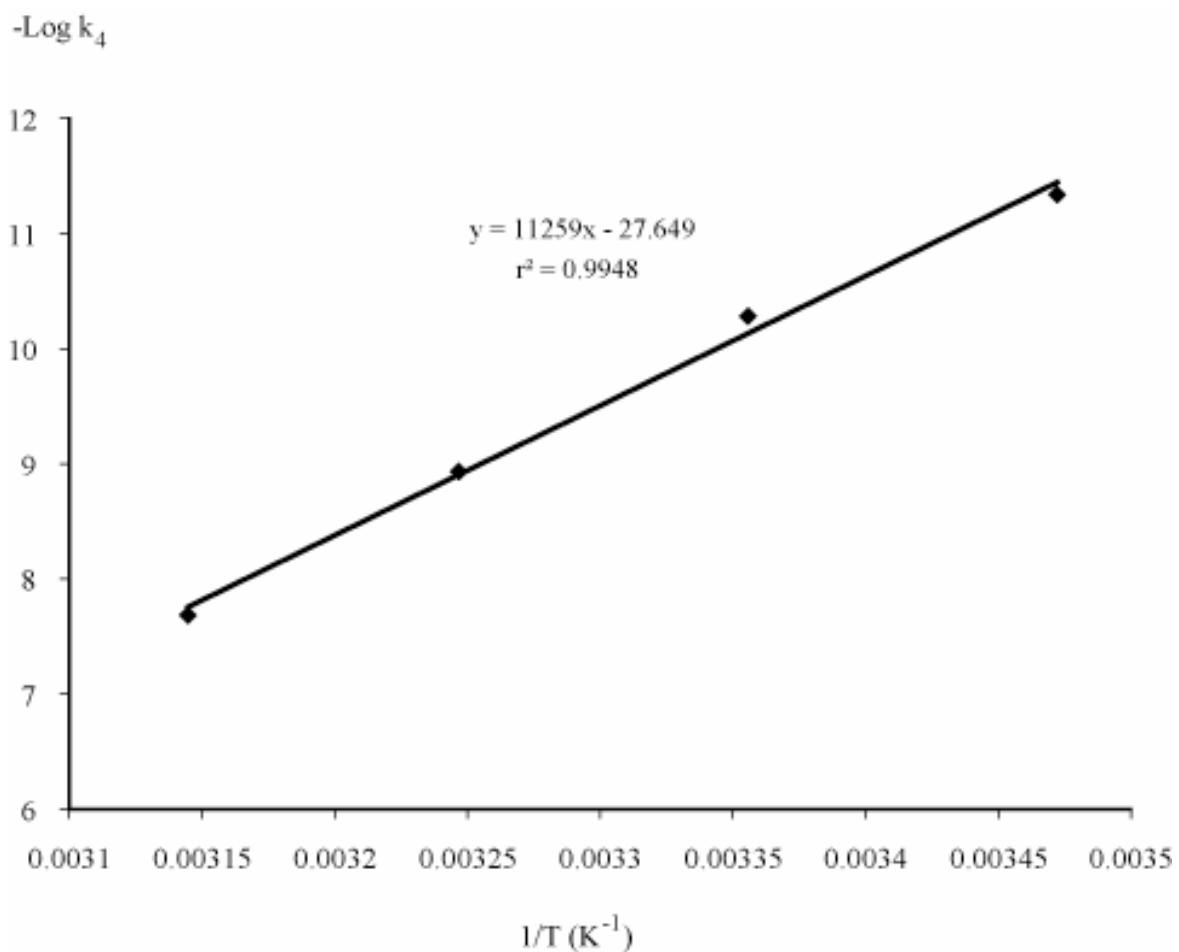


Figure 7. Kinetics of dehydrohalogenation of 1-chloropiperidine: influence of temperature ($[C_5H_{10}NCl]_0 = 2 \times 10^{-3}$ M, $[NaOH]_0 = 0.1$ M).