Chlorine-Atom Transfer Reactions between Chloramine (=Chloramide) and Piperidine: Kinetic Reactivity and Characterization in a *Raschig* Medium

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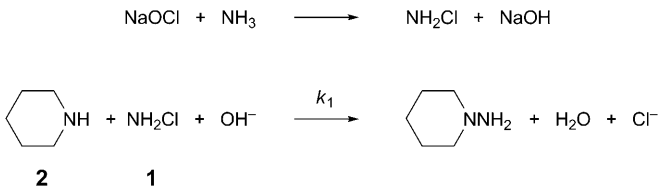
The kinetics of the Cl-transfer reaction between chloramine (**1**) and piperidine (**2**) in a *Raschig* medium ($8 < pH < 9$) was studied at various temperatures, with variable concentrations of the two reactants. The influence of the pH on the interaction of **1** and **2** was examined at a pH ranging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

1. Introduction. – This work is part of a complete study involving the preparation of an unsymmetrical substituted hydrazine – piperidin-1-amine – in an ammoniacal hypochlorite ('*Raschig*') medium, which is used in the pharmaceutical industry as a precursor of medicinal drugs.

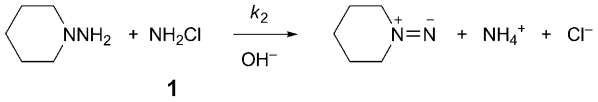
For the hydrazine preparation, *Raschig* synthesis [1–4] can be considered the most environmentally friendly route among the various syntheses described in the literature [5–25]. It is also the most suitable synthetic route for a large-scale preparation. In the case of piperidin-1-amine, *Raschig* synthesis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

However, the *Raschig* synthesis presents the major drawback of leading to numerous by-products. This behavior is particularly due to the pH-dependent reactivity of NH_2Cl (**1**), which may exhibit, depending on the pH value, an aminating (see *Scheme 1*), oxidizing (see *Scheme 2*) [26], or even chlorinating character (see below, *Scheme 3*).

Scheme 1

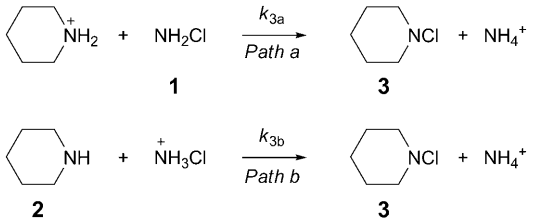


Scheme 2



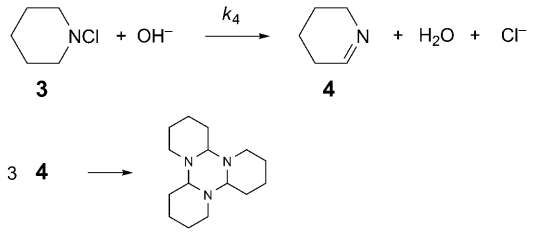
In particular, the Cl-transfer reaction (*Scheme 3*) between chloramine (=chloramide; **1**) and piperidine (**2**) is one of the principal side reactions observed during the synthesis of piperidin-1-amine in the *Raschig* process [27]. A change of orientation in the interaction of **1** and **2** is observed on acidification of the reaction medium, involving the protonation of either **2** or **1** (*Scheme 3*). In a slightly alkaline medium, the amount of piperidin-1-amine decreases in favor of 1-chloropiperidine (**3**). The latter preponderates at pH *ca.* 8. Therefore, an accidental lack in the NaOH supply of our pilot plant resulted in the formation of **3**.

Scheme 3



In an alkaline medium, 1-chloropiperidine (**3**) undergoes a dehydrohalogenation, leading to the formation of an endocyclic imine derivative, 2,3,4,5-tetrahydropyridine (**4**) (*Scheme 4*). Tetrahydropyridine **4** is likely to precipitate in monomeric, trimeric, or polymeric form. Hence, when 1-chloropiperidine molecules are surrounded by NaOH

Scheme 4



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 of piperidin-1-amine and lead to the precipitation of by-products, which are difficult to separate during the continuous extraction of piperidin-1-amine [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 the Cl-transfer reaction (*Scheme 3*) and the dehydrohalogenation reaction (*Scheme 4*) as well as on the efficient syntheses of **3** and **4** and their characterization by several analytical and thermochemical techniques.

2. Results and Discussion. – 2.1. *Characterization of 1-Chloropiperidine* (**3**). The UV-absorption parameters of **3** ($\varepsilon = f(\lambda)$) were determined by calibration, with a series of solutions of different concentrations ($1 \cdot 10^{-3}$, $2 \cdot 10^{-3}$, $4 \cdot 10^{-3}$, and $6 \cdot 10^{-3}$ M) prepared from freshly distilled **3** diluted in H_2O. The solutions were titrated by iodometry [28]. *Fig. 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 NaOH, the absorption parameters obtained were identical to those determined in H_2O. UV: (λ in nm (ε in $M^{-1} \cdot cm^{-1}$)): 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). The IR-absorptions (KBr; in cm^{-1}) 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*), and N–Cl (881*w*, 864*w*, 823*w*, 679*s*, 513*m*). ^{1}H-NMR ((D$_6$)DMSO, 400.18 MHz, 25°; δ in ppm rel. to Me_4Si): 3.40 (*m*, 2 H–C(2), 2 H–C(6)); 1.67 (*m*, 2 H–C(3), 2 H–C(5)); 1.40 (*m*, 2 H–C(4)); many ^{1}H,^{1}H couplings were observed, however, it was not possible to determine the corresponding coupling constants. ^{13}C{^{1}H}-NMR ((D$_6$)DMSO, 100.63 MHz, 25°; δ in ppm rel. to Me_4Si): 63.7 (C(2), C(6)); 27.4 (C(3), C(5)); 22.7 (C(4)). EI-MS (70 eV; in *m*/*z* (rel. %)): 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 results of the elemental analysis corroborate the purity grade of **3** determined by differential scanning calorimetry (DSC). Anal. calc. for $C_5H_{10}ClN$: C 50.21, H 8.43, Cl 29.64, N 11.71; found: C 50.17, H 8.38, Cl 29.51, N 11.84.

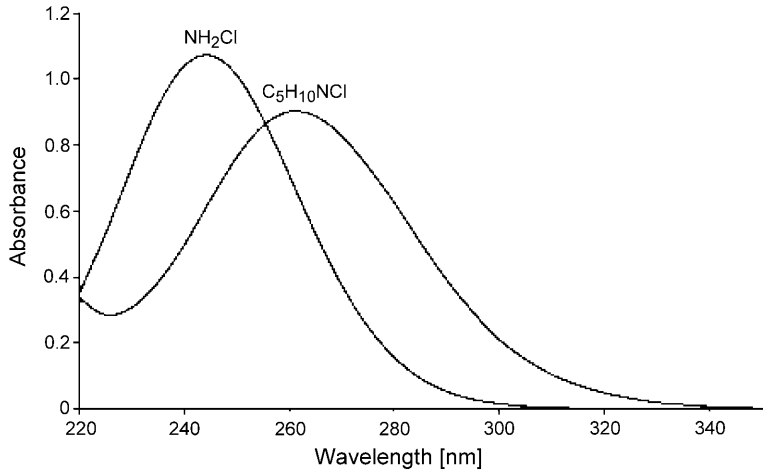


Fig. 1. *Superposition of UV absorption spectra of chloramine* (**1**) *and 1-chloropiperidine* (**3**) *in aqueous solutions.* $[NH_2Cl] = 2.34 \cdot 10^{-3}$ M, $[C_5H_{10}NCl] = 2.60 \cdot 10^{-3}$ M.

The molar purity and the melting parameters of **3** were determined in a first DSC experiment by cooling a sample of freshly distilled **3** from 0 to $-100°$ (cooling rate = 5°/min): purity = $98.95 \pm 403.74 \cdot 10^{-6}$ mol-% or 99.84%, and m.p. $-59.03°$ (ΔH(melting) = 8.68 kJ/mol). A second experiment was carried out to determine the thermal stability by heating **3** from -30 up to 250° with a heating rate of 5°/min. The decomposition of **3** started at *ca.* 125°, became more and more violent and reached its apogee at *ca.* 140°. The heat of decomposition released, ΔH(dec.), was evaluated to *ca.* 31.55 kJ/mol.

2.2. *Characterization of 2,3,4,5-Tetrahydropyridine* (**4**). Imino groups have UV absorption maxima at *ca.* 225 nm (*Fig. 2*); the absorption parameters of **4** ($\varepsilon = f(\lambda)$) were determined by calibration with a series of solutions of different concentrations ($1 \cdot 10^{-3}$, $2 \cdot 10^{-3}$, $3 \cdot 10^{-3}$, and $4 \cdot 10^{-3}$ M) prepared by dissolving a small amount of **4** in 2 ml of Et_2O and diluting in 100 ml of H_2O. The UV reference cell contained 2 ml of Et_2O diluted in 100 ml of H_2O. UV: (λ in nm (ε in $M^{-1} \cdot cm^{-1}$)): 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).

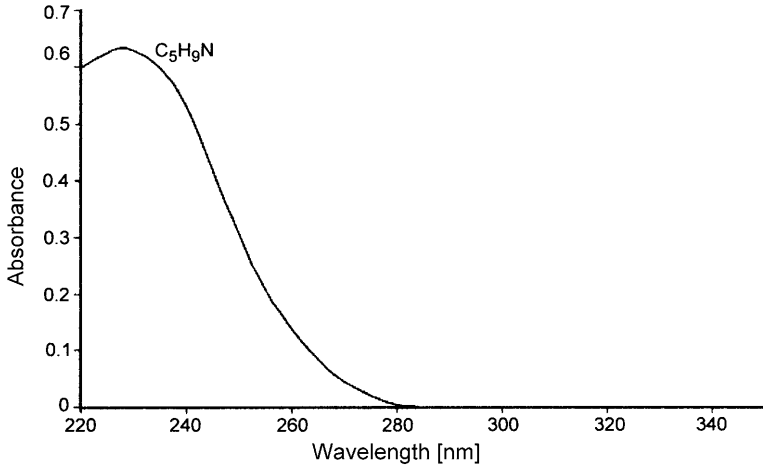


Fig. 2. *UV Absorption spectrum of an aqueous solution of 2,3,4,5-tetrahydropyridine* (**4**). $[C_5H_9N] = 3.61 \cdot 10^{-3}$ M.

Similar IR absorptions (KBr; in cm^{-1}) to those observed for **3** are found for C–H (2958*s*, 2923*s*, 2846*m*, 2807*m*), C–N (1372*s*, 1303*m*, 1238*m*), and C–C (1108*m*, 1022*m*, 1031*m*, 667*m*, 507*m*), besides a weak absorption for C=N (1653). Due to the equilibrium between the monomer, dimer, and trimer form of **4**, the ^{1}H- 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 (D_6)DMSO 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 H_2O, the concentration was too low to detect peaks. ^{1}H-NMR ((D_6)DMSO, 400.18 MHz, 25°; Me_4Si): mixture of *m*. ^{13}C{^{1}H}-NMR ((D_6)DMSO, 100.63 MHz, 25°; Me_4Si): many peaks. EI-MS (70 eV; in *m*/*z* (rel. %)): 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). The MS data show that **4** may exist in its dimer (*m*/*z* 166) or even trimer form (*m*/*z* 249) (see *Scheme 4*), which explains the weak IR 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 H_2O, it is hydrolyzed into its monomer form. Anal. calc. for C_5H_9N: C 72.24, H 10.91, N 16.85; found: C 71.03, H 10.52, N 17.48.

By heating a sample (6.06 mg) of **4** from -20 and to 250° (heating rate 5°/min), a sharp peak was observed at *ca.* 60°, which corresponds to the melting point of **4**, followed by a decomposition starting at

ca. 120° and reaching its highest stage at 167°. From the melting phase, it was possible to determine the molar purity and melting parameters of **4**: purity = $98.19 \pm 26.29 \cdot 10^{-3}$ mol-% or 99.60%, and m.p. 60.50° (ΔH(melting) = 7.07 kJ/mol).

2.3. *Kinetics of the Cl-Transfer Reaction between Chloramine* (**1**; NH_2Cl) *and Piperidine* (**2**; $C_5H_{10}NH$). 2.3.1. *Reaction Order and Stoichiometry.* At $8 < pH < 9$, 1-chloropiperidine (**3**) becomes the exclusive product of the interaction of **1** and **2**. Therefore, to measure the rate constant with the utmost precision, experiments were conducted at 25° and pH *ca.* 8. *Fig. 3* shows the UV spectrophotometric evolution of a **1**/**2** mixture in H_2O at different times of the reaction ($[C_5H_{10}NH]_0 = 10 \cdot 10^{-3}$ M, $[NH_2Cl]_0 = 2 \cdot 10^{-3}$ M, pH 8.20, and *T* 25°). While the UV absorption of **1** decreased at 243 nm, the one of **3** increased simultaneously creating an isosbestic point at 257 nm, which can be expressed by *Eqn. 1*.

$$[NH_2Cl]_0 - [NH_2Cl] = [C_5H_{10}NCl] \quad (1)$$

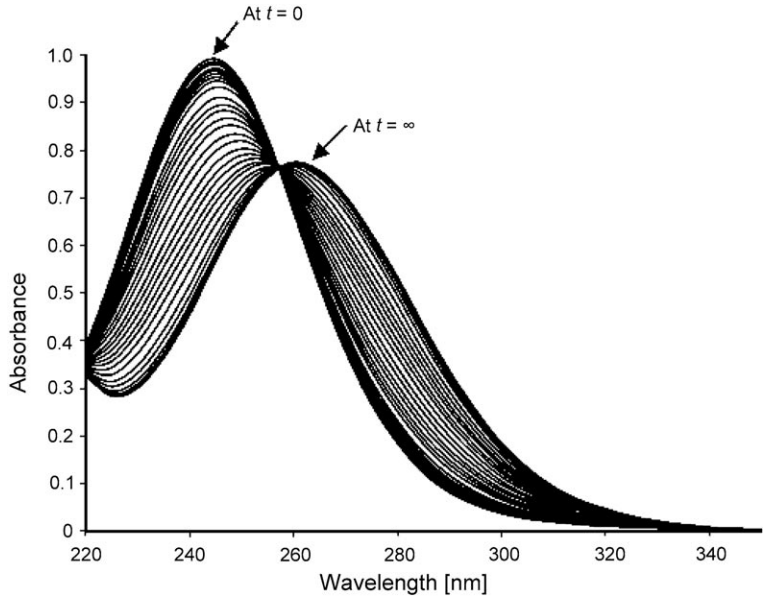


Fig. 3. *Kinetics of Cl-transfer: UV spectrophotometric evolution of the reaction mixture.* $[C_5H_{10}NH]_0 = 10 \cdot 10^{-3}$ M, $[NH_2Cl]_0 = 2 \cdot 10^{-3}$ M, pH 8.20, *T* 25°.

Since an overlap of the UV absorption spectra of chloramine (**1**) and chloropiperidine (**3**) is observed (see *Fig. 1*), we chose to work at two wavelengths (λ_1 243 nm and λ_2 280 nm), at which absorbencies can be expressed by *Eqns. 2* and *3* ($l = 1.00$ cm). Instantaneous concentrations of **1** and **3** (*Fig. 4*) are then given by *Eqns. 4* and *5*, where $\varepsilon^{\lambda_1=243}_{NH_2Cl} = 458$, $\varepsilon^{\lambda_1=243}_{C_5H_{10}NCl} = 224$, $\varepsilon^{\lambda_2=280}_{NH_2Cl} = 62$, and $\varepsilon^{\lambda_2=280}_{C_5H_{10}NCl} = 239$ M^{-1} cm^{-1}.

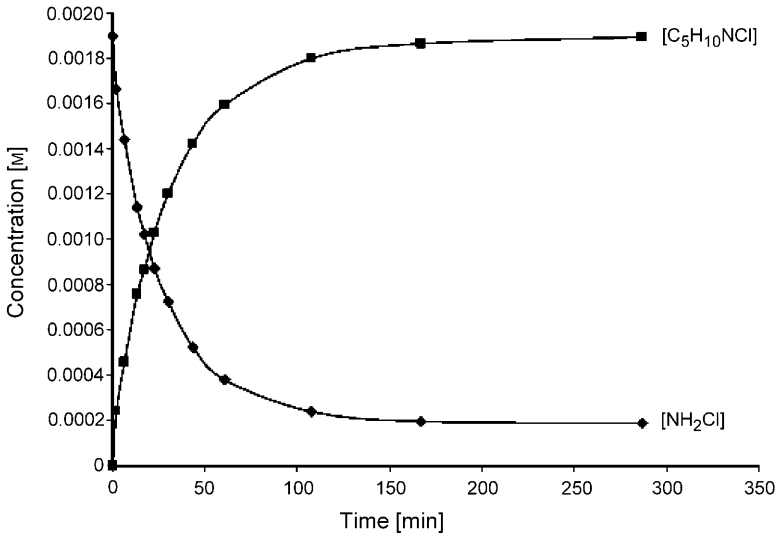


Fig. 4. *Evolution of the concentrations of* **1** *and* **3** *with the reaction time.* Initial conditions: $[C_5H_{10}NH_2^+]_0 = 10 \cdot 10^{-3}$ M, $[NH_2Cl]_0 = 2 \cdot 10^{-3}$ M, T 25°, pH 8.25.

$$D(\lambda_1) = \varepsilon^{\lambda_1}_{NH_2Cl}[NH_2Cl] + \varepsilon^{\lambda_1}_{C_5H_{10}NCl}[C_5H_{10}NCl] \quad (2)$$

$$D(\lambda_2) = \varepsilon^{\lambda_2}_{NH_2Cl}[NH_2Cl] + \varepsilon^{\lambda_2}_{C_5H_{10}NCl}[C_5H_{10}NCl] \quad (3)$$

$$[NH_2Cl] = \frac{[\varepsilon^{\lambda_2}_{C_5H_{10}NCl}D(\lambda_1,t) - \varepsilon^{\lambda_1}_{C_5H_{10}NCl}D(\lambda_2,t)]}{\varepsilon^{\lambda_1}_{NH_2Cl}\varepsilon^{\lambda_2}_{C_5H_{10}NCl} - \varepsilon^{\lambda_2}_{NH_2Cl}\varepsilon^{\lambda_1}_{C_5H_{10}NCl}} \quad (4)$$

$$[C_5H_{10}NCl] = \frac{[\varepsilon^{\lambda_1}_{NH_2Cl}D(\lambda_2,t) - \varepsilon^{\lambda_2}_{NH_2Cl}D(\lambda_1,t)]}{\varepsilon^{\lambda_1}_{NH_2Cl}\varepsilon^{\lambda_2}_{C_5H_{10}NCl} - \varepsilon^{\lambda_2}_{NH_2Cl}\varepsilon^{\lambda_1}_{C_5H_{10}NCl}} \quad (5)$$

To represent the Cl-transfer in the **2**/**1** interaction, two reactions to give **3** are plausible, *Path a* and *Path b* in *Scheme 3*. The rate law can thus be expressed by *Eqn. 6*, with k_{3a} (or k_{3b}) and α and β being the rate constant and partial orders of the reaction, respectively. Taking the acid-dissociation equilibrium of **1** and **2** into account, this leads to *Eqns. 7* and *8*. Hence *Eqn. 6* becomes *Eqn. 9*.

$$r = d[C_5H_{10}NCl]/dt = k_{3a}\,[NH_2Cl]^{\alpha}\,[C_5H_{10}NH_2^+]^{\beta} = k_{3b}\,[NH_3Cl^+]^{\alpha}\,[C_5H_{10}NH]^{\beta} \quad (6)$$

$$[NH_2Cl] = x_{\mathbf{1}}\,[NH_2Cl]_{all} \qquad [NH_3Cl^+] = y_{\mathbf{1}}\,[NH_2Cl]_{all} \quad (7)$$

$$[C_5H_{10}NH] = x_{\mathbf{2}}\,[C_5H_{10}NH]_{all} \qquad [C_5H_{10}NH_2^+] = y_{\mathbf{2}}\,[C_5H_{10}NH]_{all} \quad (8)$$

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

$$x_{\mathbf{1}} = \frac{K_a^{NH_3Cl^+}}{[H^+] + K_a^{NH_3Cl^+}};\ y_{\mathbf{1}} = 1 - x_{\mathbf{1}};\ x_{\mathbf{2}} = \frac{K_a^{C_5H_{10}NH_2^+}}{[H^+] + K_a^{C_5H_{10}NH_2^+}};\ y_{\mathbf{2}} = 1 - x_{\mathbf{2}}$$

$$\begin{aligned} r &= k_{3a}\,[NH_2Cl]^{\alpha}[C_5H_{10}NH_2^+]^{\beta} = k_{3b}\,[NH_3Cl^+]^{\alpha}[C_5H_{10}NH]^{\beta} \\ &= \chi\,[NH_2Cl]_{all}^{\alpha}[C_5H_{10}NH]_{all}^{\beta} \end{aligned} \tag{9}$$

with $\chi = k_{3a}\,x_{\mathbf{1}}\,y_{\mathbf{2}} = k_{3b}\,x_{\mathbf{2}}\,y_{\mathbf{1}}$ and $k_{3b} = k_{3a}\,\dfrac{K_a^{NH_3Cl^+}}{K_a^{C_5H_{10}NH_2^+}}$

Furthermore, according to the acid-ionization constant K_a values of the two reactants **1** and **2** ($K_a^{NH_3Cl^+} = 3.41 \cdot 10^{-2}$ M [29] and $K_a^{C_5H_{10}NH_2^+} = 7.53 \cdot 10^{-12}$ M [30]), at pH 8.20, the neutral and protonated species have the following percentages: for **1**, *ca.* 100% NH_2Cl and $0.18 \cdot 10^{-4}$% NH_3Cl^+, and for **2**, 99.88% $C_5H_{10}NH_2^+$ and 0.12% $C_5H_{10}NH$.

Therefore, at this pH value, *Path a* is the preferred reaction (*Scheme 3*). As the kinetic parameters were determined by the *Ostwald* method, the corresponding rate law is given by *Eqn. 10*.

$$r = k_{3a}\,[NH_2Cl]^{\alpha}\,[C_5H_{10}NH]_0{}^{\beta}{}_{all}\ ([C_5H_{10}NH_2^+]_0 \approx [C_5H_{10}NH]_{0all}) \tag{10}$$

To evaluate the partial order α, a series of three measurements was carried out, with a constant concentration of **2** ($20 \cdot 10^{-3}$ M) and chloramine (**1**) concentrations ranging from $1 \cdot 10^{-3}$ to $4 \cdot 10^{-3}$ M (pH 8.20, *T* 25°). The curves Log $([NH_2Cl]_0/[NH_2Cl]) = f(t)$ came up to be straight lines with the slope $\psi = k_{3a}\,[C_5H_{10}NH]_0{}^{\beta}{}_{all}$, indicating that $\alpha = 1$. Similarly, β was determined by the same method and under the same conditions by maintaining the concentration of **1** constant ($2 \cdot 10^{-3}$ M) and varying the concentration of **2** ($10 \cdot 10^{-3}$ to $60 \cdot 10^{-3}$ M). The curve Log $\psi = f(\text{Log}\ [C_5H_{10}NH]_{0all})$ was also a straight line with the slope $\beta = 1.00$ and a *Y* intercept = Log k_{3a} ($r^2 = 0.997$). Results are shown in *Table 1*.

Table 1. *Kinetics of Cl-Transfer between Chloramine* (**1**) *and Piperidine* (**2**)*: Determination of Partial Orders* α *and* β *and Rate Constants. T* 25°, pH 8.20.

$[NH_2Cl]_0$ [M]	$[C_5H_{10}NH]_{0all}$ [M]	ψ [s^{-1}]	k_{3a} [$M^{-1}\,s^{-1}$]
$2 \cdot 10^{-3}$	$10 \cdot 10^{-3}$	$5.13 \cdot 10^{-4}$	$51.3 \cdot 10^{-3}$
$2 \cdot 10^{-3}$	$20 \cdot 10^{-3}$	$1.13 \cdot 10^{-3}$	$56.6 \cdot 10^{-3}$
$2 \cdot 10^{-3}$	$30 \cdot 10^{-3}$	$1.66 \cdot 10^{-3}$	$55.5 \cdot 10^{-3}$
$2 \cdot 10^{-3}$	$40 \cdot 10^{-3}$	$2.24 \cdot 10^{-3}$	$55.9 \cdot 10^{-3}$
$2 \cdot 10^{-3}$	$60 \cdot 10^{-3}$	$3.20 \cdot 10^{-3}$	$53.3 \cdot 10^{-3}$
$1 \cdot 10^{-3}$	$20 \cdot 10^{-3}$	$1.10 \cdot 10^{-3}$	$54.2 \cdot 10^{-3}$
$3 \cdot 10^{-3}$	$20 \cdot 10^{-3}$	$1.10 \cdot 10^{-3}$	$54.7 \cdot 10^{-3}$
$4 \cdot 10^{-3}$	$20 \cdot 10^{-3}$	$1.14 \cdot 10^{-3}$	$56.8 \cdot 10^{-3}$

The plot $\Delta[NH_2Cl] = f([C_5H_{10}NCl])$ (*Fig. 5*) shows that the amounts ratio of chloramine consumed and chloropiperidine formed is linear and *ca.* 1, which establishes

that the stoichiometry of the reaction is 1:1. Consequently, the second-order rate constant, at pH 8.20 and T 25°, was found to be equal to $k_{3a} = 54.8 \cdot 10^{-3} \pm 1.8 \cdot 10^{-3}$ M^{-1} s^{-1} ($k_{3b} = 24.8 \cdot 10^{7}$ M^{-1} s^{-1}).

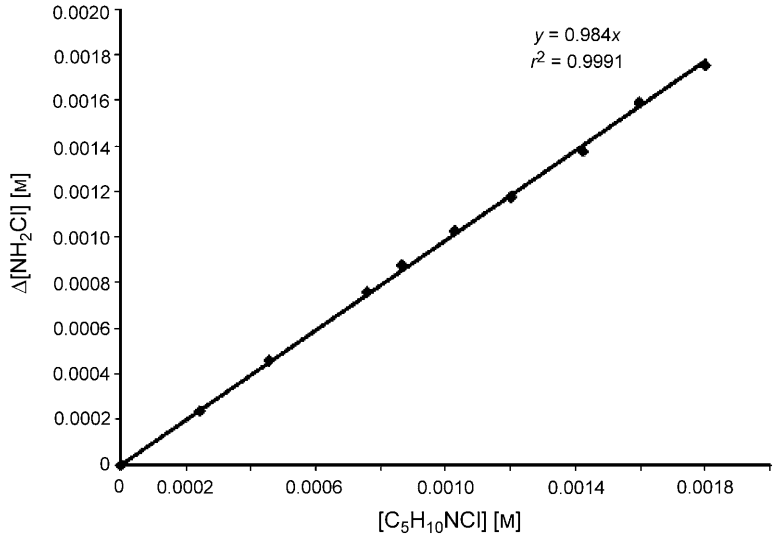


Fig. 5. *Δ[NH$_2$Cl] vs. [C$_5$H$_{10}$NCl] Plot*. Exper. conditions at $t = 0$: $[C_5H_{10}NH_2^+]_0 = 10 \cdot 10^{-3}$ M, $[NH_2Cl]_0 = 2 \cdot 10^{-3}$ M, T 25°, pH 8.25.

2.3.2. *Influence of pH.* To study the pH effect on the chloramine (**1**)/piperidine (**2**) interaction, another series of measurements was performed, with constant concentrations of **1** and **2** titrating $2 \cdot 10^{-3}$ M and $20 \cdot 10^{-3}$ 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 Cl-transfer and of piperidin-1-amine by *N*-amination of piperidine (**2**). The values of the observed rate constant were determined from the slopes r_0 of the curves $[NH_2Cl] = f(t)$, at $t = 0$ (*Eqn. 11*). The values of k_{obs} with respect to the pH values are summarized in *Table 2*.

$$k_{obs} = -\frac{r_0}{[C_5H_{10}NH]_{0\,all}[NH_2Cl]_0} \tag{11}$$

Table 2. *pH Effect on the Rate Constant of the Chloramine* (**1**)*/Piperidine* (**2**) *Interaction. T* 25°.

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

Under these conditions, the rate of the interaction of **1** and **2** can be expressed by *Eqn. 12*, where k_{1a} is the rate constant of piperidin-1-amine formation, and x_2 and y_2 are

the neutral and protonated fractions of piperidine, respectively. Hence, at $t=0$ *Eqn. 13* holds. 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 piperidin-1-amine (k_{1a}). The plot $k_{obs} = f(\mathrm{pH})$ can be determined as well from *Eqn. 13*.

$$-\mathrm{d}[NH_2Cl]/\mathrm{d}t = [x_2 k_{1a} + y_2 k_{3a}] \cdot [NH_2Cl] \cdot [C_5H_{10}NH]_{all} \quad (12)$$

$$k_{obs} = (1 - y_2)\, k_{1a} + y_2\, k_{3a} \quad (13)$$

2.3.3. *Influence of Temperature.* The temperature effect was studied at pH 8.20 between 15 and 45°. Concentrations used for **1** and **2** were equal to $2 \cdot 10^{-3}$ M and $10 \cdot 10^{-3}$ M, respectively. The variation of k_{3a} with temperature was found to comply with the *Arrhenius* law (*Eqn. 14*). The curve Log $k_{3a} = f(1/T)$ is a straight line of slope $= -E_{3a}/R$ and Y intercept $=$ Log A_{3a} ($r^2 = 0.999$). A_{3a} and E_{3a}/R represent the *Arrhenius* factor and activation energy, respectively. The enthalpy and entropy of activation can be deduced from the *Eqns. 15* and *16*, where k_B is *Boltzmann*'s constant and h is *Planck*'s constant ($k_B = 1.38033 \cdot 10^{-23}$ J K^{-1} and $h = 6.623 \cdot 10^{-23}$ J s). The calculated values are: $\Delta H^{\circ\ddagger}_{3a} = 58.22$ kJ mol^{-1} and $\Delta S^{\circ\ddagger}_{3a} = -73.59$ J mol^{-1} K^{-1}.

$$k_{3a} = 2.38 \cdot 10^9 \exp(-60.69/RT)\ (E_{3a} \text{ in kJ mol}^{-1}) \quad (14)$$

$$\Delta H^{\circ\ddagger}_{3a} = E_{3a} - RT \quad (15)$$

$$\Delta S^{\circ\ddagger}_{3a} = \mathrm{Log}\ (A_{3a}\, h)/(\mathrm{e}\ k_B\ T) \quad (16)$$

2.4. *Kinetics of the Dehydrohalogenation of 1-Chloropiperidine* (**3**) *in Alkaline Media.* 2.4.1. *Reaction Order and Influence of Temperature. Fig. 6* shows the UV spectrophotometric evolution of a 1-chloropiperidine (**3**)/NaOH mixture in H_2O at different times of the reaction ($[C_5H_{10}NCl]_0 = 2 \cdot 10^{-3}$ M, $[NaOH]_0 = 0.1$M, T 25°): a decrease in the intensity of the UV absorption of **3** is occurring simultaneously to an absorption shift to the shorter wavelengths; the isosbestic 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. To identify the product resulting from the dehydrohalogenation of **3**, further experiments were carried out (see synthesis (*Exper. Part*) and characterization (*Sect. 2.2*) of **4**). It was established that, in alkaline medium, **3** was converted into **4**.

Experiments were conducted at 25° with concentrations of NaOH and **3** ranging from 0.1 to 1M and from $1 \cdot 10^{-3}$ to $4 \cdot 10^{-3}$ M, respectively. The kinetic parameters were determined by the *Ostwald* method, and the rate law can be expressed by *Eqn. 17*, with k_4 and α and β being the rate constant and partial orders of the reaction, respectively.

$$r = -\mathrm{d}[C_5H_{10}NCl]/\mathrm{d}t = k_4\, [C_5H_{10}NCl]^{\alpha}\, [OH^-]_0^{\beta} \quad (17)$$

A first series of measurements was carried out, using a constant concentration of NaOH (0.1M) and variable concentrations of **3** ranging from $1 \cdot 10^{-3}$ to $4 \cdot 10^{-3}$ M (T

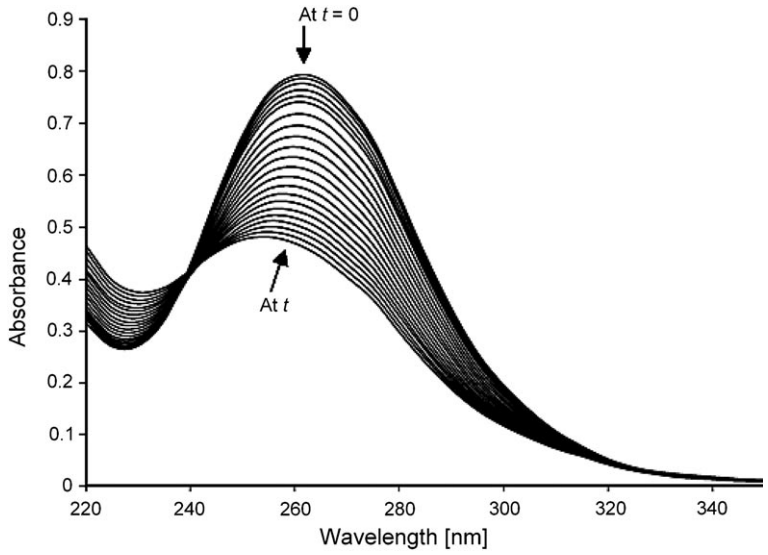


Fig. 6. *Kinetics of dehydrohalogenation of 1-chloropiperidine* (**3**): *UV spectrophotometric evolution of the reaction mixture.* $[C_5H_{10}NCl]_0 = 2 \cdot 10^{-3}$ M, $[NaOH]_0 = 0.1$M, *T* 25°.

25°). The curves 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 ($4 \cdot 10^{-3}$ M) and varying the concentration of NaOH from 0.1 to 1M. The curves Log $\varphi =$ f(Log $[OH^-]_0$) were straight lines with the slope $\beta = 1.00$ ($r^2 = 0.999$) and Y intercept = Log k_4. All results are summarized in *Table 3*. In consequence of this, the rate constant of the dehydrohalogenation of **3** at *T* 25° can be expressed by *Eqn. 18*.

$$k_4 = \frac{-\,\mathrm{d}[C_5H_{10}NCl]/\mathrm{d}t}{[C_5H_{10}NCl][OH^-]} = 34.2 \cdot 10^{-6} \pm 0.64 \cdot 10^{-6}\ \mathrm{M}^{-1}\ \mathrm{s}^{-1} \qquad (18)$$

Table 3. *Kinetics of Dehydrohalogenation of 1-Chloropiperidine* (**3**) *in Alkaline Medium: Determination of Partial Orders* α *and* β *and Rate Constants. T* 25°.

$[C_5H_{10}NCl]_0$ [M]	$[NaOH]_0$ [M]	φ [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	$8.52 \cdot 10^{-6}$	$34.1 \cdot 10^{-6}$

The influence of temperature was studied between 15 and 45°; with concentrations of **3** and NaOH equal to $2 \cdot 10^{-3}$ M and 0.1M, respectively. *Fig. 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}). Thus, one deduces *Eqn. 19* for the rate constant; and the following values for the enthalpy and entropy of activation (see *Eqns. 15* and *16*): $\Delta H_4^{\neq} = 90.98$ kJ mol^{-1} and $\Delta S_4^{\neq} = -23.29$ J mol^{-1} K^{-1}.

$$k_4 = 1.02 \cdot 10^{12} \exp(-93.45/RT) \text{ M}^{-1} \text{ s}^{-1} \quad (19)$$

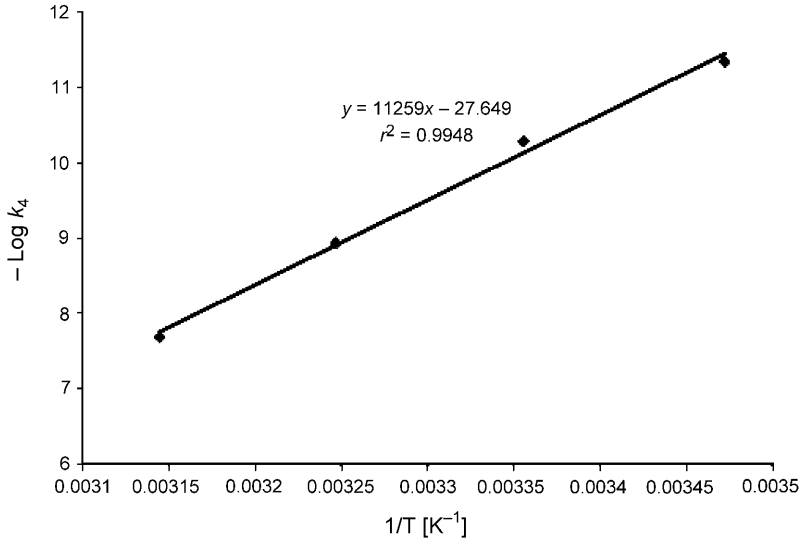
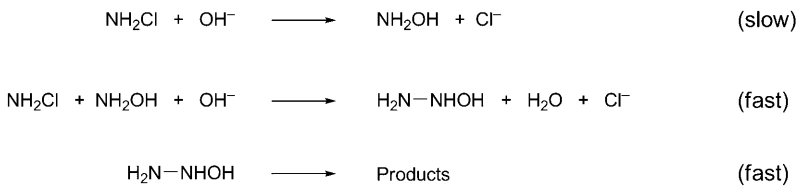


Fig. 7. *Kinetics of dehydrohalogenation of 1-chloropiperidine* (**3**): *influence of temperature.* $[C_5H_{10}NCl]_0 = 2 \cdot 10^{-3}$ M, $[NaOH]_0 = 0.1$M.

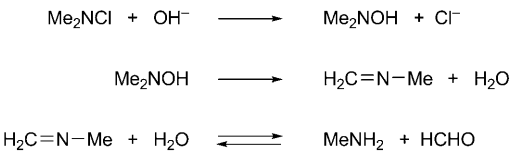
2.4.2. *Mechanism.* To suggest a mechanism for the dehydrohalogenation of 1-chloropiperidine (**3**), an overview of the reactivity of similar chloramines is worthy of mention. The reactivity of chloramine (**1**) in alkaline medium has been the subject of previous studies [31–34]. The suggested mechanism involves the formation of NH_2OH, which reacts with another molecule of **1** to form an unstable hydroxyhydrazine (*Scheme 5*). The latter might be oxidized to nitrite and peroxonitrite ions with N_2 (g) emission.

Scheme 5



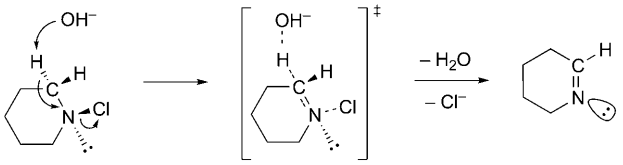
As for *N*-chlorodimethylamine, the formation of *N*-hydroxydimethylamine may correspond to the first elementary step (S_N2) of *Scheme 6*. To confirm this hypothetic scheme, a precise amount of *N*-hydroxydimethylamine hydrochloride (= *N*,*N*-dimethylhydroxylamine hydrochloride; 99%; *Aldrich*) was dissolved in alkaline medium (addition of NaOH), 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 ($10 \cdot 10^{-3}$ M) of *N*-hydroxydimethylamine and *N*-chlorodimethylamine at pH 12.89 (*T* 25°), a gas emission was observed, and new derivatives, which were not observed in the dehydrohalogenation of *N*-chlorodimethylamine, were detected [35].

Scheme 6



These results exclude the hypothetic formation of a substituted hydroxylamine compound from 1-chloropiperidine (**3**). Since OH^- ions have both basic and nucleophilic properties, there exists a competition between an S_N2 and *E*2 process. Furthermore, when bulky substituents are present next to the electrophilic site, they create sterical limitations for an S_N2 reaction, and hence the *E*2 process becomes preponderant (*Scheme 7*).

Scheme 7



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Experimental Part

Reagents. All reagents and salts used were reagent-grade products from *Aldrich*® and *Prolabo RP*®. H_2O was passed through an ion-exchange resin, and then distilled twice.

Chloramine (**1**). NH_2Cl is unstable in H_2O, thus it was prepared *in situ* at $-10°$ by reacting 2M sodium hypochlorite (25 ml) and aq. NH_3/NH_4Cl soln. ($[NH_4Cl] = 2.3$M, $[NH_3] = 3.6$M; 20 ml) in the presence of Et_2O (40 ml). The org. layer (0.8 – 1M of NH_2Cl) was shaken and washed several times with aliquots of dist. H_2O. An aq. soln. of **1** was obtained by re-extraction from the Et_2O phase. Its conc. was determined by UV spectroscopy at λ 243 nm ($\varepsilon = 458$ M^{-1} cm^{-1}) [36].

1-Chloropiperidine (**3**). At 0°, 2.4M aq. piperidine soln. (100 ml) was treated with 2.25M sodium hypochlorite (100 ml). The chlorination was instantaneous and gave a mixture of two phases. The upper

yellow phase was distilled under 0.05 bar leading to a pure fraction of **3** at 65°. Purity as determined by DSC: 99.84%.

2,3,4,5-Tetrahydropyridine (**4**). At 25°, dist. 1-chloropiperidine (**3**); 5 g was treated with KOH (10 g) in MeOH (90 g). The mixture was stirred overnight, and a white precipitate of KCl was formed and filtered off. The filtrate was concentrated and then treated with 0.1M aq. HCl soln. which resulted in the precipitation of the product that was filtered off and washed with small amounts of cold H_2O: 1.8 g (52%) of **4**.

Kinetic Apparatus. The apparatus consisted of two thermostated vessels of borosilicate glass, one on the top of the other and joined by a conical fitting. The lower reactor (200 ml) had inlets allowing the measurement of pH and temperature, and removal of aliquots for analysis. This set-up allowed 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, and the reactor temp. was kept constant to $\pm 0.1°$ (thermocouple). A glass electrode (*Tacussel* TB/HS) and a calomel reference electrode connected to a *Tacussel-Isis-20000* pH meter were used for pH control.

Cl-Transfer Reaction. Reactant solns. were prepared at the same pH, and piperidine (**2**) was introduced into the lower reactor. The pH value was adjusted by addition of an aq. KH_2PO_4/K_2HPO_4 buffer soln. As soon as the thermal equilibrium was reached, the aq. soln. of chloramine (**1**; prepared according to the above-mentioned procedure) of identical pH was added from the upper vessel.

The conc. of **1** consumed and of 1-chloropiperidine (**3**) formed were monitored by their UV absorptions, analyzed with a *Cary-1E* double-beam UV-spectrophotometer.

Dehydrohalogenation. As described for the Cl transfer, but **3** was introduced into the lower reactor, and its disappearance with respect to time was monitored by UV spectrophotometry ($\varepsilon_3 = 348\ M^{-1}\ cm^{-1}$ at λ 261 nm).

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