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Synthesis of 1-Amino-2-methylindoline by Raschig Process: Kinetics of the Oxidation of 1-Amino-2-methylindoline by Chloramine

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ABSTRACT: The synthesis of 1-amino-2-methylindoline by the Raschig process was undertaken in aqueous solution. The principal side reaction that occurs in the medium is the oxidation of 1-amino-2-methylindoline formed by chloramine. To increase the yield of 1-amino-2-methylindoline, its oxidation by chloramine was studied by GC and HPLC at various concentrations of reactants and for a pH interval ranging between 9.9 and 13.5. The reaction is bimolecular and exhibits a specific acid catalysis. In alkaline medium, 1-amino-2-methylindole is the principal product. The enthalpy and entropy of activation were determined at pH 12.89. In unbuffered solution, the interaction was autocatalyzed by the ammonium ions formed, which indicates a competitive oxidation of neutral and ionic forms of 1-amino-2-methylindoline by chloramine. A mathematical treatment based on one implicit equation allows a quantitative interpretation of all the phenomena observed over the above pH interval. It takes both acid–base dissociation equilibrium and alkaline hydrolysis of chloramine into account. © 2002 Wiley Periodicals, Inc. Int J Chem Kinet 34: 515–523, 2002

INTRODUCTION

1-Amino-2-methylindoline **1** (NAMI) is used in the pharmaceutical industry as a precursor of antihypertensive drugs whose common international name is *Indapamide*.
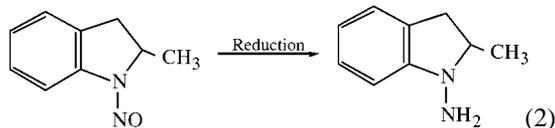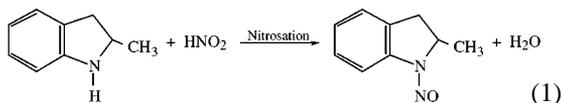
NAMI
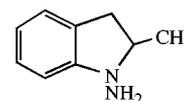
At present it is prepared by the Wright and Willette process [1], which is carried out in two steps: (a) nitrosation of 2-methylindoline **2** by addition of sodium

nitrite to an acid solution of amine and (b) reduction of 1-nitroso-2-methylindoline **3** formed by chemical or catalytic way:

$$2\,NaNO_2 + H_2SO_4 \rightleftharpoons 2\,HNO_2 + Na_2SO_4$$

(1)

(2)

Reaction (1) leads to a high yield (96%, $T = 5°C$, $[H_2SO_4] = 2.5$ M) but, before reduction, **3** must be always purified by distillation or recrystallization. Several methods have been proposed to reduce 1-nitroso-2-methylindoline [1–5]. Nevertheless, **3** must be handled with many precautions because of its highly carcinogenic properties [6,7], which cause problems of industrial exploitation.

To avoid the nitrosamines, we have undertaken the study of the amination of **2** in aqueous medium by the Raschig process [8,9]. This most environmentally sound route is schematized by the following two reactions:

$$NaOCl + NH_3 \longrightarrow NH_2Cl + NaOH \qquad (3)$$

(4)
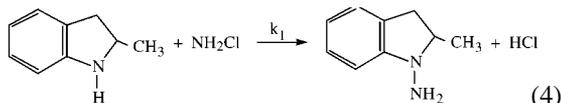
However, it presents the disadvantage to lead to several by-products. This behavior is due to the oxidation and amination properties of chloramine, which appear simultaneously. In particular, the reaction between **1** and NH_2Cl is one of principal side reactions observed during the synthesis of 1-amino-2-methylindoline by Raschig process [10]. Depending on the pH, this reaction leads to 1-amino-2-methylindole **4** or azo(2-methyl)indoline **5**:

(5)
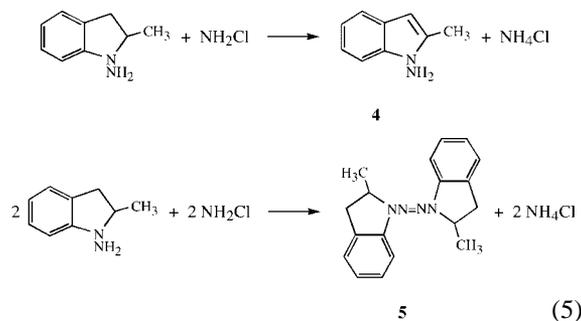
Reaction (5) limits the yield and leads to product, which is difficult to separate during the continuous extraction of **1** [11]. Another side reaction consists in the alkaline degradation of chloramine with formation of hydroxylamine intermediate [12].

To increase the yield in 1-amino-2-methylindoline, it is thus necessary to determine the optimum conditions of concentrations, pH, and temperature, which limit the quantities of by-products formed, in particular the 1-amino-2-methylindole. This work relates to the determination of kinetic parameters of the oxidation of 1-amino-2-methylindoline by chloramine. This reaction has not been the object of any former study.

EXPERIMENTAL

Reagents

All reagents and salts used were reagent grade products from Aldrich and Prolabo RP.

Water was passed through an ion-exchange resin, then distilled twice, deoxygenated, and stored under nitrogen.

NH_2Cl is unstable in water. It was, therefore, prepared at $-10°C$ extemporaneously by reacting 25 ml of sodium hypochlorite 2 M and 20 ml of NH_3–NH_4Cl aqueous solution ($[NH_4Cl] = 2.3$ M, $[NH_3] = 3.6$ M) in the presence of diethylether (40 ml). The organic layer (0.8–1 M in NH_2Cl) was shaken and washed several times with aliquots of distilled water. Chloramine in aqueous solution was obtained by reextraction from the ethereal phase. Its content was determined by UV spectroscopy at $\lambda = 243$ nm ($\varepsilon = 458$ M^{-1} cm^{-1}) [13].

1-Amino-2-methylindoline is not commercially available. It was provided by Oril Industrie in the mesylate form after treatment by methane sulphonic acid. The extraction and purification of NAMI have been described previously [10,11].

Apparatus

The apparatus consisted of two thermostated vessels, one on top of the other and joined by a conical fitting. The lower reactor (200 cm^3) contained a magnetic stirrer and had inlets to allow measurement of pH and temperature, influx of circulating nitrogen, and removal of aliquots for analysis. Because of the lability of hydrazines to oxidation in air, the mixture was monitored by an oxygen-sensitive electrode connected to a numerical indicator. The upper cylindrical vessel (100 cm^3) was blocked at its base by a solid machined stopper (17 mm i.d.) fastened to a control rod. This set-up allowed a rapid introduction of the ampoule contents

into reactor and therefore a precise definition of the beginning of reaction. A slightly reduced pressure was maintained throughout the experiment and the temperature in the reactor was defined to $\pm 0.1^\circ$C. A glass electrode (TACUSSEL TB/HS model) and a calomel reference electrode were used for pH measurements after suitable standardization with N.B.S. buffer solutions; the instrument used was a pH meter TACUSSEL ISIS 20000.

Procedure and Analysis

The reactant solutions were prepared at the same pH. NAMI was dissolved in deoxygenated water to avoid the oxidation process. It was introduced into reactor after adjusting of pH by addition of sodium hydroxide or a buffer solution. When the thermal equilibrium was reached, an aqueous solution of chloramine was prepared, then rapidly treated according to the above procedure.

Chloramine shows a UV absorption in water at $\lambda = 243$ nm ($\varepsilon = 458$ M^{-1} cm^{-1}). It was analyzed by HPLC at its maximum wavelength by using a HP 1100 chromatograph equipped with a Diode Array Detector. The separation was done on a 250×4.6 mm ODS column (dp $= 5\mu$m). The mobile phase was a H$_2$O/MeOH mixture (75:25%, v/v) with a flow rate of 1 ml min^{-1}.

1-Amino-2-methylindoline exhibits two absorption bands in water at $\lambda_1 = 239$ nm ($\varepsilon_1 = 7150$ M^{-1} cm^{-1}) and $\lambda_2 = 284$ nm ($\varepsilon_2 = 2060$ M^{-1} cm^{-1}) [11]. Taking into account impossibility of simultaneous determination of NAMI and chloramine by UV, **1** was analyzed by HPLC and GC. HPLC analyses were conducted under the same conditions as those of chloramine. GC analysis was realized according to an extraction method because of the presence of chloramine. It consists in quenching the reaction by transferring **1** into an organic solvent where chloramine is insoluble. The samples were analyzed after toluene extraction. GC analyses were carried out on a HP 6890 chromatograph equipped with EPC modules allowing to control and to measure gas flows and pressures at different levels of the apparatus. The separation was done on a 30-m long HP1 column (100% dimethylpolysiloxane, $d_f = 1.5$ μm, 530 μm i.d.).

RESULTS AND DISCUSSION

Kinetics of NAMI–NH$_2$Cl Interaction

Study at pH 12.89. The reaction carried out at equimolar conditions (15×10^{-3} M) and pH 12.89 ($T = 25^\circ$C) shows the formation of a single product whose instantaneous concentration is proportional to that of reagents. Figure 1 presents a selection of chromatograms obtained at various moments of the reaction. We observe the decrease of **1** and correlatively the appearance of a signal at 2.88 min.

The rate law was first established at pH 12.89. Thus, the dissociation of NH$_2$Cl in NHCl$^-$ and the protonation of **1** can be neglected. Its acidity constant was measured at 25°C by using a series of buffer solutions (0.025 M sodium hydrogen phosphate + 0.025 M sodium dihydrogen phosphate pH 6.86, 0.025 M potassium hydrogen phthalate pH 4.00, and 0.01 M borax pH 9.18), then controlled by UV spectroscopy. $K_a^{\text{NAMIH}^+}$ was found to be 8.51×10^{-5}.

Under these conditions, the rate of disappearance of NAMI is calculated from the relation (6) where α, β, ν_2, and k_2 represent, respectively, partial orders, stoichiometry, and rate constant:

$$-\text{d[NAMI]}/\text{d}t = \nu_2 k_2 [\text{NH}_2\text{Cl}]^\alpha [\text{NAMI}]^\beta \quad (6)$$

The partial orders are determined by an integration method. The experiments were conducted at various equimolar concentrations (5–15×10^{-3} M) and with molar ratios $1 \leq [\text{NAMI}]_0/[\text{NH}_2\text{Cl}]_0 < 3.25$ (Table I). These concentrations allow to limit the reaction rate without affecting sensitivity of GC analyses (F. I. Detector).

The decrease in reagent contents verifies systematically the equality

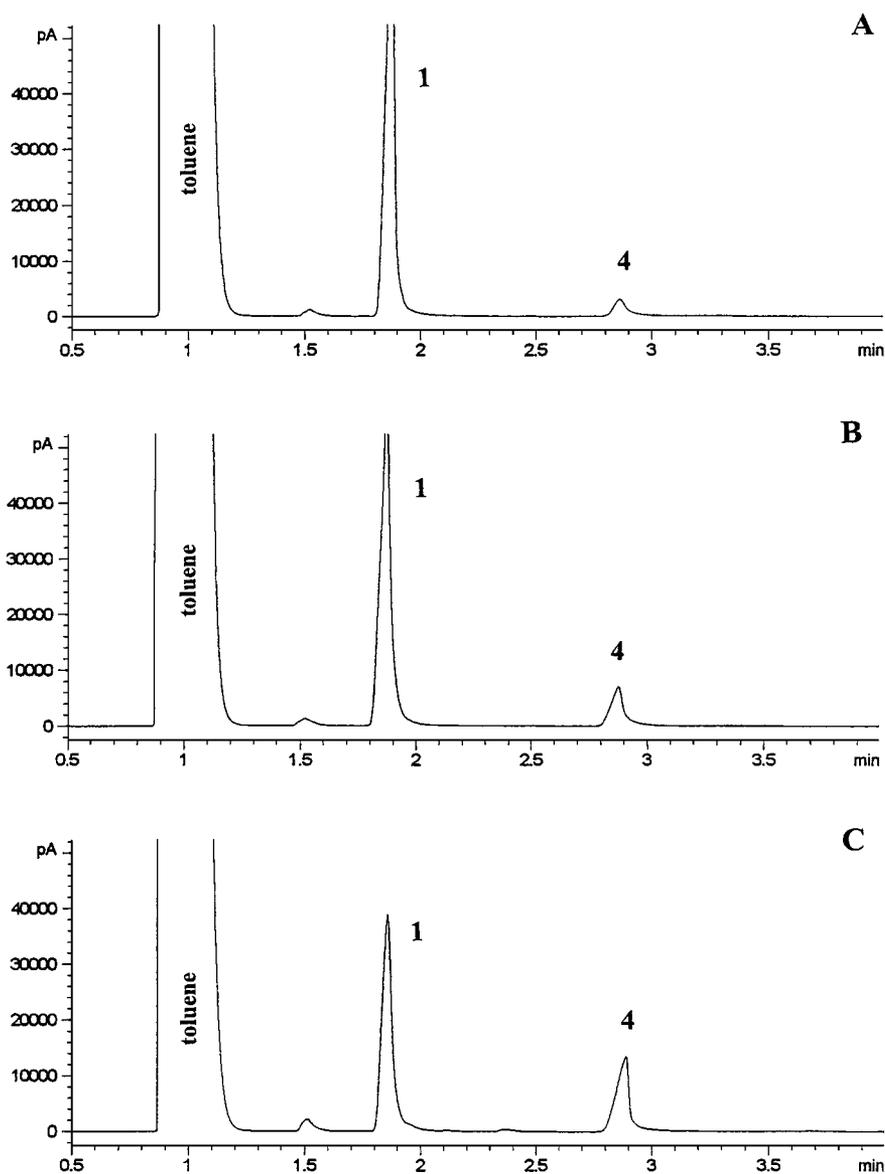$$-\text{d[NAMI]}/\text{d}t = -\text{d[NH}_2\text{Cl]}/\text{d}t$$

Furthermore, the graphs (for $[\text{NAMI}]_0 \neq [\text{NH}_2\text{Cl}]_0$)

$$\{\text{Log[NH}_2\text{Cl]}_0[\text{NAMI}] - \text{Log[NAMI]}_0[\text{NH}_2\text{Cl}]\}$$
$$1/([\text{NAMI}]_0 - [\text{NH}_2\text{Cl}]_0) = f(t)$$

are in all cases lines with the same slope k_2. We deduce the following values: $\alpha = \beta = 1$, $k_2 = 3.17 \times 10^{-3}$ M^{-1} s^{-1} at 25°C. A complete structural characterization of

Table I Determination of Kinetic Parameters of Oxidation of 1-Amino-2-methylindoline by Chloramine (pH 12.89 and $T = 25^\circ$C)

$[\text{NH}_2\text{Cl}]_0$ (10^3 M)	$[\text{NAMI}]_0$ (10^3 M)	$[\text{NAMI}]_0/$ $[\text{NH}_2\text{Cl}]_0$	k_2 (10^3 M^{-1} s^{-1})
15.0	15.0	1.00	3.25
10.5	10.4	1.01	3.18
7.16	7.34	1.03	3.17
6.27	15.4	2.46	3.10
4.80	15.4	3.23	3.15

Figure 1 Oxidation of 1-amino-2-methylindoline by chloramine. GC analyses recorded as a function of time t (A) 1 min, (B) 53 min, and (C) 299 min ($T = 25°C$, pH 12.89, and $[NAMI]_0 = [NH_2Cl]_0 = 15 \times 10^{-3}$ M).

reaction product leads to 1-amino-2-methylindole [10]. The reaction is represented by the following equation:
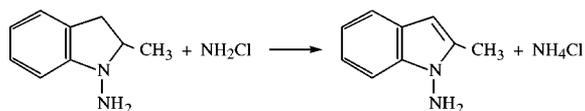
The temperature effect was studied between 25 and 45°C, at pH 12.89, and for molar ratio $[NAMI]_0/[NH_2Cl]_0 \approx 1$ (15×10^{-3} M). The curve Log $k_2 = f(1/T)$ is a line with a slope $-E_2/R$ and a Y

intercept Log A_2 ($r^2 = 0.996$). E_2 and A_2 represent, respectively, Arrhenius factor and activation energy of the reaction.

$$k_2 = 92.8 \times 10^6 \exp(-59.7/RT) \text{ M}^{-1} \text{ s}^{-1}$$

$$(E_2 \text{ in kJ mol}^{-1})$$

The enthalpy and entropy of activation can be deduced to

$$\Delta H_2^{\circ\#} = E_2 - RT \quad \Delta S_2^{\circ\#} = R \text{ Log}(A_2 h)/(e k_B T)$$

where k_B is Boltzmann constant and h is Planck constant. The numerical values are the following:

$$\Delta H_2^{\circ\#} = 57.2 \, \text{kJ mol}^{-1} \quad \Delta S_2^{\circ\#} = -100.7 \, \text{J mol}^{-1} \, \text{K}^{-1}$$

Influence of pH. Measurements were performed at 25°C in pH interval ranging between 9.9 and 13.5 (Table II). The established rate law (partial orders and stoichiometry) were preserved. On the other hand, the constant k_2 increases as pH decreases without change of the product of first elementary step (Fig. 2). Furthermore, at a fixed pH, the reaction rate is independent of the nature of buffer solution and its concentration.

To interpret the results, it is convenient to distinguish between two domains where pH is above or below 12.89. Figure 3 shows the change in reactant concentrations under the following conditions: $[\text{NAMI}]_0 = [\text{NH}_2\text{Cl}]_0 = 15 \times 10^{-3}$ M, pH 13.5, and $T = 25$°C. The ratio $\delta([\text{NAMI}])/\delta([\text{NH}_2\text{Cl}])$ progressively diverges from linearity with the degree of reaction progress. To determine k_2 it is necessary to take into account the alkaline hydrolysis of chloramine. This reaction has been studied by several authors [12,14–17]. The first elementary step corresponds to the formation of hydroxylamine intermediate, which immediately reacts to give several products (NO^-, N_2O, $\text{N}_2\text{O}_2{}^{2-}$, ONOO^-):
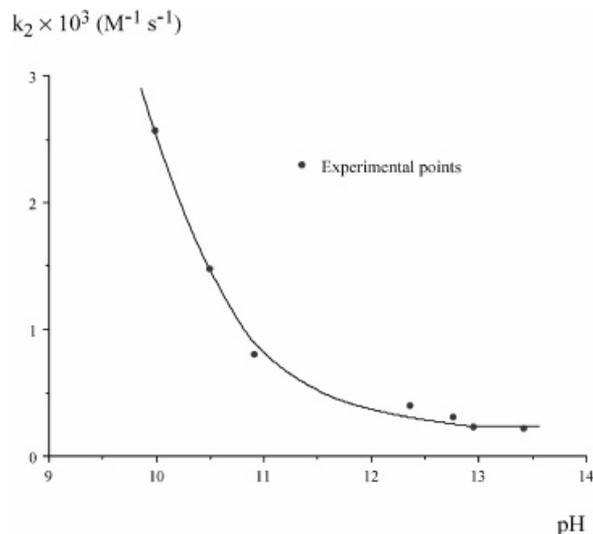
$$\text{NH}_2\text{Cl} + \text{OH}^- \longrightarrow \text{NH}_2\text{OH} + \text{Cl}^- \qquad (7)$$

Reaction (7) follows a second-order rate law. The rate constant with respect to NH_2Cl is found from the relation

$$-\text{d}[\text{NH}_2\text{Cl}] = k_3[\text{NH}_2\text{Cl}][\text{OH}^-]$$

where $k_3 = 62 \times 10^{-6}$ M^{-1} s^{-1} at 25°C [12]. By designating, respectively, as x, y, and u the instantaneous concentration of NH_2Cl, OH^-, and NAMI, the evolution of the system over time is described by the

Figure 2 Oxidation of 1-amino-2-methylindoline by chloramine. Variation of the concentrations in NAMI and NH_2Cl according to time ($T = 25$°C, pH 13.5, and $[\text{NAMI}]_0 = [\text{NH}_2\text{Cl}]_0 = 15 \times 10^{-3}$ M).
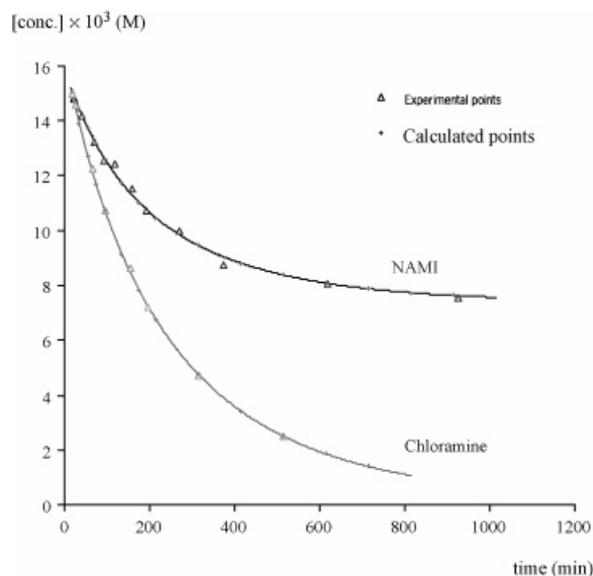
following differential equations:

$$-\text{d}x/\text{d}t = k_2 xu + k_3 xy \qquad (8)$$

$$-\text{d}u/\text{d}t = k_2 xu \qquad (9)$$

$$-\text{d}y/\text{d}t = k_2 xu + k_3 xy \qquad (10)$$

The supplementary term in $\text{d}y/\text{d}t$ is due to the liberation of ammonium ions by reaction (5), which are immediately neutralized by sodium hydroxide. The relations

Table II Kinetics of NAMI–NH_2Cl Interaction. Influence of pH ($T = 25$°C)

$[\text{NH}_2\text{Cl}]_0$ (10^3 M)	$[\text{NAMI}]_0$ (10^3 M)	pH	k_2 (10^3 M^{-1} s^{-1})
9.60	14.9	9.92	42.2
11.1	16.3	10.43	24.0
9.78	15.1	10.85	12.7
9.15	15.2	12.3	4.67
9.65	15.0	12.7	3.62
15.0	15.0	12.89	3.17
9.59	15.4	13.35	3.17
15.0	15.0	13.50	3.17

Figure 3 Influence of pH on the oxidation of NAMI by chloramine ($T = 25$°C).

(8) and (10) being identical, we deduce

$$y = (y_0 - x_0) + x \qquad (11)$$

Combining Eqs. (8), (9), and (11) and considering the initial conditions (at $t = 0$, $x = x_0$, $y = y_0$, and $u = u_0$), we obtain an equation which is a function of instantaneous concentrations of NAMI and NH_2Cl:

$$x = x_0 - y_0[1 - (u/u_0)^{k_3/k_2}]$$
$$- \{k_2 u[1 - (u/u_0)^{k_3/k_2 - 1}]\}/(k_3 - k_2) \quad (12)$$

u and x are experimentally measured, so the constant k_2 was calculated by resolution of the implicit Eq. (13):

$$x - x_0 + y_0[1 - (u/u_0)^{k_3/k_2}]$$
$$+ \{k_2 u[1 - (u/u_0)^{k_3/k_2 - 1}]\}/(k_3 - k_2) = 0 \quad (13)$$

The calculation realized for $[OH^-] = 0.5$ M and $T = 25°C$ shows that k_2 remains about constant, which confirms the hypothesis concerning partial orders. The adjusted value is determined by least-squares method.

Knowing k_2 and k_3 at given pH and temperature allows to check the validity of mathematical model under the operating conditions (initial concentrations, temperature, pH). By replacing x by its value in Eq. (9), we obtain a differential equation whose numeric resolution permits to express $u = f(t)$:

$$du/dt = -k_2 u \{x_0 - y_0[1 - (u/u_0)^{k_3/k_2}]$$
$$- (k_2 u(u/u_0)^{k_3/k_2 - 1})/(k_3 - k_2)\} \quad (14)$$

The kinetic curves giving x and g as a function of time are deduced from analytical expressions (12) and (15):

$$g = (y_0 - y) + (u - u_0) \qquad (15)$$

where g is the instantaneous concentration of hydroxylamine. As shown in Fig. 3, a good concordance between experimental and theoretical curves is observed.

In weakly alkaline medium (pH < 12.89), the application of formulas shows that reaction (7) can be neglected ($k_3 \to 0$). The phenomenon of specific acid catalysis can be interpreted as a competitive oxidation of neutral and ionic forms of **1** by NH_2Cl, which leads to a rate equation as follows:

$$-d[NAMI]/dt = k_2'[NH_2Cl][NAMI]$$
$$+ k_2''[NH_2Cl][NAMIH^+]$$

or

$$du_t/dt = u_t x (k_2' + k_2'' a_{H^+}/K_a^{NAMIH^+})/$$
$$(1 + a_{H^+}/K_a^{NAMIH^+}) \qquad (16)$$

The chloroammonium ion is neglected due to its high acidity constant ($K_a^{NH_3Cl^+} = 3.41 \times 10^{-2}$ [18,19]), and k_2' and k_2'' in Eq. (16) are the rate constants of the neutral and ionic processes and u_t is the total concentration of NAMI:
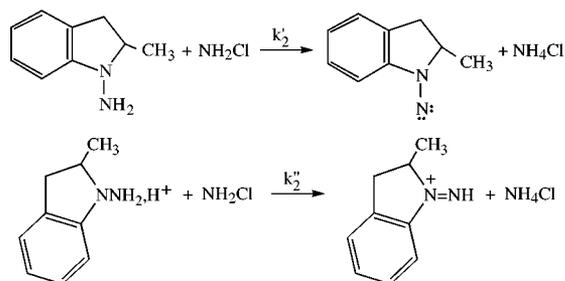
In the pH interval studied, $a_{H^+}/K_a^{NAMIH^+}$ is negligible compared to unity. Under these conditions, k_2 includes two terms one of which is relative to the catalytic effect:

$$k_2 = k_2' + k_2'' a_{H^+}/K_a^{NAMIH^+} \qquad (17)$$

k_2' and k_2'' were obtained by adjusting the curve $k_2 = f(pH)$ by the least-squares method. The calculations performed using the approximation $a_{H^+} \approx [H^+]$ lead to

$$k_2' = 3.17 \times 10^{-3} \, M^{-1} \, s^{-1} \quad k_2'' = 10.6 \times 10^3 \, M^{-1} \, s^{-1}$$

Unbuffered Medium

Oxidation of **1** leads to the formation of ammonium ions and thus causes a decrease of pH. While operating in unbuffered slightly alkaline medium, we must observe an acceleration of oxidation of NAMI according to an autocatalytic mechanism. In order to verify the accuracy of Eq. (17), the experiments were carried out in unbuffered medium. Only NAMI concentration and pH were followed as a function of time. To limit the initial reaction rate, starting pH was fixed at 11 by addition of titrated sodium hydroxide solution. Figures 4 and 5 show, respectively, the variation of NAMI concentration and pH over time at $T = 25°C$ and for approximately stoichiometric mixture ($[NAMI]_0 = 10 \times 10^{-3}$ M, $[NH_2Cl]_0 = 9.04 \times 10^{-3}$ M).

Each curve presents an inflection point characteristic of an autocatalytic effect linked to the acidification
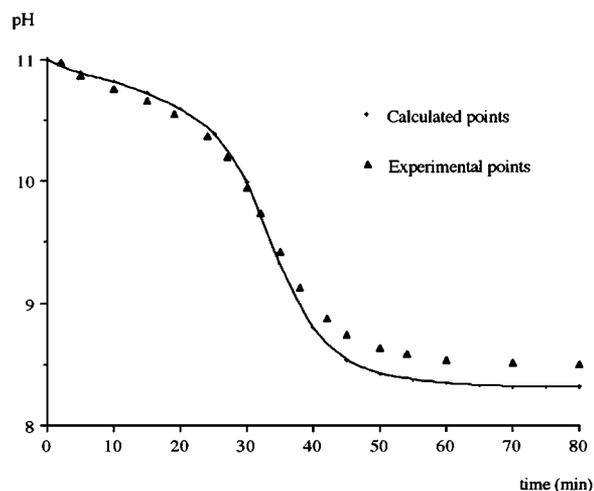
[conc.] × 10³ (M)
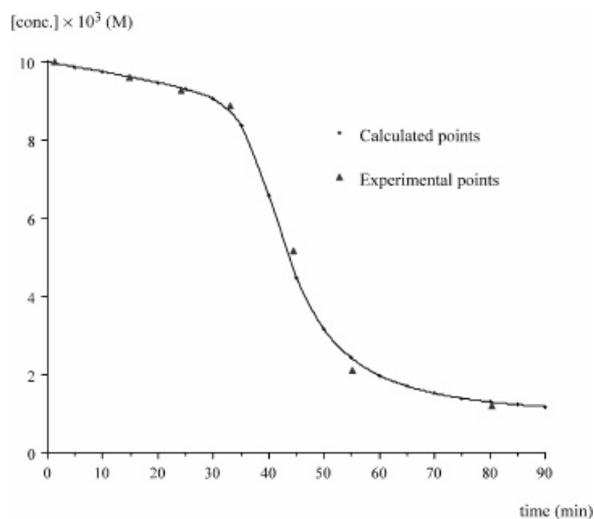
Figure 4 Autocatalytic oxidation of 1-amino-2-methylin-doline by chloramine. Variation of the concentration of NAMI as a function of time ($T = 25°C$, $[NAMI]_0 = 10 \times 10^{-3}$ M and $[NH_2Cl]_0 = 9.04 \times 10^{-3}$ M).

by ammonium ions. In order to recalculate the kinetic curves, let us designate by ξ and $[NH_3]^T$, respectively, the instantaneous concentrations of reacted NAMI and total ammonia.

Using the above formalism the rate law is then written:

$$d\xi/dt = \left\{ k_2' + k_2''[H^+]/K_a^{NAMIH^+} \right\}(u_0 - \xi)(x_0 - \xi)$$

To integrate this relation, it is necessary to express $[H^+] = f(\xi)$. By considering the laws of material conserva-

pH

Figure 5 Autocatalytic oxidation of 1-amino-2-methylin-doline by chloramine. Variation of pH according to time ($T = 25°C$, $[NAMI]_0 = 10 \times 10^{-3}$ M, and $[NH_2Cl]_0 = 9.04 \times 10^{-3}$ M).

tion and electrical neutrality as well as the dissociation equilibria of NAMIH$^+$ and NH$_4$$^+$ ($K_a^{NH_4^+} = 5.62 \times 10^{-10}$), we can write

$$z + z^+ = \xi \quad u + u^+ = u_0 - \xi$$
$$\sum_i [C_i]^+ = \sum_j [C_j]^-$$

where z is the instantaneous concentration of ammonia. The term $[H^+]$ is the root of a fourth degree equation, which can be simplified by noting that $[H^+]$ is always less than 8×10^{-9} M:

$$(u_0 - \xi) + y_0 + [H^+] - K_a^{NH_4^+} \xi / \left(K_a^{NH_4^+} + [H^+] \right)$$
$$- K_a^{NAMIH^+}(u_0 - \xi) / \left(K_a^{NAMIH^+} + [H^+] \right)$$
$$- K_e/[H^+] = 0$$

Under these conditions, $K_a^{NAMIH^+} + [H^+] \approx K_a^{NAMIH^+}$ ($K_a^{NAMIH^+}/[H^+] \geq 2.7 \times 10^4$) and $[H^+]$ is the positive root of the equation:

$$[OH^-]_0[H^+]^2 + [H^+]\left\{ K_a^{NH_4^+}([OH^-]_0 - \xi) - K_e \right\}$$
$$- K_a^{NH_4^+} K_e = 0$$

The rate equation becomes

$$d\xi/dt = \left\{ k_2' + 0.5k_2'' \left\{ \left[K_a^{NH_4^+}([OH^-]_0 - \xi) - K_e \right]^2 \right. \right.$$
$$\left. + 4K_a^{NH_4^+} K_e[OH^-]_0 \right\}^{1/2}$$
$$+ 0.5 \left(K_a^{NH_4^+}(\xi - [OH^-]_0) + K_e \right) \right\}$$
$$\times \left([NAMI]_0^T - \xi \right)([NH_2Cl]_0 - \xi)$$

A numerical solution is obtained with the Runge–Kutta method according to a fourth-order step procedure. Calculated points are in good agreement with experimental curves with a maximum error below 5%. The formula (17) conveniently explains the observed phenomena at 25°C in the considered pH range. Moreover, the study of autocatalytic effect has permitted to verify the partial orders and the stoichiometry pre-determined at pH 12.89.
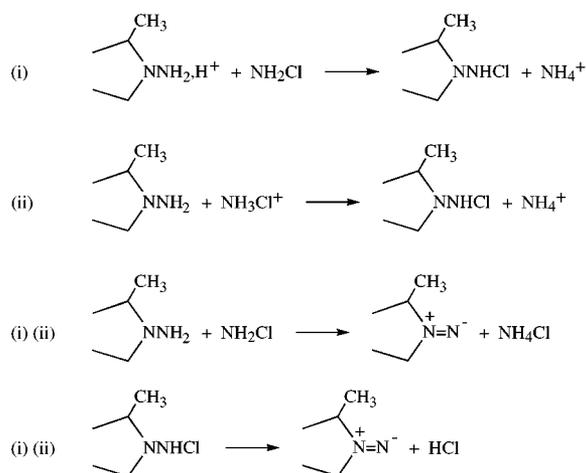
Mechanism

The pH plays a fundamental role in hydrazines chemistry, which manifests either in a rate acceleration or in a change of the nature and ratio of reaction products [11,20,21]. The phenomenon of specific acid catalysis can be explained by considering the nature of reactive

species. Chloramine being a very weak base, acidity constant of NH_3Cl^+ is $K_a^{NH_3Cl^+} = 3.41 \times 10^{-2}$. In the case of substituted hydrazines, two basic sites are available to capture the protons [22–24].
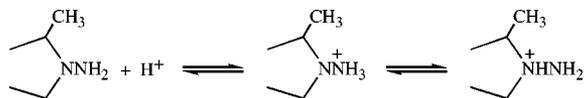
Two schemes are then possible to describe the catalytic effect: (i) an interaction between chloramine and neutral and ionic forms of **1** (NH_2Cl-NAMI-NAMIH$^+$) and (ii) a direct interaction between NAMI and neutral and ionic forms of chloramine (NAMI-NH_2Cl-NH_3Cl^+).

The reducing character of NAMIH$^+$/aminonitrene is enhanced due to the positive charge on nitrogen atom (Scheme i), which leads to an increase of rate constant ($k_2'' > k_2'$). The second mechanism (Scheme ii) suggested by Synder et al. [19] and Isaac et al. [25,26] involves the reaction of NH_3Cl^+ with free nitrogen. This implicates a nucleophilic attack of ammoniacal nitrogen lone pair on the positive chlorine site. The low concentration of NH_3Cl^+ ([NH_3Cl^+]/([NH_2Cl] = 2.93×10^{-7} at pH 8) in the experimental pH interval leads to a high value of NAMI–NH_3Cl^+ rate constant.

Although Scheme (ii) seems unlikely because of the very low concentration of NH_3Cl^+ in reaction mixture, the results can be interpreted quantitatively by considering either the ionization of **1** or that of chloramine. The two hypotheses are equivalent and lead kinetically to the same formalism within a proportionality constant. In all cases, the interaction can be considered as a superposition of neutral and ionic mechanisms leading quantitatively to the relation (17).

1-Amino-2-methylindoline is an important intermediate used for the preparation of antihypertensive drugs. Its synthesis was undertaken in our laboratory from a reaction between chloramine and 2-methylindoline in alkaline environment. The principal side reaction observed is the oxidation of the useful product by chloramine. To increase the yield of 1-amino-2-methylindoline, it is thus necessary to determine the best conditions of concentrations, pH, and temperature, which limit the formation of by-products. The study of the oxidation of 1-amino-2-methylindoline shows that the interaction is bimolecular and exhibits a specific acid catalysis. In alkaline medium (pH $\geq$ 12.89), the rate constant is equal to 3.17×10^{-3} M^{-1} s^{-1} and the reaction leads principally to 1-amino-2-methylindole. The enthalpy and entropy of activation were determined at pH 12.89. In unbuffered solution, the interaction is autocatalyzed by the ammonium ions formed, which indicates a competitive oxidation of neutral and ionic forms of 1-amino-2-methylindoline by chloramine. A mathematical treatment including the kinetic parameters of this interaction allows a quantitative interpretation of all the phenomena occuring in the reaction medium and to define the optimum conditions of synthesis of 1-amino-2-methylindoline.

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