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Study of a Reduction Step during the Continuous Synthesis of *N*-Amino-3-azabicyclo[3.3.0]octane. Kinetics, Modelling, and Optimization[1]

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Abstract—The reduction of *N*-chloro-3-azabicyclo[3.3.0]octane with sodium borohydride at different pH values and variable concentrations of the haloamine and reducing agent was studied. The reaction was found to be second order and exhibited a specific acid catalysis. The enthalpy and entropy of activation were determined at pH 12.89. A mathematical treatment of the kinetic data allowed a complete characterization of the final state and the determination of percentage of haloamine reduced as a function of temperature, $[NaBH_4]$/[haloamine] ratio, arid pH. A reaction mechanism is proposed.

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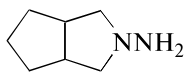
The aim of this work is to develop the Raschig method of synthesizing substituted hydrazines into a powerful way of making *N*-amino-3-azabicyclo[3.3.0]octane (**1**).



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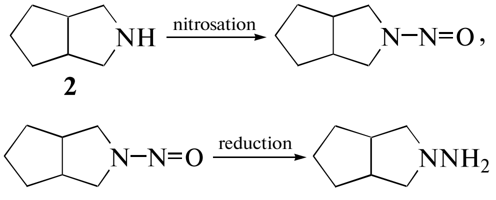
Unsymmetrical alicyclic hydrazines are used in the pharmaceutical industry as precursors of hypoglycemic, diuretic, anti-infectious, and cardiovascular drugs [1–4]. In particular, **1** reacts with arylsulfonylurethanes to lead to a glycolazide that is used for treatment of non-insulin dependent diabetics [5].

Up to date, the only method reported in literature for the synthesis of **1** from 3-azabicyclo[3.3.0]octane (**2**) consists of the nitrosation of **2** followed by the reduction of the resulting 1-nitroso-3-azabicyclo[3.3.0]octane [4–10]:

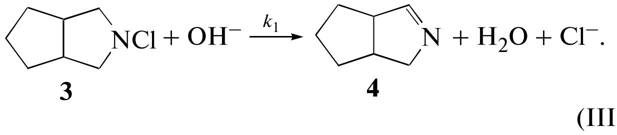


Although this process leads to high yields (96% at 25°C) yet it involves toxic intermediates (nitrosamines) and inflammable solvents that make it unfeasible for industrial application. In order to avoid these inconveniences, we have adopted the Raschig method [11–13] which is summarized by the following two steps:

$$NH_3 + OCl^- \longrightarrow NH_2Cl + OH^-, \qquad (I)$$

$$RR'NH + NH_2Cl + OH^- \longrightarrow RR'NNH_2 + H_2O + Cl^-. \qquad (II)$$

A major disadvantage of this method is presented by the formation of numerous byproducts which are a result of the reactive nature of the intermediates that undergo several side reactions. One particular side reaction that leads to several by-products is the *trans*-chlorination of chloramine and 3-azabicyclo[3.3.0]octane to yield *N*-chloro-3-azabicyclo[3.3.0]octane (**3**) [14, 15] which in turn loses HCl under the reaction conditions to give 3-azabicyclo[3.3.0]oct-2-ene (**4**):



(III)

Kinetic studies conducted at different temperatures and variable concentrations of **3** and NaOH showed that the reaction **(III)** is bimolecular (E_2 mechanism) [14, 16]:

$$k_1 = 2.95 \times 10^{11} \exp(-91.63/RT)\ \mathrm{l\ mol^{-1}\ s^{-1}}$$
$$(E_1 \text{ in kJ/mol}),$$

$$k_1 = 103 \times 10^{-6}\ \mathrm{l\ mol^{-1}\ s^{-1}} \text{ at } 25°\mathrm{C},$$

$$\Delta H_1^{0\#} = 89\ \mathrm{kJ/mol}, \quad \Delta S_1^{0\#} = -33.6\ \mathrm{J\ mol^{-1}\ K^{-1}}.$$

The imine that is produced precipitates in monomeric or polymeric forms. More concentrated solu-

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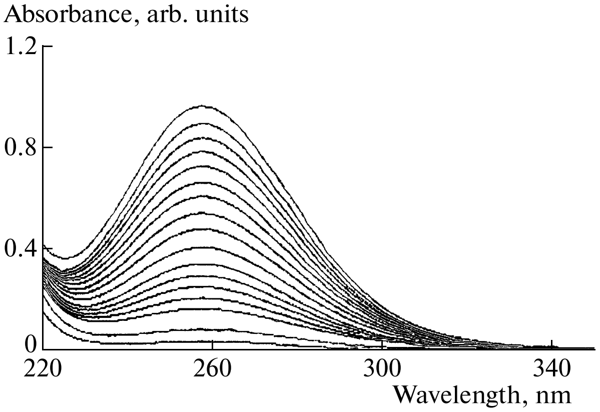
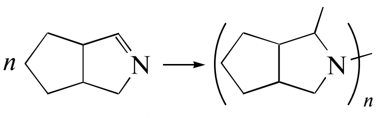


Fig. 1. UV absorption spectra of reduction of *N*-chloro-3-azabicyclo[3.3.0]octane by sodium borohydride ($[C_5H_{12}NCl]_0 = 2.03 \times 10^{-3}$ mol/l, $[BH_4^-]_0 = 0.1$ mol/l, pH 12.89, $T = 25$°C, [KCl] = 1 mol/l, reaction time from 0 to 100 min).

tions of **3** increase the rate of precipitation of **4** which is very sparingly soluble in aqueous solutions:



(n = 2 or 3).

Earlier studies show that *N*-amino-3-azabicyclo[3.3.0]octane must be synthesized in an alkaline medium (pH 12.89) [14]. Under these conditions, the dehydrohalogenation step is inescapable. To avoid the formation of a precipitate, a suitable reducing agent must be used to either reduce **3** before being converted to the imine or reduce the imine **4** back to 3-azabicyclo[3.3.0]octane as soon as it is formed.

EXPERIMENTAL

Reagents

Water was passed through an ion-exchange resin, distilled, deoxygenated, and stored under nitrogen. All reagents and salts used were reagent grade products from Prolabo RP and Aldrich.

N-Chloro-3-azabicyclo[3.3.0]octane is not commercially available, and it was obtained quantitatively by chlorinating excess of 3-azabicyclo[3.3.0]octane (2–3%) with sodium hypochlorite [14, 16].

Procedure and Analysis

Solutions of **3** and sodium borohydride of identical pH and KCl concentration ([KCl] = 1 mol/l) were prepared, warmed to 25°C and introduced into a reaction vessel. The initial concentration of $NaBH_4$ was determined iodometrically [17]. The concentration of **3** was monitored by making use of its maximum ultraviolet absorption [14]. The UV spectra were measured with a Cary 1E double beam spectrophotometer. 3-Azabicyclo[3.3.0]octane was determined by gas chromatography. GC analyses were carried out on an HP 6890 chromatograph equipped with EPC modules allowing to control and to measure gas flows and pressures at different levels of the instrument. The separation was done on a 25 m long CP Wax 51 column (the thickness of the film inside the column d_f was 2 μm and the internal diameter of the column was 530 μm). The apparatus and the experimental procedure were published elsewhere [16, 18].

RESULTS AND DISCUSSION

Kinetics of the Reduction of N-chloro-3-azabicyclo[3.3.0]octane with Sodium Borohydride

The low solubility of **3** in aqueous media ($\leq 10^{-2}$ mol/l in water, $\leq 4 \times 10^{-3}$ mol/l in 1 M sodium hydroxide solution at 25°C) makes our task more difficult since the study and analyses have to be done in homogeneous media. GC analysis proved to be unsuitable due to the partial decomposition of **3** in the injector. Preliminary trials have shown that the reaction between 3-azabicyclo[3.3.0]octane and *N*-chloro-3-azabicyclo[3.3.0]octane is negligible under experimental conditions. The reaction kinetics were monitored by UV spectrophotometry.

Reaction Order and Stoichiometry

Measurements were conducted at 25°C and sodium borohydride concentrations ranging between 0.05 and 0.50 mol/l. The rate law was first established at pH 12.89 (0.1 M NaOH) in order to limit the decomposition of **3** and sodium borohydride. To maintain a constant ionic strength, experiments were carried out by using 1 M potassium chloride solutions. Under these conditions, the rates of disappearance of **3** and BH_4^- may be expressed as follows:

$$-d[\mathbf{3}]/dt = k_2[\mathbf{3}]^{\alpha}[BH_4^-]^{\beta} + k_1[\mathbf{3}][OH^-],$$

$$-d[BH_4^-]/dt = \nu_2 k_2[\mathbf{3}]^{\alpha}[BH_4^-]^{\beta} + k_3[BH_4^-],$$

in which the term $k_3[BH_4^-]$ represents the rate of hydrolysis of sodium borohydride.

The hydrolysis of BH_4^- was studied and reported by several authors [19–22]. Experiments performed in our laboratory show that the rate of hydrolysis of sodium borohydride is very slow ($k_3 = 2.4 \times 10^{-5}$ l mol^{-1} s^{-1}) under experimental conditions. Moreover, UV analyses eliminate the formation of the imine **4** since this substance is not detected in the spectrum (Fig. 1).

The kinetic parameters were determined by the Ostwald method. To evaluate α, three series of measurements were performed using a fixed concentration of $NaBH_4$ (0.1 mol/1) and concentrations of **3** ranging from 1×10^{-3} to 4×10^{-3} mol/l (pH 12.89, $T = 25$°C,

[KCl] = 1 mol/l). In all cases, the curves log $[\mathbf{3}]_0/[\mathbf{3}] = f(t)$ came up to be straight lines with the slop: $\phi = k_2[BH_4^-]_0^\beta$ indicating that $\alpha = 1$ (Table 1). Similarly, β was determined by the same method and under the same conditions by fixing the concentration of **3** (2×10^{-3} mol/l) and varying the concentration of $NaBH_4$ from 0.05 to 0.50 mol/l. The dependence $\log\phi = f(\log[BH_4^-]_0^\beta)$ came out to be a line of slope $\beta \approx 0.99$ and Y axis intercept $\log k_2$ ($R^2 = 0.999$). Consequently, the second order rate constant at pH 12.89 and $T = 25$°C was found to be equal to $k_2 = 2.06 \times 10^{-3}$ $l\ mol^{-1}\ s^{-1}$.

The possibility of formation of organoborane compounds [23] was eliminated by NMR spectroscopy. The reaction mixture was extracted with hexane and its NMR ^{11}B spectrum recorded at 96.28 MHz with $BF_3 \cdot Et_2O$ as internal standard. The spectrum showed the presence of BH_4^- and its hydrolysis product $B(OH)_4^-$ only (Fig. 2). Furthermore, GC analysis indicated that **1** was formed in stoichiometric proportion with respect to **3**. These results prove that 3-azabicyclo[3.3.0]octane is the only product of reduction of *N*-chloro-3-azabicyclo[3.3.0]octane by sodium borohydride.

Table 1. Determination of partial, orders and rate constant in the reduction of *N*-chloro-3-azabicyclo[3.3.0]octane by BH_4^-

$[C_5H_{12}NCl]_0 \times 10^3$, mol/l	$[BH_4^-]_0$, mol/l	$\phi \times 10^4$, s^{-1}	$k_2 \times 10^3$, $l\ mol^{-1}\ s^{-1}$
1.01	0.10	1.99	1.99
2.00	0.11	2.26	2.04
3.10	0.10	2.07	2.07
4.05	0.10	2.15	2.15
1.97	0.50	9.98	2.00
1.97	0.25	5.38	2.15
1.96	0.05	1.06	2.12

Note: pH 12.89, [KCl] = 1 mol/l, $T = 25$°C.

Stoichiometry was determined by using equimolar concentrations of **3** and sodium borohydride (8×10^{-3} mol/l). The pH was fixed at 10.90 so as to accelerate the reduction step while limiting the degradation processes of **3** and $NaBH_4$. Access to $[BH_4^-]_\infty$ or $[\mathbf{3}]_\infty$ then made it possible to determine the reaction stoichiometry. Figure 3 represents the variation of **3** and BH_4^- concentrations as a function of time ($T = 25$°C, [KCl] = 1 mol/l). Towards the end of the reaction, $[BH_4^-]$ reached 3.79×10^{-3} mol/l, which lead to a $[\mathbf{3}]_0/([BH_4^-]_0 - [BH_4^-])$ ratio close to 2.11.

This value, being slightly larger than 2, is due to the simultaneous hydrolysis of BH_4^- in slightly alkaline media. Consequently,

$$-d[\mathbf{3}]/dt = -2d[BH_4^-]/dt \quad (\nu_2 = 2)$$

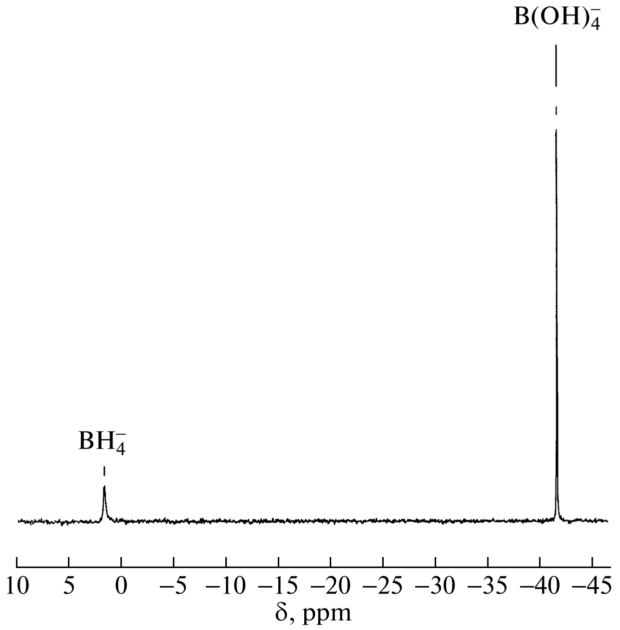


Fig. 2. Reduction of *N*-chloro-3-azabicyclo[3.3.0]octane by BH_4^-: ^{11}B NMR spectrum of aqueous mixture (96 MHz).

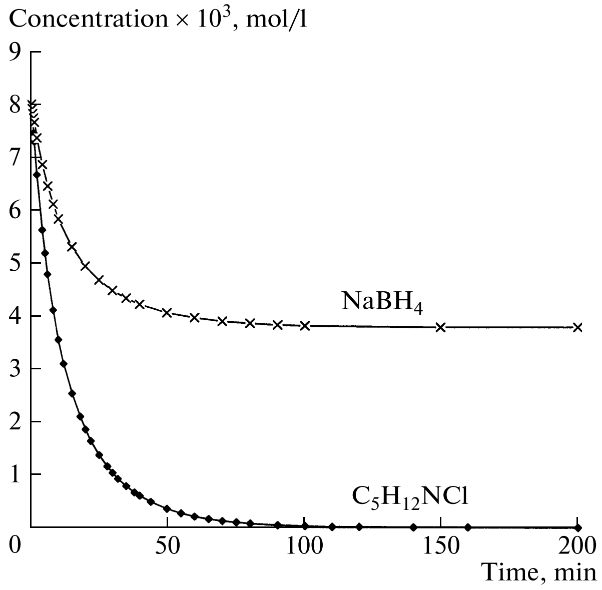


Fig. 3. Stoichiometry of *N*-chloro-3-azabicyclo-[3.3.0]octane with BH_4^- interaction ($[C_5H_{12}NCl]_0 = [BH_4^-]_0 = 8 \times 10^{-3}$ mol/l, pH 10.90, $T = 25$°C, [KCl] = 1 mol/l).

Table 2. Influence of pH on the reduction of *N*-chloro-3-azabicyclo[3.3.0]octane by BH_4^-

pH	$k_2 \times 10^3$, l mol^{-1} s^{-1}
11.84	20.00
11.86	18.00
12.03	14.20
12.11	14.00
12.22	9.85
12.30	7.36
12.60	4.20
12.89	2.06
13.50	0.84

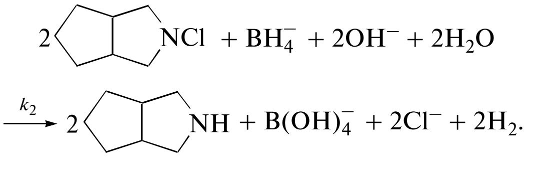
Note: $[C_5H_{12}NCl]_0 \approx 2 \times 10^{-3}$ mol/l, $[BH_4^-]_0 = 0.1$ mol/l, [KCl] = 1 mol/l, $T = 25$°C.

Table 3. Influence of buffer solution on the reduction of *N*-chloro-3-azabicyclo[3.3.0]octane by BH_4^-

$[Na_2HPO_4]$, mol/l	$[Na_2CO_3]$, mol/l	pH	$k_2 \times 10^3$, l mol^{-1} s^{-1}
0.025	–	11.90	19.96
0.050	–	11.90	18.20
0.100	–	11.90	20.00
0.200	–	11.90	18.72
0.025	–	12.00	14.00
0.050	–	12.00	14.12
–	0.025	12.00	14.08
–	0.050	12.00	14.03

Note: $[C_5H_{12}NCl]_0 \approx 2 \times 10^{-3}$ mol/l, $[BH_4^-]_0 = 0.1$ mol/l, [KCl] = 1 mol/l, $T = 25$°C.

and the reaction may be represented by the following equation:



(IV)

Influence of Temperature

The temperature effect was studied between 15 and 45°C (pH 12.89). Concentrations of BH_4^- and **3** used were equal to 0.1 and 2×10^{-3} mol/l respectively ([KCl] = 1 mol/l). The variation of k_2 with temperature was found to comply with Arrhenius law. The curve $\log k_2 = f(1/T)$ is a line of slope $-E_2/R$ and a *Y* axis intercept $\log A_2$ ($R = 0.999$). A_2 and E_2 represent the Arrhenius factor and activation energy, respectively.

$$k_2 = 1.01 \times 10^9 \exp(-66.36/RT) \text{ l mol}^{-1} \text{ s}^{-1}$$
$$(E_2 \text{ in kJ/mol}).$$

The enthalpy and entropy of activation can be shown to be:

$$\Delta H_2^{0\#} = E_2 - RT$$

$$\text{and } \Delta S_2^{0\#} = \log(A_2 h)/(e k_B T),$$

where k_B is the Boltzmann constant and h is the Planck constant ($k_B = 1.38033 \times 10^{-23}$ J/K, $h = 6.623 \times 10^{-34}$ J s). The calculated values are:

$$\Delta H_2^{0\#} = 63.9 \text{ kJ/mol}$$

$$\text{and } \Delta S_2^{0\#} = -80.8 \text{ J mol}^{-1} \text{ K}^{-1}.$$

Influence of pH

Kinetic measurements of 2×10^{-3} mol/l *N*-chloro-3-azabicyclo[3.3.0]octane and 0.1 mol/l $NaBH_4$ solutions at pH values ranging between 11.80 and 13.50 were carried out ($T = 25$°C, [KCl] = 1 mol/l). pH adjustments were made by either concentrating the sodium hydroxide or the use of a Na_2HPO_4–NaOH buffer. In strongly alkaline media, dehydrohalogenation of **3** becomes competitive ($k_1 = 103 \times 10^{-6}$ l mol^{-1} s^{-1}) and thus must be considered in the rate of disappearance of **3**:

$$-d[\mathbf{3}]/dt = k_2[BH_4^-]_0[\mathbf{3}] + k_1[OH^-]_0[\mathbf{3}] = y[\mathbf{3}],$$

where $k_2 = (y - k_1[OH^-]_0)/[BH_4^-]_0$.

The experimental results are consigned in Table 2. It was observed that k_2 increases as pH decreases without affecting the established rate law (partial orders and stoichiometry). While calculated to be equal to 0.84×10^{-3} l mol^{-1} s^{-1} at pH 13.5, k_2 increases rapidly to reach 20×10^{-3} l mol^{-1} s^{-1} at pH 11.84.

This phenomenon may be explained by considering a specific acid catalysis, which leads to an expression of k_2 in the form (**3** = $C_5H_{12}NCl$ or RR'NCl)

$$k_2 = k_2' + k_2'' a_{H^+}^{\gamma} / K_a^{C_5H_{12}NHCl^+}, \quad (1)$$

where γ is the partial order with respect to H^+, $K_a^{C_5H_{12}NHCl^+}$ is the acidity constant of the protonated form of **3**, and k_2', k_2'' are the rate constants of the neutral and catalyzed process, respectively. The curve $k_2 = f$(pH) indicates that the global rate constant depends on the H^+ ions over the entire pH range. This result shows that the neutral process is very slow and k_2' can be neglected in relation (1). For $a_{H^+} \approx [H^+]$, the curve

$\log k_2 = f(\mathrm{pH})$ is a straight line of slope 0.97 ($R^2 = 0.997$):

$$\log k_2 = \log k_{\mathrm{H^+}} - \gamma(\mathrm{pH}),$$

where $k_{\mathrm{H^+}} = k_2''/K_{\mathrm{a}}^{\mathrm{C_5H_{12}NHCl^+}}$. Taking into account the experimental errors on rate constants and activity coefficients, it may be deduced that $\gamma = 1$ and $k_{\mathrm{H^+}} = 5.82 \times 10^9\ \mathrm{l^2\ mol^{-2}\ s^{-1}}$ at 25°C.

To verify the specific acid catalysis hypothesis, experiments were carried out by modifying the nature and the concentration of the buffer solution. KG concentration and pH are nevertheless kept constant. Table 3 shows that k_2 remains constant, which confirms the above hypothesis. Accordingly the rate law follows:

$$-\mathrm{d}[\mathrm{C_5H_{12}NCl}]/\mathrm{d}t = k_2'[\mathrm{C_5H_{12}NCl}][\mathrm{BH_4^-}] + k_2''[\mathrm{C_5H_{12}NHCl^+}][\mathrm{BH_4^-}]. \quad (2)$$

By replacing $[\mathrm{C_5H_{12}NHCl^+}]$ by its value,

$$[\mathrm{C_5H_{12}NHCl^+}] = [\mathrm{C_5H_{12}NCl}][\mathrm{H^+}]/K_{\mathrm{a}}^{\mathrm{C_5H_{12}NHCl^+}},$$

relation (2) will reduce to (3):

$$\begin{aligned}&-\mathrm{d}[\mathrm{C_5H_{12}NCl}]/\mathrm{d}t\\ &= (k_2' + [\mathrm{H^+}]k_2''/K_{\mathrm{a}}^{\mathrm{C_5H_{12}NHCl^+}})[\mathrm{C_5H_{12}NCl}][\mathrm{BH_4^-}] \quad (3)\\ &= k_2[\mathrm{C_5H_{12}NCl}][\mathrm{BH_4^-}].\end{aligned}$$

For substituted chloramines, the first term being very low ($k_2' \longrightarrow 0$), the preceding relation becomes

$$-\mathrm{d}[\mathrm{C_5H_{12}NCl}]/\mathrm{d}t \cong k_{\mathrm{H^+}}[\mathrm{C_5H_{12}NCl}][\mathrm{BH_4^-}][\mathrm{H^+}].$$

Application to the Synthesis of N-Amino-3-azabicyclo[3.3.0]octane

The optimization of the synthesis of **2** has been the subject of a previous study [14]. Under the optimal experimental conditions, the concentration of **3** reaches 0.02 mol/1 (0.3%). Once **2** and **3** are formed, the dehydrohalogenation of $\mathrm{C_5H_{12}NCl}$ is slow and requires several hours. Its reduction by sodium borohydride must then intervene before its conversion into **4**.

Since the synthesis of **1** is carried out at constant pH 12.89 ([NaOH] = 0.1 mol/1) [14], then the factors that influence the reduction step are the concentration of sodium borohydride and temperature. Their effects can be evaluated by resolving the following differential system derived from reactions **(III)** and **(IV)**:

$$-\mathrm{d}[\mathrm{C_5H_{12}NCl}]/\mathrm{d}t = k_2[\mathrm{C_5H_{12}NCl}][\mathrm{BH_4^-}] + k_1[\mathrm{C_5H_{12}NCl}][\mathrm{OH^-}], \quad (4)$$

$$-\mathrm{d}[\mathrm{BH_4^-}]/\mathrm{d}t = 0.5k_2[\mathrm{C_5H_{12}NCl}][\mathrm{BH_4^-}], \quad (5)$$

Table 4. Reduction of *N*-chloro-3-azabicyclo[3.3.0]octane by sodium borohydride. Variation of imine concentration as a function of temperature for pH 12.89 and 13.50

T, °C	pH 12.89	pH 13.50
	[imine] × 10^4, mol/l	
5	4.90	65.4
15	7.08	82.8
25	9.78	104.3
50	20.6	137.1
75	36.7	161.9
100	56.1	176.9

Note: $[\mathrm{C_5H_{12}NCl}]_0 = 0.02$ mol/l, $[\mathrm{BH_4^-}]_0 = 0.1$ mol/l.

$$\mathrm{d}[\mathrm{imine}]/\mathrm{d}t = k_1[\mathrm{C_5H_{12}NCl}][\mathrm{OH^-}], \quad (6)$$

$$\mathrm{d}[\mathrm{C_5H_{12}NCl}]/\mathrm{d}t = k_2[\mathrm{C_5H_{12}NCl}][\mathrm{BH_4^-}]. \quad (7)$$

If $[\mathrm{BH_4^-}]_0$ and $[\mathrm{C_5H_{12}NCl}]_0$ were the initial concentrations and if *t* were eliminated from Eqs. (4) and (5), relation (8) would be obtained:

$$[\mathrm{C_5H_{12}NCl}] = [\mathrm{C_5H_{12}NCl}]_0 + 2\{[\mathrm{BH_4^-}] - [\mathrm{BH_4^-}]_0 + \log([\mathrm{BH_4^-}]/[\mathrm{BH_4^-}]_0)^r\}, \quad (8)$$

where $r = k_1/k_2$. When **3** is completely consumed, $[\mathrm{BH_4^-}]_\infty$ may be calculated from the equation

$$[\mathrm{C_5H_{12}NCl}]_0 + 2\{[\mathrm{BH_4^-}]_\infty - [\mathrm{BH_4^-}]_0 + \log([\mathrm{BH_4^-}]_\infty/[\mathrm{BH_4^-}]_0)^r\} = 0. \quad (9)$$

Equations (6), (7), and (8) allowed the determination of the reaction time and the final concentrations of 3-azabicyclo[3.3.0]octane and 3-azabicyclo[3.3.0]oct-2-ene:

$$[\mathrm{C_5H_{12}NCl}]_\infty = 2([\mathrm{BH_4^-}]_0 - [\mathrm{BH_4^-}]_\infty),$$

$$[\mathrm{imine}]_\infty = [\mathrm{C_5H_{12}NCl}]_0 - [\mathrm{C_5H_{12}NCl}]_\infty,$$

$$\int\limits_{[\mathrm{BH_4^-}]_0}^{[\mathrm{BH_4^-}]} \frac{\mathrm{d}[\mathrm{BH_4^-}]}{[\mathrm{BH_4^-}]g(r,\ [\mathrm{BH_4^-}])} - 0.5k_2\int\limits_0^t \mathrm{d}t = 0.$$

To optimize the process, it is necessary to examine the effect of the ratio of the initial concentrations ($m = [\mathrm{BH_4^-}]_0/[\mathrm{C_5H_{12}NCl}]_0$) and temperature on the reduction of **3**. Table 4 expresses the temperature effect for $m = 5$ and pH 12.89, and 13.50. At higher temperatures, reduction of **3** becomes less favourable. For example, the yield of the reduced product decreases by 7% when the temperature is increased from 15 to 50°C. At 50°C and pH 12.89, *N*-chloro-3-azabicyclo[3.3.0]octane is consumed in less than

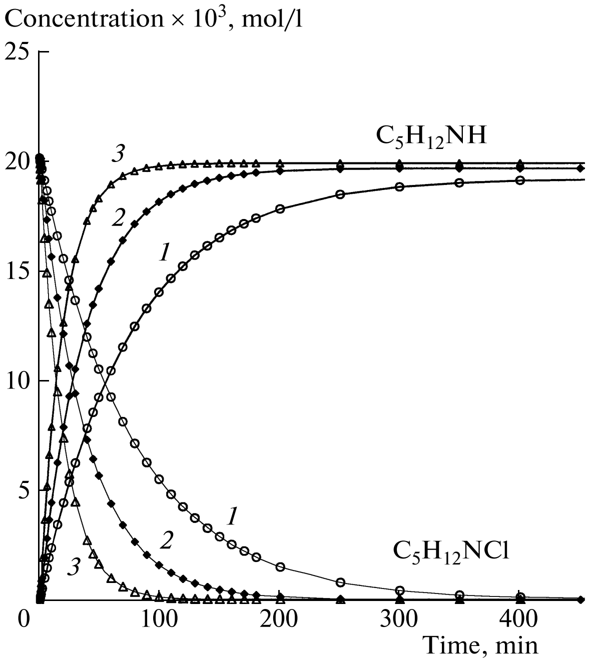


Fig. 4. Reduction of *N*-chloro-3-azabicyclo[3.3.0]octane by BH_4^-. Variation of $C_5H_{12}NH$ and $C_5H_{12}NCl$ concentrations as a function of $[NaBH_4]_0/[C_5H_{12}NCl]_0$ ratio (*m*): *1*—5, *2*—10, *3*—20. pH 12.89, ($[C_5H_{12}NCl]_0$ = 0.02 mol/l, *T* = 25°C.

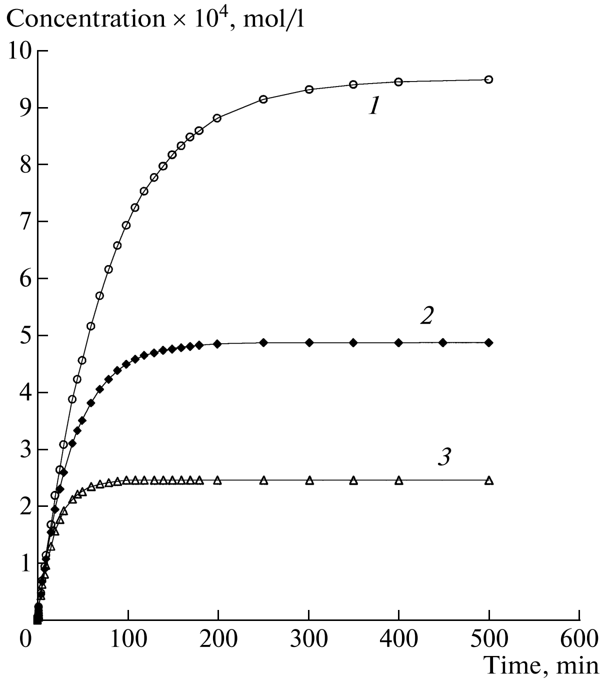


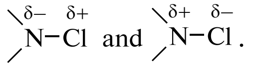
Fig. 5. Reduction of *N*-chloro-3-azabicyclo[3.3.0]octane by BH_4^-. Variation of imine concentration as a function of $[NaBH_4]_0/[C_5H_{12}NCl]_0$ ratio (*m*): *1*—5, *2*—10, *3*—20. pH 12.89, ($[C_5H_{12}NCl]_0$ = 0.02 mol/l, *T* = 25°C.

60 min, but the yield of 3-azabicyclo[3.3.0]oct-2-ene reaches 10.3%.

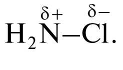
Figures 4 and 5 show the results of a mathematical treatment at T = 25°C and pH 12.89 based on $[BH_4^-]_0/[C_5H_{12}NCl]_0$ ratio. These are the optimal conditions for the quantitative reduction of the substituted chloramine formed. Thus, the percentage of reduced **3** reaches 95% when *m* exceeds 5, and is close to 98.8% when *m* = 50.

Mechanism

The experimental results show that RR'NCl–$NaBH_4$ reaction follows a second order rate law and presents specific acid catalysis. This phenomenon can be interpreted by noting that substituted chloramines may be represented by the following two configurations depending on the nature of substituents and experimental conditions:

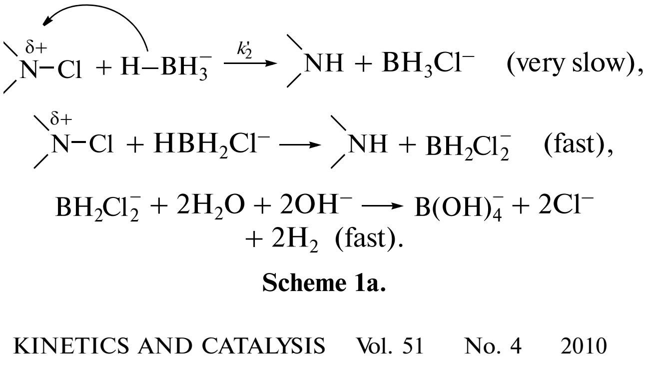


In the case of chloramine (R = R' = H), the polarization of N–Cl bond is induced by chlorine electronegativity:

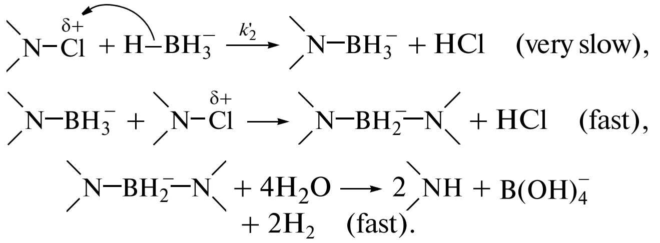

$$\overset{\delta+}{H_2N}-\overset{\delta-}{Cl}.$$

This configuration is confirmed by theoretical studies [24, 25]. Moreover, NH_2Cl has been shown to be subject to nucleophilic attack by ammonia or amines leading to hydrazines [14, 26]. Substitution of hydrogen by an alkyl group decreases the partial positive character of the nitrogen atom and consequently, may cause an inversion in the N–Cl polarization. From what preceded, different mechanisms for the reduction of **3** could be postulated.

(i) The first mechanism involves an initial attack by BH_4^- on neutral substituted chloramine. In this case, this attack may be postulated to take place on the N nucleus as in Scheme 1a, or on the Cl nucleus as in Scheme 1b. Since k_2' of the reaction in neutral solution has been found to be very small, then the contribution of such a mechanism to the reduction process is insignificant.

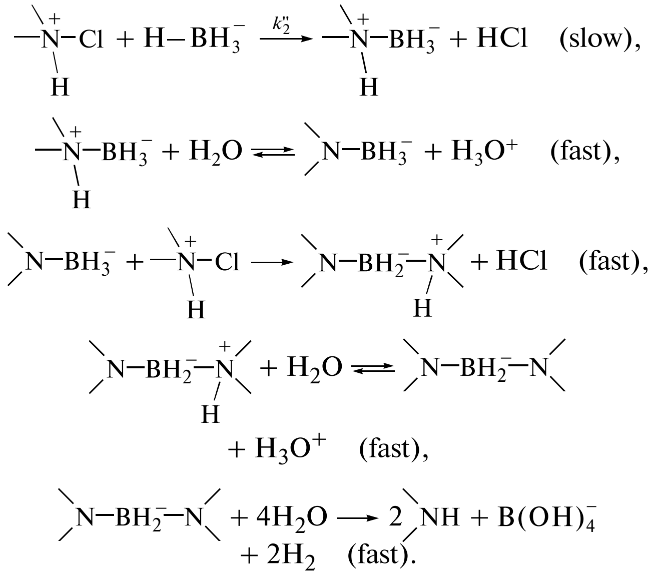


Scheme 1a.



Scheme 1b.

(ii) The second mechanism involves an initial attack by the borohydride ion on a protonated substituted chloramine. The reaction is fast and the nucleophilic attack takes place on the positive chlorine with a rate constant k_2'' resulting in the formation of borane–amine intermediates. Borane intermediates are subsequently decomposed leading to RR'NH and $B(OH)_4^-$ shown by scheme 2.



Scheme 2.

The schemes proposed are consistent with the kinetic law. They lead to the established formula (1) where the first term k_2' may be neglected. In addition, the formation of hydrogen is confirmed experimentally.

Complementary trials were carried under the same experimental conditions and the volume of the evolved gas was measured. The ratio of $[H_2]/[RR'NCl]$ is found to be slightly more than 1. This is due to the partial hydrolysis of borohydride ion that- accompanies the reduction step.

The above results show that it is possible to reduce *N*-chloro-3-azabicyclo[3.3.0]octane by sodium borohydride under mild conditions (m = 50, pH 12.89, T = 25°C). This operation eliminates the formation of 3-azabicyclo[3.3.0]oct-2-ene and subsequent formation of polymeric precipitates. In concentrated media, the rate and equilibrium constants vary with ionic strength. The kinetic treatment then remains a convenient way that describes the evolution of the reaction system.

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