JOURNAL OF PHYSICAL ORGANIC CHEMISTRY
J. Phys. Org. Chem. 2002; **15:** 363–373

Kinetics of reduction of chloramines by sodium borohydride

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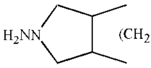
Received 23 October 2001; revised 11 February 2002; accepted 20 February 2002

ABSTRACT: The reduction of chloramine, methylchloramine, dimethylchloramine and *N*-chloro-3-azabicyclo[3.3.0]octane by sodium borohydride was studied according to pH, temperature and concentrations of haloamine and reducing agent. The interaction is bimolecular and exhibits a specific acid catalysis. The enthalpy and entropy of activation were determined at pH 12.89. A mathematical treatment of the reaction kinetics allows the complete characterization of the final state and determination of the percentage of reduced haloamine in terms of $[NaBH_4]/[R_1R_2NCl]$ ratio, pH and temperature. A reaction mechanism is proposed. Copyright © 2002 John Wiley & Sons, Ltd.

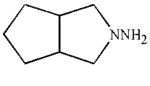
KEYWORDS: kinetics; reduction; chloramine; methylchloramine; dimethylchloramine; *N*-chloro-3-azabicyclo[3.3.0]octane; sodium borohydride; Raschig

INTRODUCTION

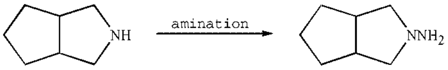
This work relates to the reactivity of chloramines with the aim of applying the Raschig synthesis to the development of a powerful process for the preparation of *N*-amino-3-azabicyclo[3.3.0]octane (**2**) (NAZA). Unsymmetrical alicyclic hydrazines described by the formula



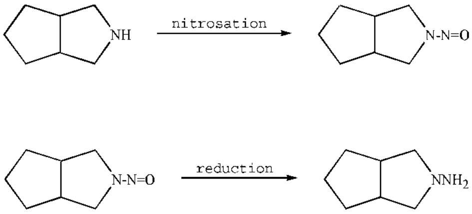
are used in the pharmaceutical industry as precursors of hypoglycemic, diuretic, anti-infectious and cardiovascular drugs.[1–4] In particular, NAZA ($n = 3$) reacts with arylsulfonylurethanes to give a glyclazide used for treatment of non-insulin-dependent diabetics:[5]



One of the greatest difficulties in the synthesis is the *N*-amination of 3-azabicyclo[3.3.0]octane (**1**) (AZA) leading to the corresponding hydrazine:



At present, the only method described in the literature involves nitrosation of 3-azabicyclo[3.3.0]octane, followed by reduction of the 1-nitroso-3-azabicyclo[3.3.0]octane formed:[4–10]



This process leads to a high yield (96%, $T = 25\,°C$, $[H_2SO_4] = 2.5\,\text{M}$), but involves toxic intermediates (nitrosamines) and flammable solvents, which imply several problems for industrial application. In order to avoid these inconveniences, we applied the Raschig procedure,[11–13] which is carried out according to the following two steps:

$$NH_3 + OCl^- \longrightarrow NH_2Cl + OH^-$$

$$R_1R_2NH + NH_2Cl + OH^- \longrightarrow R_1R_2NNH_2 + H_2O + Cl^-$$

This more environmentally sound route constitutes a

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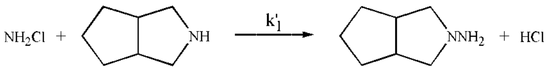
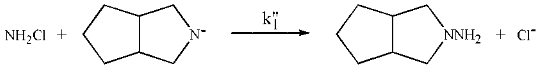
general method for the preparation of unsymmetrical substituted hydrazines. However, it has the disadvantage of leading to numerous by-products. Let us examine successively each step of the reaction chain.

1. The NH_2Cl–AZA interaction constitutes a useful step of the synthesis. It was studied in terms of concentrations, pH and temperature.[14,15] At pH $\geq$12.89, the reaction is bimolecular and involves two competitive processes, neutral (independent of pH) and ionic, implying the dissociation of either amine or chloramine. The results can be interpreted according to an S_N^2 mechanism in which chloramine interacts with the ionic and neutral forms of **1**:[15]



(1)

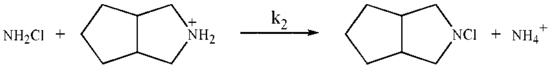


(2)

The rate constant includes two terms one of which varies as a function of the alkalinity of the medium: $k_1 = k'_1 + k''_1/a_{H^+}$. At pH <12.5, k_1 remains almost constant at 25 °C, then increases rapidly with increase in OH^- activity ($\Delta H_1^{\circ 1} = 59.8$ kJ mol^{-1}, $\Delta S_1^{\circ 1} = -86.5$ J mol^{-1} K^{-1}). At $T = 25$ °C, $k'_1 = 38.7 \times 10^{-3}$ M^{-1} s^{-1} and $k''_1 = 2.30 \times 10^{-16}$ s^{-1}.[14]

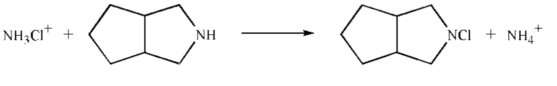
2. The NH_2Cl–AZA interaction undergoes a change of orientation according to acidification of the medium.[15,16] In slightly alkaline medium, the quantity of **2** decreases in favor of *N*-chloro-3-azabicyclo[3.3.0]octane (**3**) (CIAZA), which becomes preponderant at pH 8.

The chlorine transfer reaction is reversible and follows a first-order law with respect to **1** and chloramine. The results were quantified by an ionic mechanism involving the protonation of either amine or chloramine [$K_a^{AZAH^+} = 2.04 \times 10^{-11}$ (Ref. 15, $K_a^{NH_3Cl^+} = 3.41 \times 10^{-2}$ (Ref. 17 and 18:[16]



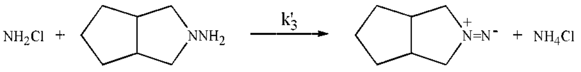
(3)

or



The rate constant and thermodynamic parameters are as follows: $k_2 = 5.02 \times 10^{10} \exp(-66.52/RT)$ M^{-1} s^{-1} (E_2 in kJ mol^{-1}), $k_2 = 114 \times 10^{-3}$ M^{-1} s^{-1} at 25 °C, $\Delta H_2^{\circ 1} = 63.9$ kJ mol^{-1} and $\Delta S_2^{\circ 1} = -48.3$ J mol^{-1} K^{-1}.

3. As NAZA is formed, it is partially oxidized by chloramine according to two consecutive steps.[15,19] The first, involving the neutral and ionic forms of **2**, leads transiently to an aminonitrene:



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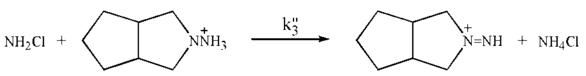


(5)

The kinetic law is expressed by

$$-\mathrm{d[NAZA]/d}t = k'_3[\mathrm{NH_2Cl}][\mathrm{NAZA}] + k''_3[\mathrm{NH_2Cl}][\mathrm{NAZAH^+}]$$

where k'_3 and k''_3 are the rate constants of reactions (4) and (5), respectively. The interaction exhibits a phenomenon of specific acid catalysis and the global rate constant is linear versus a_{H^+} [$K_a^{NAZAH^+} = 2.5 \times 10^{-7}$ (Ref. 15]:

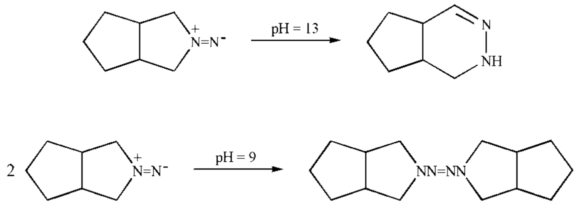
$$k_3 = k'_3 + k''_3 a_{H^+}/K_a^{NAZAH^+}$$

At $T = 25$ °C and for $a_{H^+} \approx [H^+]$:

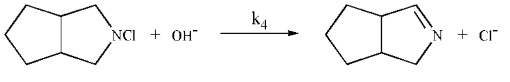
$$k'_3 = 15.8 \times 10^{-3}\mathrm{M^{-1}s^{-1}};\ k''_3 = 6.75 \times 10^2\mathrm{M^{-1}s^{-1}}$$

The activation parameters were determined at pH 12.89 where the ionic process (NH_2Cl–$NAZAH^+$) is negligible. The values obtained are as follows:[19] $\Delta H_3^{\circ 1} = 41.3$ kJ mol^{-1}, $\Delta S_3^{\circ 1} = -140$ J mol^{-1} K^{-1} and $k_3 = 0.78 \times 10^6 \exp(-43.85/RT)$ M^{-1} s^{-1} (E_3 in kJ mol^{-1}).

The second step involves the conversion of aminonitrene. Depending on the pH value, it leads to 3,4-diazabicyclo[4.3.0]non-2-ene or azo-3-azabicyclo[3.3.0]octane:[15,20,21]



4. In alkaline medium, **3** undergoes a dehydrohalogenation to give an imine derivative, the 3-azabicyclo[3.3.0]oct-2-ene **4**:[15,22]



(6)

The kinetics of 3-azabicyclo[3.3.0]oct-2-ene formation were studied as a function of temperature and the concentrations of **3** and NaOH. The reaction is bimolecular and follows an E_2 mechanism with the following parameters:[22] $k_4 = 2.95 \times 10^{11} \exp(-91.63/RT)$ M^{-1} s^{-1}

(E_4 in kJ mol^{-1}), $k_4 = 103 \times 10^{-6}\,\mathrm{M}^{-1}\ \mathrm{s}^{-1}$ at 25 °C, $\Delta H_4^{\circ 1} = 89$ kJ mol^{-1} and $\Delta S_4^{\circ 1} = -33.6$ J mol^{-1} K^{-1}.

5. NH_2Cl is unstable and must be maintained at pH ≥ 10 to avoid its conversion into $NHCl_2$ and NCl_3.[23–25] Moreover, in alkaline medium, it is decomposed with the formation of hydroxylamine as intermediate:[26–28]

$$NH_2Cl + OH^- \xrightarrow{k'_5} NH_2OH + Cl^- \quad \text{(slow)} \qquad (7a)$$

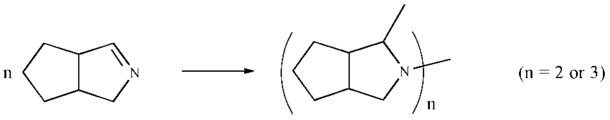
$$NH_2Cl + NH_2OH \xrightarrow{k''_5} H_2NNHOH + HCl \quad \text{(fast)} \qquad (7b)$$

NH_2OH reacts with a second molecule of chloramine leading to hydroxylhydrazine, which is transformed to several products upon contact with oxygen O_2.[29] In any case, the reaction follows a second-order law ($-\mathrm{d}[NH_2OH]/\mathrm{d}t = 0$) and the rate constant with respect to NH_2Cl is found from the relation

$$-\mathrm{d}[NH_2Cl]/\mathrm{d}t = k_5[NH_2Cl][OH^-]$$

where $k_5 = 2\ k'_5 = 62 \times 10^{-6}\,\mathrm{M}^{-1}\ \mathrm{s}^{-1}$ at 25 °C ($E_5 = 86.9$ kJ mol^{-1}).[29,30]

The imines are likely to precipitate in monomeric or polymeric form. In particular, during the synthesis of **2**, 3-azabicylo[3.3.0]oct-2-ene is accumulated and precipitates as a white solid:



To avoid its precipitation, two approaches are then possible: (i) the use of a suitable reductant to convert **4** into the corresponding amine or (ii) the reduction of **3** before its transformation into 3-azabicyclo[3.3.0]oct-2-ene.

The neutralization of mechanisms leading to the formation of precipitates requires structural characterization of solid polymer, quantification of reaction process and the use of a suitable reducing agent. The structural characterization being separately studied, this work relates to the reduction of *N*-chloro-3-azabicyclo[3.3.0]octane by sodium borohydride in aqueous medium. In order to understand the reaction mechanism, a similar study was carried out using various chloramines. To our knowledge, no study about this interaction has been published previously.

EXPERIMENTAL

Reagents

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

Chloramine was prepared immediately before use by reacting an aqueous NH_3–NH_4Cl solution with sodium hypochlorite as described previously.[31] As substituted chloramines are not commercially available, they were obtained quantitatively by chlorination of their corresponding amines by hypochlorite ion (1–2% excess of R_1R_2NH).[15,22]

Apparatus

Two thermostated vessels were used, one on top of the other and joined by a conical fitting, and each one containing a reactant. 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. 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 the rapid introduction of ampoule contents into the 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 maintained within ±0.1 °C. A glass electrode (Tacussel Model TB/HS) and a calomel reference electrode were used for pH measurements after suitable standardization with NBS buffer solutions. A Tacussel ISIS 20000 pH meter was used.

Procedure and analysis

The reactant solutions were prepared at the same pH and ionic strength ([KCl] = 1 M). Sodium borohydride was dissolved in a slightly alkaline medium in order to limit the hydrolysis processes. It was introduced into the reactor after adjusting the pH value. Its content was controlled by the iodimetric method.[32] While thermal equilibrium was being reached, an aqueous solution of haloamine was prepared, then rapidly treated according to the above procedure. Haloamines show a UV absorption in water.[33] They were analysed at their wavelengths of maximum absorption. The UV spectra were measured with a Cary 1E double-beam spectrophotometer. 3-Azabicyclo[3.3.0]octane was determined by gas chromatography (GC). GC analyses were carried out on an HP 6890 gas chromatograph (Hewlett-Packard) equipped with EPC modules allowing the control and measurement of gas flows and pressures at different levels of the apparatus. The separation was performed on a 25 m × 530 µm i.d. ($d_f = 2$ µm) CP WAX 51 column.

RESULTS AND DISCUSSION

Kinetics of reduction of *N*-chloro-3-azabicyclo[3.3.0]octane

One of the difficulties of kinetic study is the low solubility of **3** in water. To operate in homogeneous medium, it is therefore necessary to use low concentrations. For example, at 25 °C and pH 7, **3** is soluble at 10^{-2} M. At [NaOH] = 1 M, its solubility does not exceed 4×10^{-3} M. GC analysis is not suitable because **3** is partially decomposed in the injector. Preliminary trials have shown that the **1**–**3** interaction is negligible under experimental conditions. The reaction kinetics were followed by UV spectrophotometry.

Reaction order and stoichiometry. Measurements were conducted at 25 °C at an $NaBH_4$ concentration between 0.05 and 0.5 M. The rate law was first established at pH 12.89 (0.1 M NaOH) in order to limit the hydrolysis of **3** and sodium borohydride. To maintain a constant ionic strength, experiments were carried out using potassium chloride at 1 M. Under these conditions, the rates of disappearance of **3** and BH_4^- are expressed by the relations

$$-\,d[\text{ClAZA}]/dt = k_6[\text{ClAZA}]^{\alpha}[\text{BH}_4^-]^{\beta} + k_4[\text{ClAZA}][\text{OH}^-]$$

$$-\,d[\text{BH}_4^-]/dt = \nu_6 k_6[\text{ClAZA}]^{\alpha}[\text{BH}_4^-]^{\beta} + k_7[\text{BH}_4^-]$$

where $k_7[BH_4^-]$ represents the rate of hydrolysis of sodium borohydride. This interaction has been studied by several workers.[34–37] Under the operating conditions, the experiments performed in our laboratory showed that the degradation of BH_4^- is very slow ($k_7 = 2.4 \times 10^{-5}$ M^{-1} s^{-1}). Moreover, UV analyses did not show any interference between the absorption bands of **3** and **4** (Fig. 1), which confirms that the dehydrohalogenation of **3** can be neglected.

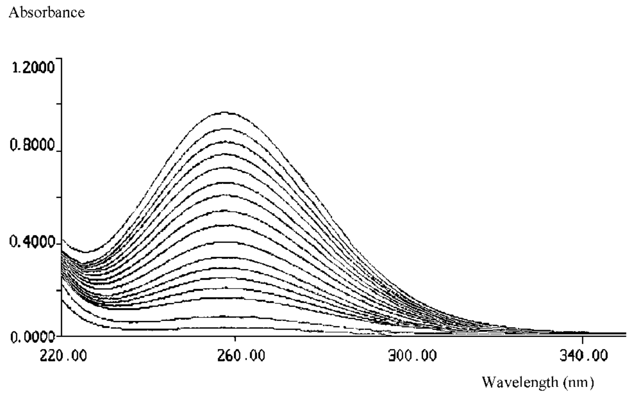


Figure 1. UV absorption spectra of reduction of *N*-chloro-3-azabicyclo[3.3.0]octane by sodium borohydride. $[\text{ClAZA}]_0 = 2.03 \times 10^{-3}$ M, $[BH_4^-]_0 = 0.1$ M, pH = 12.89 $T = 25$ °C, [KCl] = 1 M

Table 1. Reduction of *N*-chloro-3-azabicyclo[3.3.0]octane by BH_4^-: determination of partial orders and rate constant (pH 12.89, [KCl] = 1 M, T = 25 °C)

$[\text{ClAZA}]_0 \times 10^3$ (M)	$[BH_4^-]_0$ (M)	$\phi \times 10^4$ (s^{-1})	$k_6 \times 10^3$ (M^{-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

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

The curves

$$\log[\text{ClAZA}]_0/[\text{ClAZA}] = f(t)$$

are in all cases straight lines ($\alpha = 1$) with the same slope $\phi = k_6[BH_4^-]_0^{\beta}$ (Table 1). The value of β was determined under the same pH and temperature conditions with a constant concentration of **3** of 2×10^{-3} M and $NaBH_4$ concentration between 0.05 and 0.5 M. $\text{Log}\phi = f(\log[BH_4^-]_0^{\beta})$ is a straight line with a slope $\beta \approx 0.99$ and a *y*-intercept $\log k_6$ ($r^2 = 0.999$). In consequence, the bimolecular rate constant at pH 12.89 and $T = 25$ °C $k_6 = 2.06 \times 10^{-3}$ M^{-1} s^{-1}.

To check the possible formation of boron–organic compounds, the reaction mixture was extracted into hexane. ^{11}B NMR analysis at 96.28 MHz with $BF_3 \cdot Et_2O$ as internal standard showed the presence of BH_4^- and its hydrolysis product $B(OH)_4^-$. In addition, GC analysis indicated that 3-azabicyclo[3.3.0]octane is obtained in stoichiometric proportion according to **3**. These results show that **1** is the product of the reduction of **3** by sodium borohydride.

The stoichiometry was determined in equimolar conditions (8×10^{-3} M). The pH was fixed at 10.90 so as to accelerate the useful rate of reaction while limiting the degradation processes of **3** and $NaBH_4$. The access to $[BH_4^-]_\infty$ or $[\text{ClAZA}]_\infty$ means that it is possible to determine the reaction stoichiometry. Figure 2 shows the variation of ClAZA and BH_4^- concentrations as a function of time ($T = 25$ °C, [KCl] = 1 M). At the end of the reaction, the BH_4^- concentration reaches 3.79×10^{-3} M, which leads to a $[\text{ClAZA}]_0/([BH_4^-]_0 - [BH_4^-]_\infty)$ ratio close to 2.11. This value, slightly higher than 2, is due to simultaneous hydrolysis of BH_4^-

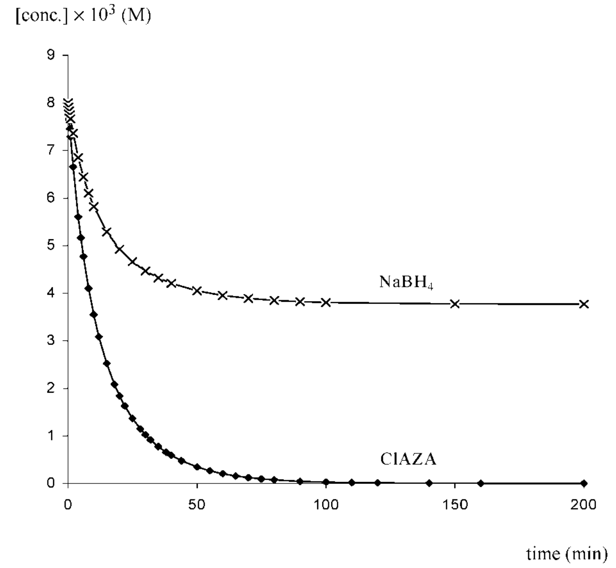
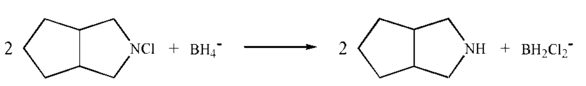


Figure 2. Stoichiometry of reduction of *N*-chloro-3-azabicyclo[3.3.0]octane by BH_4^-. $[ClAZA]_0 = [BH_4^-]_0 = 8 \times 10^{-3}$ M, pH = 10.90, T = 25 °C, [KCl] = 1 M

in alkaline medium. We deduce

$$-\mathrm{d}[\mathrm{ClAZA}]/\mathrm{d}t = -2\mathrm{d}[\mathrm{BH_4}^-]/\mathrm{d}t$$

The reaction is written as



(8)

Influence of temperature. The effect of temperature was studied at pH 12.89 between 15 and 45 °C for BH_4^- and **3** concentrations of 0.1 and 2×10^{-3} M respectively ([KCl] = 1 M). The variation of k_6 with temperature agrees with the Arrhenius law. The curve $\log k_6 = f(1/T)$ is a straight line with a slope $-E_6/R$ and a *y*-intercept $\log A_6$ ($r^2 = 0.999$). A_6 and E_6 represent the Arrhenius factor and activation energy, respectively.

$$k_6 = 1.01 \times 10^9 \exp(-66.36/RT)\mathrm{M}^{-1}\mathrm{s}^{-1} \quad (E_6 \text{ in kJ mol}^{-1})$$

The enthalpy and entropy of activation can be deduced to be $\Delta H_6^{\mathrm{o}1} = E_6 - RT$ and $\Delta S_6^{\mathrm{o}1} = \log(A_6 h)/(e k_\mathrm{B} T)$, where k_B is the Boltzmann constant and h is Planck's constant ($k_\mathrm{B} = 1.38033 \times 10^{-23}$ J K^{-1}, $h = 6.623 \times 10^{-34}$ J s). The numerical values are $\Delta H_6^{\mathrm{o}1} = 63.9$ kJ mol^{-1} and $\Delta S_6^{\mathrm{o}1} = -80.8$ J mol^{-1} K^{-1}.

Table 2. Influence of pH on the reduction of *N*-chloro-3-azabicyclo[3.3.0]octane by BH_4^- ($[ClAZA]_0 = 2 \times 10^{-3}$ M, $[BH_4^-]_0 = 0.1$ M, T = 25 °C, [KCl] = 1 M)

$[\mathrm{ClAZA}]_0 \times 10^3$ (M)	$[\mathrm{NaBH_4}]_0$ (M)	pH	$k_6 \times 10^3$ (M^{-1} s^{-1})
1.86	0.1	11.84	20
1.89	0.1	11.86	18
2.02	0.1	12.03	14.2
2.02	0.1	12.11	14
1.95	0.1	12.22	9.85
1.97	0.1	12.30	7.36
2.00	0.1	12.60	4.20
2.03	0.1	12.89	2.06
1.99	0.1	13.50	0.84

Influence of pH. Measurements were carried out at constant concentrations of **3** and sodium borohydride ($[\mathrm{ClAZA}]_0 \approx 2 \times 10^{-3}$ M, $[BH_4^-]_0 = 0.1$ M) in the pH range 11.80–13.50 ($T = 25$ °C, [KCl] = 1 M). The pH was adjusted by addition of sodium hydroxide or a buffer solution of Na_2HPO_4–NaOH mixture. In strongly alkaline medium, dehydrohalogenation of **3** must be considered ($k_4 = 103 \times 10^{-6}$ M^{-1} s^{-1}). The rate of disappearance of **3** becomes.

$$-\mathrm{d}[\mathrm{ClAZA}]/\mathrm{d}t = k_6[\mathrm{BH_4}^-]_0[\mathrm{ClAZA}] + k_4[\mathrm{OH}^-]_0[\mathrm{ClAZA}]$$
$$= y[\mathrm{ClAZA}]$$

where $k_6 = (y - \mathrm{k}_4\ [\mathrm{OH}^-]_0)/[\mathrm{BH_4}^-]_0$. The experimental results are presented in Table 2.

We observe that k_6 increases as the pH decreases without modifying the established rate law (partial orders and stoichiometry). Initially equal to 0.84×10^{-3} M^{-1} s^{-1} at pH 13.5, k_6 increases rapidly to reach 20×10^{-3} M^{-1} s^{-1} at pH 11.84.

These results can be explained by considering a specific acid catalysis phenomenon, which leads to the expression of k_6 in the form:

$$k_6 = k_6''(a_{\mathrm{H}^+})\gamma$$

where k_6'' and γ are the rate constant of the catalyzed process and the partial order in terms of H^+ ions, respectively.

For $a_{\mathrm{H}^+} \approx [\mathrm{H}^+]$, the curve $\log k_6 = f(\mathrm{pH})$:

$$\log k_6 = \log k_6'' - \gamma\,\mathrm{pH}$$

is a straight line with a slope of 0.97 ($r^2 = 0.997$). Taking into account the experimental errors in rate constants and activity coefficients, we deduce that $\gamma = 1$ and $k_6'' = 5.82 \times 10^9$ M^{-2} s^{-1} at 25 °C.

To check if the specific acid catalysis postulate is verified, experiments were performed while modifying the nature and strength of the buffer solution, with the KCl concentration and pH maintained constant. Table 3 shows that k_6 remains constant, which confirms the above hypothesis. The rate law is expressed as

$$-\mathrm{d}[\mathrm{ClAZA}]/\mathrm{d}t = k_6''[\mathrm{ClAZA}][\mathrm{BH_4}^-][\mathrm{H}^+]$$

Table 3. Reduction of *N*-chloro-3-azabicyclo[3.3.0]octane by BH_4^-: influence of buffer solution ($[ClAZA]_0 = 2 \times 10^{-3}$ M, $[BH_4^-]_0 = 0.1$ M, T = 25 °C, [KCl] = 1 M)

$[Na_2HPO_4]$ (M)	$[Na_2CO_3]$ (M)	$[ClAZA]_0 \times 10^3$ (M)	$[NaBH_4]_0$ (M)	pH	$k_6 \times 10^3$ (M)
0.025	—	2.10	0.1	11.90	19.9
0.050	—	2.04	0.1	11.90	18.2
0.100	—	2.00	0.1	11.90	20.0
0.200	—	2.01	0.1	11.90	18.7
0.025	—	2.02	0.1	12.00	14.0
0.050	—	2.00	0.1	12.00	14.1
—	0.025	2.04	0.1	12.00	14.1
—	0.050	2.01	0.1	12.00	14.0

The reduction of organic compounds by BH_4^- does not follow the same stoichiometry and leads to several products. In addition, a nucleophilic approach can occur on different atoms. In the case of *N*-chloro-3-azabicyclo[3.3.0]octane, it is very difficult to establish the approached site precisely because of the small electronic difference between N and Cl atoms. In order to understand the reaction mechanism, a similar study of the reduction of NH_2Cl, CH_3NHCl (MMC) and $(CH_3)_2NCl$ (DMC) by sodium borohydride was undertaken.

Kinetics of reduction of NH_2Cl, CH_3NHCl and $(CH_3)_2NCl$ by $NaBH_4$

The experimental results obtained at 25 °C and pH 12.89 are summarized in Table 4. As in the case of $NaBH_4$–ClAZA interaction, the kinetics follow a second-order law. For substituted chloramines, the stoichiometry was determined in the same manner as for **3**. In the case of chloramine, it was found by using an excess of NH_2Cl ($[BH_4^-]_0 = 4.08 \times 10^{-3}$ M, $[NH_2Cl]_0 = 23.54 \times 10^{-3}$ M, [KCl] = 1 M, pH = 11, T = 25 °C). ($[R_1R_2NCl]_0 - [R_1R_2NCl]_\infty)/[BH_4^-]_0$ was constant at a value close to 2, and the stoichiometry of reduction of chloramines by sodium borohydride is expressed as

$$-d[R_1R_2NCl]/dt = -2d[BH_4^-]/dt$$

The influence of pH was studied in the range 11–13.5 at a constant concentration of chloramines ($[R_1R_2NCl] = 2 \times 10^{-3}$ M) and for BH_4^- concentrations varying between 0.025 and 0.1 M (T = 25 °C, [KCl] = 1 M). We observed the specific acid catalysis previously observed in the case of **3**. For all substituted chloramines, $\log k_6 = f(\text{pH})$ is a straight line of slope unity (Fig. 3). In contrast, the curve $\log k_6 = f(\text{pH})$ corresponding to NH_2Cl includes two terms, one of which is independent of pH (Fig. 4).

The overall results are as follows for the haloamines: k_6 for NH_2Cl is $(42.7 \times 10^{-3}) + (2.83 \times 10^{10})$ $[H^+]$, for

Table 4. Reduction of chloramines by sodium borohydride: determination of partial orders and rate constants (*T* = 25 °C, [KCl] = 1 M, pH = 12.89)

RR′NCl	$[NaBH_4]_0$ (M)	$[RR'NCl]_0 \times 10^3$ (M)	$k_6 \times 10^3$ (M^{-1} s^{-1})
NH_2Cl	0.025	2.00	39.9
	0.05	2.02	41.1
	0.075	2.01	40.5
	0.1	1.02	40.9
	0.1	2.00	40.1
	0.1	4.00	41.7
CH_3NHCl	0.025	2.02	1.97
	0.05	2.03	1.91
	0.075	2.00	1.94
	0.1	2.00	1.94
	0.1	3.01	1.93
	0.1	4.01	1.98
$(CH_3)_2NCl$	0.025	2.02	3.29
	0.05	2.04	3.34
	0.075	2.02	3.39
	0.1	1.03	3.27
	0.1	2.00	3.41
	0.1	4.01	3.34

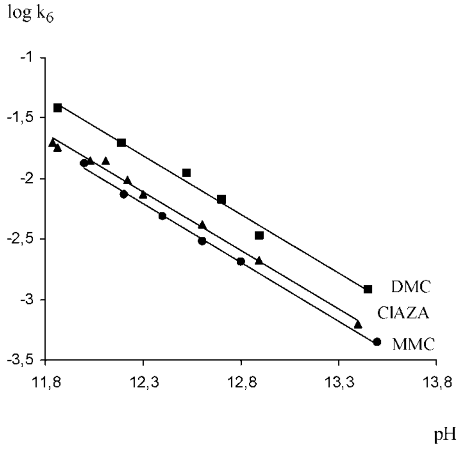


Figure 3. Plots of $\log k_6$ versus pH for reduction of *N*-chloramines by sodium borohydride. $[R_1R_2NCl]_0 = 2 \times 10^{-3}$ M, $[BH_4^-]_0 = 0.1$ M, T = 25 °C, [KCl] = 1 M

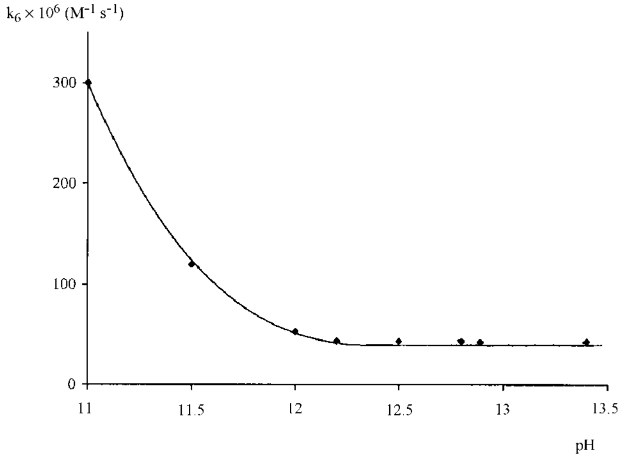


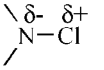
Figure 4. Influence of pH on the reduction of chloramine by sodium borohydride. $[NH_2Cl]_0 = 2 \times 10^{-3}$ M, $[BH_4^-]_0 = 0.025$ M, T = 25 °C, [KCl] = 1 M

MMC 5.20×10^9 $[H^+]$, for DMC 1.08×10^{10} $[H^+]$ and for ClAZA 5.82×10^9 $[H^+]$ M^{-1} s^{-1}.

The influence of temperature was established at pH 12.89 in the range 15–45 °C ([KCl] = 1 M). The activation parameters are given in Table 5.

Mechanism

The experimental results show that the $R_1R_2NCl–NaBH_4$ interaction is bimolecular and demonstrates a specific acid catalysis phenomenon. In the case of chloramine, we note two processes, one of which is independent of pH. At pH 12.89, its rate constant (40.7×10^{-3} M^{-1} s^{-1}) is higher than those of substituted chloramines. The latter remain close and are situated between 1.91×10^{-3} and 3.47×10^{-3} M^{-1} s^{-1}. These phenomena are interpreted by noting that R_1R_2NCl can exist in two possible forms:



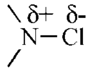
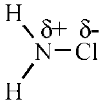


Table 5. Activation parameters of reduction of chloramines by sodium borohydride (pH = 12.89, [KCl] = 1 M)

RR′NCl	ΔH_6^{o1} (kJ mol^{-1})	ΔS_6^{o1} (J K^{-1} mol^{-1})	A_6 (M^{-1} s^{-1})	E_6 (kJ mol^{-1})
NH_2Cl	64.7	−52.9	2.45×10^{10}	66.94
MMC	65.1	−79.2	1.22×10^{9}	67.78
DMC	62.4	−82.9	7.82×10^{8}	64.85
ClAZA	63.9	−80.8	1.10×10^{9}	66.52

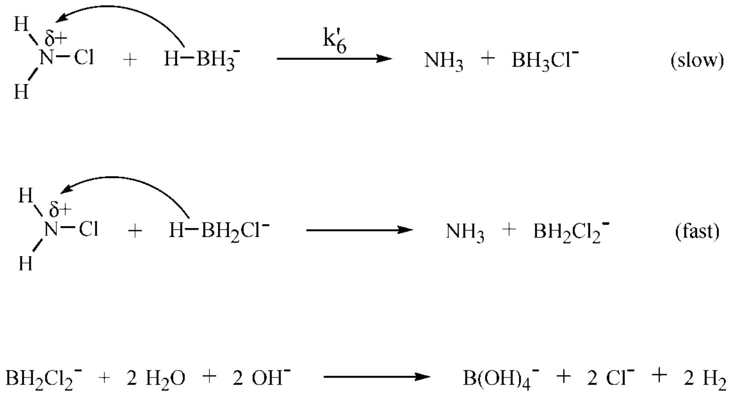
Their reactivity is thus a function of the substituents R_1, R_2 and the experimental conditions (pH, solvent, temperature). In the case of chloramine ($R_1 = R_2 = H$), the polarization of the N—Cl bond is rather induced by the chlorine electron-withdrawing effect:



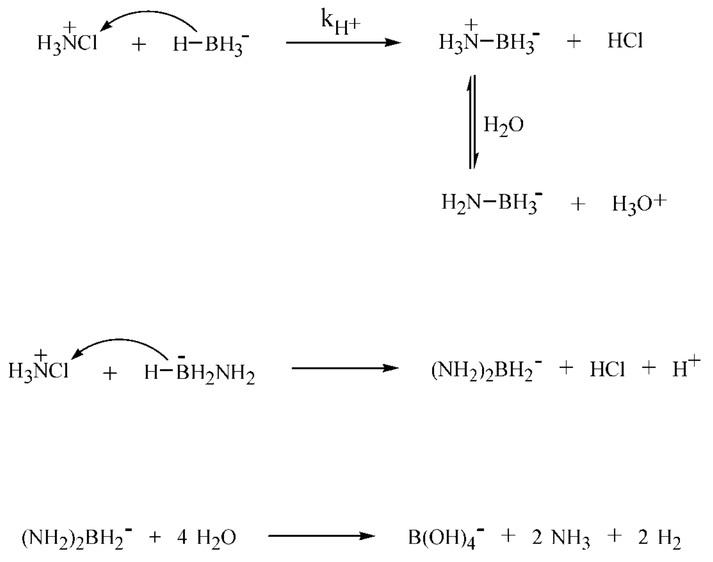
This polarization is confirmed by theoretical studies[38,39] and experimental results related to hydrazine formation after nucleophilic attack of the nitrogen lone pair of amines on the $-NH_2$ group of chloramine.[15,30] The mechanism consists in an attack of hydride ions as shown in Scheme 1 (rate constant k'_6).

In slightly alkaline medium, NH_3Cl^+ is formed. The hydride nucleophilic attack will take place on the positive chlorine (Scheme 2) according to a faster procedure (rate constant k_{H^+}). This scheme is in agreement with kinetic facts and leads to the established equation

$$k_6 = k'_6 + k''_6\ [H^+]$$



Scheme 1



Scheme 2

The rate law is then written

$$-\mathrm{d}[\mathrm{NH_2Cl}]/\mathrm{d}t = k_6'[\mathrm{NH_2Cl}][\mathrm{BH_4}^-] + k_{\mathrm{H^+}}[\mathrm{NH_3Cl^+}][\mathrm{BH_4}^-]$$

where $k_6'' = k_{\mathrm{H^+}}/K_{\mathrm{a}}^{\mathrm{NH_3Cl^+}}$.

The substitution of hydrogen by an alkyl group decreases the partial positive character of nitrogen atom and could cause an inversion of N—Cl polarization. Correlatively, the acidic character of chloramines increases as follows: $K_{\mathrm{a}}^{\mathrm{NH_3Cl^+}} < K_{\mathrm{a}}^{\mathrm{R_1NH_2Cl^+}} < K_{\mathrm{a}}^{\mathrm{R_1R_2NHCl^+}}$. The hydride nucleophilic attack becomes very slow compared with NH_2Cl and the R_1R_2NCl–$NaBH_4$ interaction will be more assisted by H^+ ions.

According to the nature of electrophilic site, two cases remain possible:

(i) a nucleophilic attack of hydride ions on the nitrogen atom $(R_1R_2\overset{\delta+}{N}-\overset{\delta-}{Cl})$ leads to a mechanism identical with that described previously (Scheme 1);

(ii) a nucleophilic attack of hydride ions on the chlorine atom $(R_1R_2\overset{\delta-}{N}-\overset{\delta+}{Cl})$ results in the formation of boron–amine intermediates, which are decomposed leading to R_1R_2NH and $B(OH)_4^-$ (Scheme 2).

The acid catalysis is then more important and follows a similar rate law. For substituted chloramines, the first term of Eqn. (9) is very small and can be neglected. The formation of hydrogen gas is confirmed by the experimental results. Moreover, the above mechanism is consistent with the established activation parameters.

Application to the synthesis of *N*-amino-3-azabicyclo[3.3.0]octane

The access to 3-azabicyclo[3.3.0]oct-2-ene formed during the synthesis of **2** is related to the resolution of the differential equations defined by the rate laws of reactions (1)–(7).

Let us represent by *a, x, y, u, z* and *s* the instantaneous concentrations of AZA, NH_2Cl, ClAZA, NAZA, OH^- and imine, respectively. The differential system is written as

$$-\mathrm{d}x/\mathrm{d}t = (k_1\alpha_{\mathrm{a}} + k_2\beta_{\mathrm{a}})xa_{\mathrm{t}} + (k_3'\alpha_{\mathrm{u}} + k_3''\beta_{\mathrm{u}})xu_{\mathrm{t}} + k_5xz \tag{10}$$

$$-\mathrm{d}a_{\mathrm{t}}/\mathrm{d}t = (k_1\alpha_{\mathrm{a}} + k_2\beta_{\mathrm{a}})xa_{\mathrm{t}} \tag{11}$$

$$\mathrm{d}y/\mathrm{d}t = k_2\beta_{\mathrm{a}}xa_{\mathrm{t}} - k_4yz \tag{12}$$

$$\mathrm{d}u_{\mathrm{t}}/\mathrm{d}t = k_1\alpha_{\mathrm{a}}xa_{\mathrm{t}} - (k_3'\alpha_{\mathrm{u}} + k_3''\beta_{\mathrm{u}})xu_{\mathrm{t}} \tag{13}$$

$$-\mathrm{d}z/\mathrm{d}t = k_4yz + k_5xz \tag{14}$$

$$\mathrm{d}s/\mathrm{d}t = k_4yz \tag{15}$$

where $a_{\mathrm{t}} = [\mathrm{AZA}] + [\mathrm{AZAH^+}]$, $u_{\mathrm{t}} = [\mathrm{NAZA}] + [\mathrm{NAZAH^+}]$ and α_i and β_i are the neutral and ionic fractions of a species *i*. At $t = 0$, $x = x_0$, $a_{\mathrm{t}} = a_0$, $z = z_0$ and $u_{\mathrm{t}} = y = s = 0$.

A numerical solution was obtained with the Runge–Kutta method according to a step procedure of fourth order. The results were verified experimentally in dilute medium (3×10^{-3}–60×10^{-3} M) and in the pH range 8–13.5.[15] In particular, Fig. 5 indicates the yield variation of **3** ($\rho = y_\infty/x_0$) according to the pH. Thus, at $T = 25\,°\mathrm{C}$, ρ

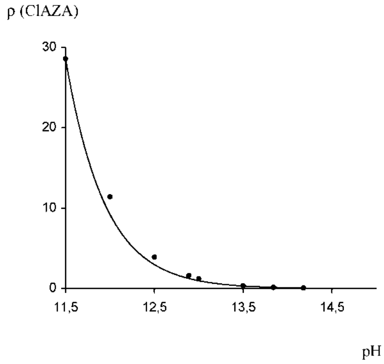


Figure 5. Variation of yield of ClAZA with respect to pH during the synthesis of *N*-amino-3-azabicyclo[3.3.0]octane. $T = 25\,°C$, pH = 12.89

increases from 0.15 to 4% when the pH varies between 13.9 (1 M NaOH) and 12.5.

An increase in temperature supports the formation of **3** and consequently leads to a greater quantity of **4**. For example, at pH 12.89 and $T = 60\,°C$, ρ reaches 2%, which corresponds to an increase of 35% compared with that obtained at 25 °C. This result is due to the activation energy of reaction (3), which is higher than that of NAZA formation. Thus, the temperature has little influence on limiting the chlorine transfer reaction leading to *N*-chloro-3-azabicyclo[3.3.0]octane.

At the exit of hydrazine reactor, the **3** formed is not still transformed. Its reduction by sodium borohydride must intervene before its dehydrohalogenation into **4**. The latter is slow and requires several hours ($k_4\ [OH^-] = 10.3 \times 10^{-6}\ s^{-1}$). In this case, only reactions (3) and (8) are to be considered.

As the synthesis of NAZA is carried out at 0.1 M sodium hydroxide concentration,[15] only temperature and sodium borohydride concentration will determine the efficiency of the reduction step. Their effects can be evaluated by solving the following differential equations:

$$-d[ClAZA]/dt = k_6[ClAZA][BH_4^-] + k_4[ClAZA][OH^-] \qquad (16)$$

$$-d[BH_4^-]/dt = 1/2k_6[ClAZA][BH_4^-] \qquad (17)$$

$$d[imine]/dt = k_4[ClAZA][OH^-] \qquad (18)$$

$$d[AZA]/dt = k_6[ClAZA][BH_4^-] \qquad (19)$$

By designating as $[BH_4^-]_0$ and $[ClAZA]_0$ the initial concentration at the exit of the NAZA reactor and by eliminating t from Eqns (16) and (17), we obtain ($r = k_4/k_6$)

$$[ClAZA] = [ClAZA]_0 + 2\,\{[BH_4^-] - [BH_4^-]_0 + \log([BH_4^-]/[BH_4^-]_0)^r\} \qquad (20)$$

Table 6. Reduction of *N*-chloro-3-azabicyclo[3.3.0]octane by sodium borohydride: variation of imine concentration as a function of temperature at pH 12.89 and 13.5 ($[ClAZA]_0 = 0.02$ M, $[BH_4^-]_0 = 0.1$ M)

	[Imine] × 10^4 (M)	
T (°C)	pH 12.89	pH 13.50
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

When 3 is completely consumed, $[BH_4^-]_\infty$ can be found from the implicit equation

$$[ClAZA]_0 + 2\,\{[BH_4^-]_\infty - [BH_4^-]_0 + \log([BH_4^-]_\infty/[BH_4^-]_0)^r\} = 0$$

From Eqns (18) and (19), we deduce

$$[AZA]_\infty = 2([BH_4^-]_0 - [BH_4^-]_\infty)$$

and

$$[imine]_\infty = [ClAZA]_0 - [AZA]_\infty$$

Moreover, by designating as $g(r, [BH_4^-], [ClAZA]_0, [BH_4^-]_0) = g(r, [BH_4^-])$, the second term in Eqn. (20), it is possible to determine the reaction time via the following equality:

$$\int_{[BH_4^-]_0}^{[BH_4^-]} \frac{d[BH_4^-]}{[BH_4^-]g(r, [BH_4^-])} - 0.5k_6 \int_0^t dt = 0$$

Under the operating conditions defined from the above differential system [Eqns (10)–(15)], the concentration of ClAZA reaches 0.02 M (0.3%). Let us examine the influence of the ratio $R = [BH_4^-]_0/[ClAZA]_0$ and tem-

Table 7. Reduction of *N*-chloro-3-azabicyclo[3.3.0]octane by BH_4^-: variation of final concentrations of AZA and imine according to the ratio $R = [NaBH_4]_0/[ClAZA]_0$ (pH = 12.89, $[ClAZA]_0 = 0.02$ M, T = 25 °C)

R	[AZA] × 10^3 (M)	[Imine] × 10^3 (M)
5	11.72	8.28
10	14.82	5.18
15	16.24	3.76
20	17.05	2.95
25	17.57	2.43
40	18.41	1.59
50	18.71	1.29

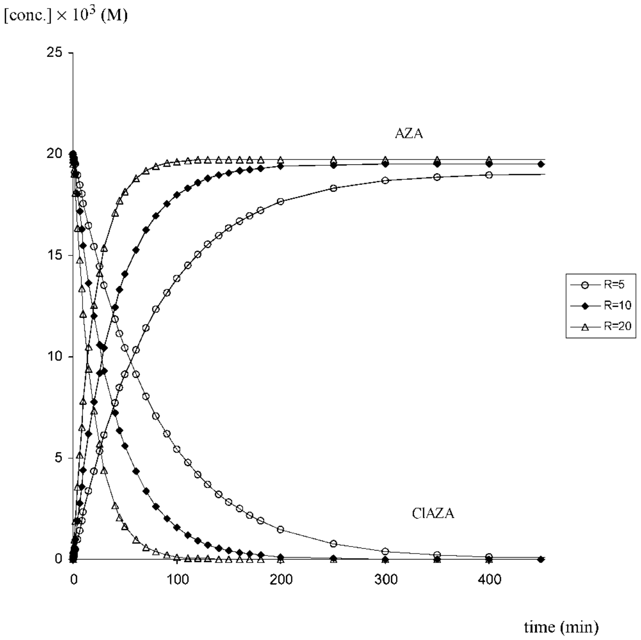


Figure 6. Reduction of *N*-chloro-3-azabicyclo[3.3.0]octane by BH_4^-. Variation of AZA and ClAZA concentrations as a function of the ratio $R = [NaBH_4]_0/[ClAZA]_0$. pH = 12.89, $[ClAZA]_0 = 0.02$ M, T = 25 °C

perature on the reduction of **3**. Table 6 expresses the temperature effect for $[BH_4^-]_0/[ClAZA]_0 = 5$ and pH 12.89 and 13.5. An increase in this parameter is not very favorable for reducing **3**. In particular, at pH 12.89, the yield of the reduction step decreases by 7% when the temperature increases from 15 to 50 °C. At 50 °C and pH 12.89, **3** is consumed in less than 60 min but the 3-azabicyclo[3.3.0]oct-2-ene yield reaches 10.3%.

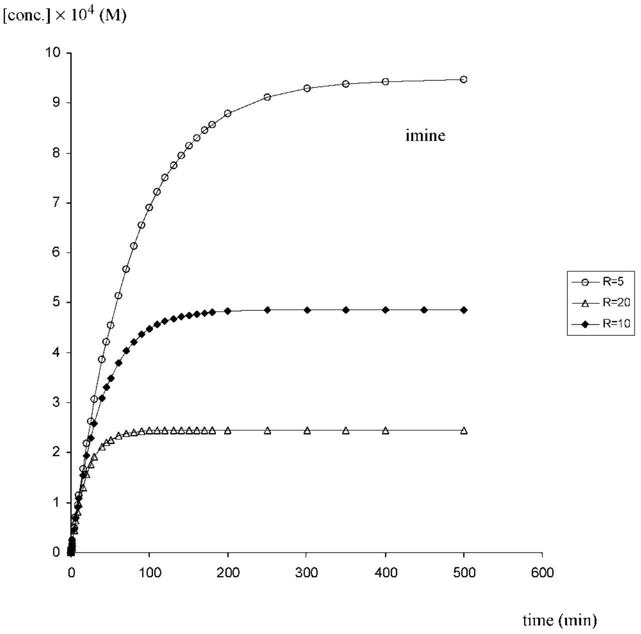


Figure 7. Reduction of *N*-chloro-3-azabicyclo[3.3.0]octane by BH_4^-. Variation of imine concentration according to the ratio $R = [NaBH_4]_0/[ClAZA]_0$. pH = 12.89, $[ClAZA]_0 = 0.02$ M, T = 25 °C

Table 7 and Figs 6 and 7 show the results of a simulation at $T = 25$ °C and pH 12.89 according to the ratio $R = [BH_4^-]_0/[ClAZA]_0$ report. These conditions are the best for reducing the totality of **3** formed. Thus, the converted substituted chloramine reaches 95.12% as soon as R exceeds 5 and becomes close to 98.8% for $R = 50$.

These results show that it is possible to reduce *N*-chloro-3-azabicyclo[3.3.0]octane under soft conditions ($T = 25$ °C, pH 12.89, $R = 50$). This operation avoids the formation of 3-azabicyclo[3.3.0]oct-2-ene and thereafter the appearance of polymeric precipitates. In concentrated medium, the rate and equilibrium constants vary with ionic strength. The kinetic model then constitutes an approximate solution able to describe conveniently the evolution of system.

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