Kinetics of Dehydrohalogenation of N-Chloro-3-Azabicyclo[3,3,0]Octane in Alkaline Medium. NMR and ES/MS Evidence of the Dimerization of 3-Azabicyclo[3,3,0]Oct-2-Ene

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ABSTRACT: The formation of 3-azabicyclo[3,3,0]oct-2-ene in the course of the synthesis of *N*-amino-3-azabicyclo[3,3,0]octane using the Raschig process results from the following two consecutive reactions: chlorine transfer between the monochloramine and the 3-azabicyclo[3,3,0]octane followed by a dehydrohalogenation of the substituted haloamine. The kinetics of the reaction were studied by HPLC and UV as a function of temperature (15 to 44°C), and the concentrations of NaOH (0.1 to 1 M) and the chlorinated derivative (1 to 4×10^{-3} M). The reaction is bimolecular ($k = 103 \times 10^{-6}$ M^{-1} s^{-1}; $\Delta H^{0\#} = 89$ kJ mol^{-1}; and $\Delta S^{0\#} = -33.6$ J mol^{-1} K^{-1}) and has an E2 mechanism. The spectral data of 3-azabicyclo[3,3,0]oct-2-ene were determined. IR, NMR, and ES/MS analysis show dimerization of the water-soluble monomer into a white insoluble dimer. © 1998 John Wiley & Sons, Inc. Int J Chem Kinet: **30:** 129–136, 1998.

INTRODUCTION

This work concerns the reactivity of chloramine with mono- and di-substituted amines when using the Raschig process, shown in reaction (1), for the synthesis of asymmetric bicyclic hydrazines, in particular *N*-amino-3-azabicyclo[3,3,0]octane **1** (NAZA):

$$RR'NH + NH_2Cl \longrightarrow RR'NNH_2 + HCl \quad (1)$$

Where R, R′ = H, alkyl, aryl, and alicyclic.

During the synthesis of this molecule and under certain pH conditions, one can observe the forma-

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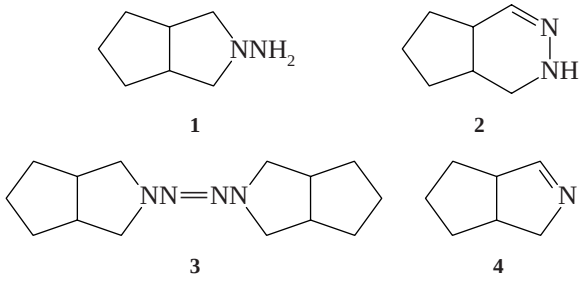
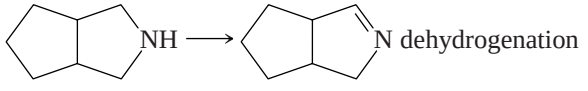
tion of several by-products, in particular 3,4-diaza-bicyclo[4,3,0]non-2-ene **2**, *N,N′*-azo-3-azabicyclo[3,3,0]octane **3**, and 3-aza-bicyclo[3,3,0]oct-2-ene **4** which precipitates in the form of a white solid.

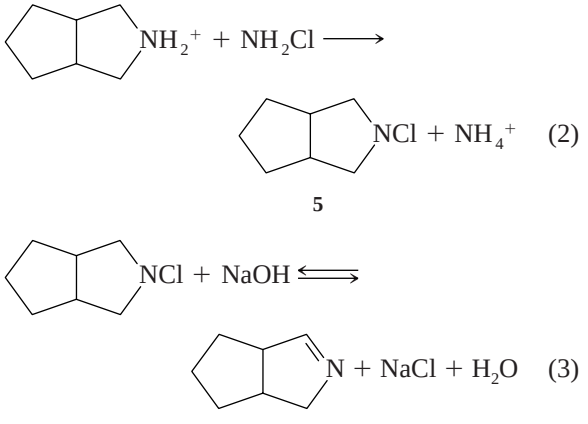


1 **2** **3** **4**

The first two of these were the object of previous investigations [1–4]. The present study has the objective of researching the mechanism of the formation of **4** and of determining the kinetic parameters in order to define the optimal synthesis conditions. The most simple reaction scheme would consist of a direct dehydrogenation of 3-azabicyclo[3,3,0]octane (AZA) to form imine:



Experiments performed in the laboratory in the presence of oxygen or of monochloramine exclude this route as a source of **4**. Analysis of the reaction mixture during the preparation of hydrazine reveals the existence of small quantities of an organohaloamine **5**, *N*-chloro-3-azabicyclo[3,3,0]octane (ClAZA). In these conditions, imine would result from the following two consecutive reactions: chlorine exchange between the chloramine and 3-aza-bicyclo[3,3,0]octane [5–11] followed by a dehydrohalogenation [12–27] of the substituted haloamine (reactions 2 and 3):



5 (2) (3)

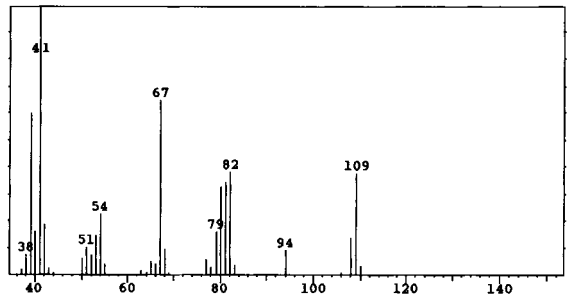


Figure 1 Mass spectrum of 3-azabicyclo[3,3,0]oct-2-ene by direct injection (70 eV).

This hypothesis has been reported in the literature of analogous compounds, but comprehensive quantification of the phenomena involved has never been performed.

RESULTS AND DISCUSSION

With the goal of verifying the above hypothesis concerning the formation of imine in the course of the synthesis of NAZA, preliminary identification attempts were effected in concentrated media.

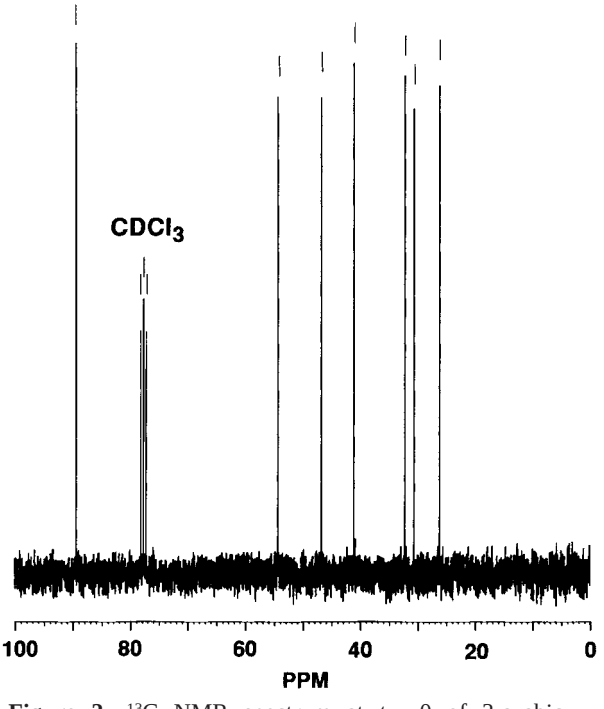


Figure 2 ^{13}C NMR spectrum at $t = 0$ of 3-azabicyclo[3,3,0]oct-2-ene after dissolution of the dimer in $CDCl_3$.

Characterization of 3-Azabicyclo[3,3,0]Oct-2-Ene

The reaction of dehydrohalogenation of ClAZA was conducted by introducing into a 500 mL reactor 40 g NaOH (1 mol), 2.33 g anhydrous AZA (0.021 mol), and 10 mL sodium hypochlorite (0.02 mol). Initially one obtains an emulsion that gradually disappears. At the end of the reaction, the white precipitate formed is filtered, washed several times with water, and dried under reduced pressure.

The direct injection mass spectrum is presented in Figure 1. The molecular ion obtained ($M^+ = 109$) and the isotopic study of the ion fragments lead to an empirical formula of $C_7H_{11}N$. Elemental analysis of the product shows good agreement between calculated and experimental percentages (C: 0.065%; H: − 0.20%; N: 0.155%). The UV spectrum obtained after dissolution of **4** in basic solutions exhibits an absorption at $\lambda = 225$ nm with a molar extinction coefficient $\epsilon = 172\ M^{-1}\ cm^{-1}$.

The IR analysis of the white powder surprisingly shows an absence of the band due to the C═N stretch. These results allow us to postulate the existence of a monomer in aqueous solution which then precipitates in dimeric form. In order to confirm this hypothesis, multinuclear NMR analysis were undertaken immediately after dissolution of the dimer in $CDCl_3$.

Figure 2 presents the ^{13}C NMR spectrum at time $t = 0$ of the solubilized compound. One can observe seven peaks that each correspond to two carbon atoms, implicating the existence of a symmetry element. Following the spectra as a function of time shows the appearance of seven new peaks (Fig. 3) representing the monomeric structure. Increase in temperature drives the disappearance of the dimer in favor of the monomer.

Furthermore, in order to clarify the form of the imine in the reaction mixture, 100 mL were treated by 2 mL deuterated chloroform containing 1% tetramethylsilane. The ^1H and ^{13}C NMR spectra of the organic phase shows that the benchmark signals are superimposed over those caused by the dissociation of the solid. DEPT analysis of the monomeric and dimeric forms reveals the presence of two and three peaks, respectively, corresponding to methyne carbons (CH).

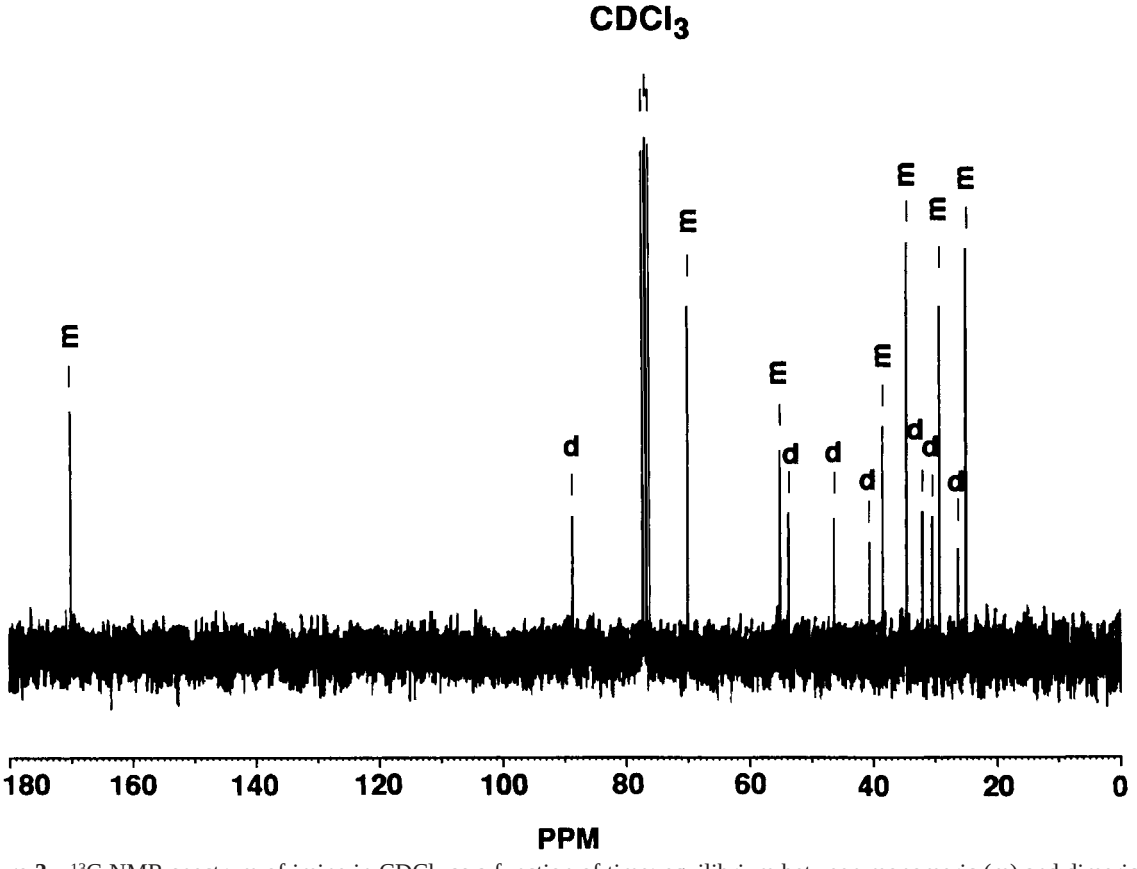


Figure 3 ^{13}C NMR spectrum of imine in $CDCl_3$ as a function of time: equilibrium between monomeric (m) and dimeric (d) forms.

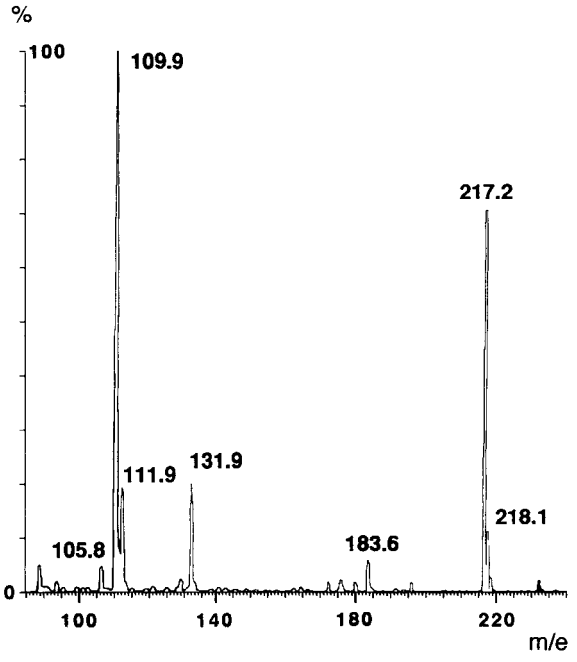
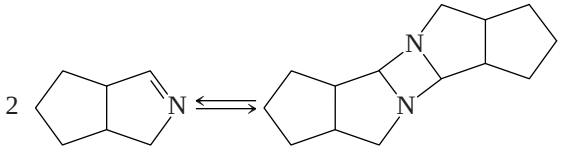


Figure 4 Mass spectrum of 3-azabicyclo[3,3,0]oct-2-ene by ES/MS at 35 eV. Existence of two peaks corresponding to monomeric ($M^+ = 109$) and dimeric ($M^+ = 218$) forms.

Examination of the chemical shifts suggests the following structure:



The direct injection mass spectrum ($M^+ = 109$) does not allow unambiguous determination because the dimeric imine dissociates under the analysis conditions. Because of its lability, nondestructive characterization by ES/MS spectroscopy was undertaken at 35 eV. Figure 4 shows the presence of two peaks situated at $M^+ = 109$ and $M^+ = 218$, which definitely proves the dimerization of 3-azabicyclo[3,3,0]oct-2-ene. Thermodynamic and X-ray diffraction studies are in progress in order to determine the complete structure of this new molecule.

Kinetics of Formation of 3-Azabicyclo[3,3,0]Oct-2-Ene

One of the difficulties of the kinetic study results from the low solubility of ClAZA and the imine in water. To follow the reaction in one phase, it is necessary to use low concentrations. For example, at pH = 7 and $T = 25$°C, the solubility limit of the chlorinated derivative is 10^{-2} M. At 1 M NaOH, the limit is no more than 4×10^{-3} M. GC analysis is not suitable because *N*-chloro-3-azabicyclo[3,3,0]octane partially decomposes in the injector. Preliminary tries have shown that AZA/ClAZA interaction is negligible under the conditions of the study. The reaction kinetics were followed simultaneously by HPLC and UV spectrophotometry.

Order and Stoichiometry

The measurements were carried out at 25°C over a NaOH concentration interval of 0.1 to 1 M. The ClAZA contents were fixed between 1 and 4×10^{-3} M in order to avoid phase demixtion. The HPLC chromatograms recorded at different times on a mixture initially 4.02×10^{-3} M in **5** and 0.25 M in NaOH show a decrease in the chlorinated derivative peak at $t_R = 6.56$ mn and the formation of a second peak at $t_R = 4.02$ mn characteristic of the imine.

Figure 5 presents, as an example, the evolution of the UV spectrum as a function of temperature. One can observe the decrease of the haloamine absorption band at $\lambda = 257$ nm and, correlatively, the appearance

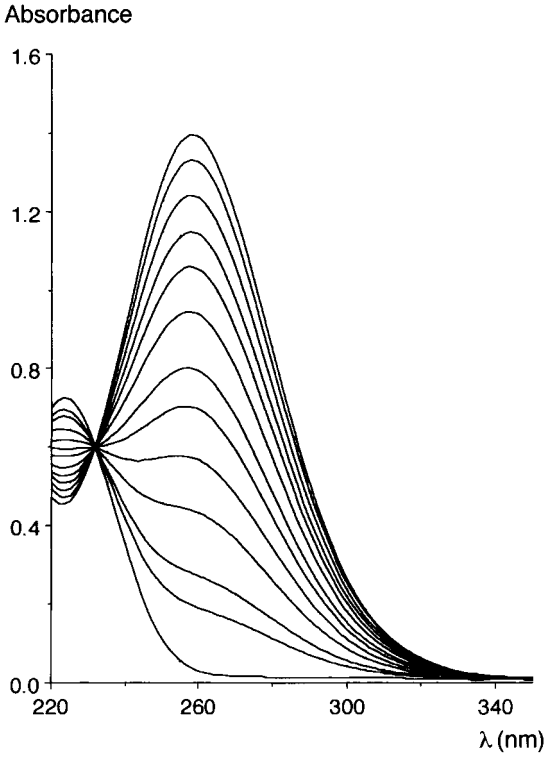


Figure 5 Dehydrohalogenation of *N*-chloro-3-azabicyclo[3,3,0]octane. UV absorption spectra of ClAZA (257 nm) and imine (225 nm) with time.

Table I Dehydrohalogenation of *N*-Chloro-3-Azabicyclo[3,3,0]Octane in Alkaline Medium: Stoichiometry Imine/ClAZA

Time (mn)	[ClAZA] × 10^3 (M)	δ[ClAZA] × 10^3 (M)	[imine] × 10^3 (M)	[imine]/δ[ClAZA]
25	3.86	0.16	–	–
97	3.43	0.59	0.59	1.007
199	2.96	1.06	1.05	0.992
329	2.43	1.59	1.62	1.022
467	2.02	2.00	2.08	1.039
564	1.67	2.35	2.36	1.004
695	1.37	2.65	2.63	0.992
829	1.10	2.92	2.88	0.986
1009	0.82	3.20	3.11	0.972
1197	0.61	3.41	3.43	1.005
1619	0.32	3.70	3.71	1.003

of the characteristic band of **4** at $\lambda = 225$ nm. One note an isosbestic point at $\lambda = 232$ nm, proving that only these two compounds coexist in the reaction medium and that they are linked by a stoichiometric relation.

Table I shows that ClAZA/imine ratio is constant and close to unity. Figure 6 shows the variations of ClAZA and imine concentrations with respect to time. Under these conditions, the rate of organohaloamine disappearance is obtained from the equation:

$$-\,d[C_7H_{12}NCl]/dt = k[C_7H_{12}NCl]^{\alpha}[HO^-]_0^{\beta}$$

The kinetic parameters were determined by Ostwald method. To evaluate α, we performed three series of measurements corresponding to a constant concentration of 0.25 M NaOH and to ClAZA concentrations going from 1 to 4.02×10^{-3} M. The curves $\mathrm{Log}[ClAZA]_0/[ClAZA] = f(t)$ are in all cases straight lines ($\alpha = 1$) of the same slope $\varphi = k[HO^-]_0^{\beta}$. The value of β was determined under the same temperature conditions with a constant concentration of 2×10^{-3} M in **5** and NaOH strengths between 0.1 and 1 M. $\mathrm{Log}\ \varphi = f(\mathrm{Log}[HO^-]_0^{\beta})$ is a line passing through the origin Log k and of slope $\beta = 1$ ($r^2 = 0.999$). The overall results are summarized in Table II. In consequence, the bimolecular rate constant of the reaction at $T = 25$°C is equal to $k = 103 \times 10^{-6}$ ($\pm 3 \times 10^{-6}$) $M^{-1}\ s^{-1}$.

Influence of Temperature

The temperature influence was studied between 15 and 44.4°C for NaOH and $C_7H_{12}NCl$ concentrations of 0.25 M and 4×10^{-3} M, respectively. The variation of k as a function of temperature agrees with the Arrhenius law. The curve $\mathrm{Log}\ k = f(1/T)$ is a line of slope $-E/R$ and ordinate at the origin Log A ($r^2 = 0.999$). E and A represent the energy and the activation energy of the reaction, respectively (E en kcal mol^{-1}).

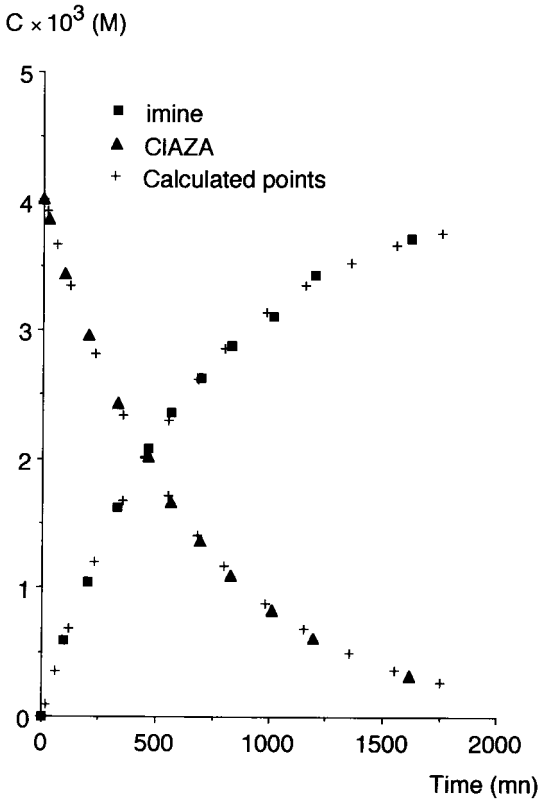


Figure 6 Kinetics of *N*-chloro-3-azabicyclo[3,3,0]octane/NaOH reaction. Variation of imine and ClAZA concentrations as a function of time ([ClAZA] = 4.06×10^{-3} M; [NaOH] = 0.25 M; and $T = 25$°C).

Table II Kinetics of Dehydrohalogenation of *N*-Chloro-3-Azabicyclo[3,3,0]-Octane. Determination of the Bimolecular Rate Constant k at $T = 25°C$

[ClAZA] $\times 10^3$(M)	[NaOH](M)	$\varphi \times 10^6(s^{-1})$	$k \times 10^6(M^{-1}\ s^{-1})$
1.01	0.25	25.2	101
2.02	0.25	26.0	104
4.02	0.25	25.5	102
2.03	0.10	10.3	103
2.05	0.50	51.5	103
2.04	0.75	78.0	104
2.02	1.00	105.0	105

$$k = 2.95 \times 10^{11} \exp(-21.9/RT)\ M^{-1}\ s^{-1}$$

From these one can determine the reaction entropy and activation enthalpy:

$$\Delta H^{0\#} = E - RT;\ \Delta S^{0\#} = \mathrm{R\ Log}\ \frac{\mathrm{Ah}}{\mathrm{e}k_B T} \qquad (5)$$

where k_B and h are the Boltzmann and Planck constants, respectively ($k_B = 1.380 \times 10^{-23}$ J K^{-1}; h = 6.623×10^{-34} J s). The quantities (5) have the following numerical values.

$$\Delta H^{0\#} = 89(\pm 6)\ \mathrm{kJ\ mol^{-1}};$$
$$\Delta S^{0\#} = -33.6(\pm 3.5)\ \mathrm{J\ mol^{-1} K^{-1}}$$

Mechanistic Aspects

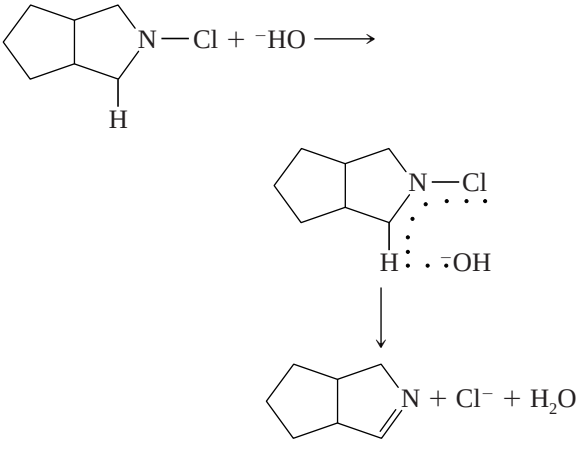
The existence of an isosbestic point indicates synchronization between the disappearance of ClAZA and the formation of imine. Therefore, the reaction does not pass through a stable intermediate. According to ANBAR and YAGIL [15], in the case of dimethylchloramine, the reaction should pass through dimethylhydroxylamine (SN2 mechanism) that then dehydrates to form *N*-methylmethanimine:

$$(CH_3)_2NCl + NaOH \longrightarrow (CH_3)_2NOH + NaCl$$

$$(CH_3)_2NOH \longrightarrow CH_3N{=}CH_2 + H_2O$$

Laboratory trials investigating dimethylhydroxylamine reactivity show that it is stable and can therefore not be the origin of the imine. Also, an interaction between dimethylchloramine and dimethylhydroxylamine is excluded because that leads to liberation of gas and other products.

The formation of imine thus results from one single elementary process that corresponds to an E2 elimination of which the mechanism could be the following:



The hydrogen in vicinal position to the nitrogen atom has acidic character due to the inductive effect of the chlorine atom. When exposed to a strong base the proton is removed with simultaneous elimination of chlorine.

In conclusion, the present study describes the synthesis and characterization of a new molecule, 3-azabicyclo[3,3,0]oct-2-ene, that dimerizes to form a white solid. The application of the Raschig process to the synthesis of bicyclic hydrazines requires very strict operating conditions in order to avoid the precipitation of the dimer. This work underscores the necessity of operating in strongly alkaline medium to neutralize the transient formation of organohaloamine as a precursor of the imine. However, this operating condition presents the disadvantage of requiring a heterogeneous medium and of diminishing the hydrazine yield on account of the hydrolysis of the monochloramine to hydroxylamine. A global kinetic model taking all of the interactions into account is forthcoming.

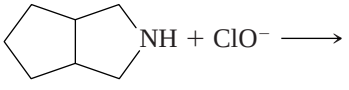
EXPERIMENTAL PART

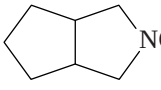
Reactants

Reactants and salts used were reagent grade products of Prolabo RP and Aldrich. The water used was treated by passage through an ion exchange resin then twice distilled in a silice apparatus, deoxygenated, and stored under nitrogen.

3-azabicyclo[3,3,0]octane is not commercially available. It is prepared starting from an acidic solution of AZA sulfate (16%) obtained from ORIL SA. After neutralization, the mixture is distilled at 760 torr. One obtains at the head of the column a heteroazeotropic solution (bp = 98.4°C) titrating 29.8% in amine. Treatment with NaOH followed by redistillation under vacuum leads to the 99.9% pure product (GC).

N-chloro-3-azabicyclo[3,3,0]octane is obtained quantitatively by chlorination of 3-azabicyclo-[3,3,0]octane (1–2% excess AZA) by hypochlorite ion (reaction 4).





(4)

Thus, upon combining equal volumes (100 mL) of NaOCl (60×10^{-3} M) and amine (62×10^{-3} M) solutions at room temperature, the solution phase separates to give a pale yellow oil phase. This product, slightly soluble in water, decomposes at 70°C during distillation by liberating a gas and depositing carbon. Hexane extraction followed by cryogenic transfer leads to a liquid that immediately degrades. It is therefore prepared in situ under quasistoichiometric conditions.

Because of its instability in the pure state and its thermodegradability, the mass spectrum was realized by ES/MS. One can observe two intense peaks of mass 146 and 148 (32% relative abundance) that are characteristic of the presence of chlorine 37 and 35 isotopes. This result was confirmed by the ion fragment of $m/e = 111$ that corresponds to the loss of a Cl atom. The spectral data of **5** were determined in aqueous medium after preliminary determination by iodometry [28]. This compound alternatively was prepared by the direct action of a chloramine solution on protonated AZA at pH = 8 and $T = 25$°C (reaction 2). The two methods lead to identical UV and mass spectra. The molar extinction coefficient is consistent with those observed for secondary chloramines [29].

3-azabicyclo[3,3,0]oct-2-ene is prepared at ambient temperature in concentrated solution by the action of NaOH on a ClAZA solution. The reaction is slow and takes several days. The white precipitate formed is separated, washed, and dried. Its purity was determined by GC (99.9%).

Apparatus

Ultraviolet spectra were obtained with a CARY 1E double beam spectrometer with 1 cm pathlengh quartz cells. HPLC analysis were carried out on a BECKMAN 421A chromatograph equipped with a UV detector of variable wavelength. The column was a 250 × 4.6 mm ODS (dp = 5 μm) and the mobile phase was H_2O/CH_3OH (22%/78% v/v) with a flow rate of 1 mL mn^{-1}. NMR data were obtained with a high resolution BRUKER AM300 spectrometer at 300 MHz for ^1H and 75 MHz for ^{13}C. All NMR analysis were recorded in $CDCl_3$ solution. Chemical shifts are given in δ values (ppm) against $Si(CH_3)_4$ as the internal standard. IR spectra were measured with a BECKMAN 842 instrument with CsI cells.

MS analysis were performed on DELSI NERMAG apparatus consisting of a GC chromatograph and an electron impact (70 eV) mass spectrometer. The chromatographic separation was done on a 30 m long DB17 capillary column (50% phenyl). The analytical conditions follow: Helium = 2 mL mn^{-1}, $T_{inj.}$ = 250°C, and $T_{col.}$ = 60°C/200°C (8°C mn^{-1}). The ES/MS spectra were performed using a HP electrospray 59987A linked with a HP 5989A mass spectrometer. This technique requires preliminary extraction with methanol and the addition of acetic acid until the aliquot reaches 1%. The mixture is then introduced to the chamber by injection with a flow rate of 2 μL mn^{-1} and the spectrum is obtained at 35 eV.

Procedure and Analysis

It consists of two thermostated vessels of borosilicate glass, one on top of the other and joined by a conical fitting. Each one contains one of the two reactants. The lower reactor (200 mL), contains a magnetic stirrer and has inlets to allow the measurement of temperature and removal of aliquots for analysis. The upper cylindrical vessel (100 mL), is blocked at its base by a solid machined stopper (17 mm i.d.) fastened to a control rod. This setup allows the rapid introduction of the ampoule contents into the reactor, and therefore a precise definition of the start of the reaction. The HPLC

analysis of the chlorinated derivative does not present any difficulty as the molecule contains a chromophore and a sufficiently high absorption coefficient. This contrasts with compound **4**, which absorbs more weakly and at a wavelength of 225 nm. Direct injection of the basic aliquot does not allow the imine evolution to be monitored with sufficient sensitivity.

To alleviate these difficulties, we extracted the reaction mixture into hexane. This operation presents a double advantage. It allows us to quench the reaction by separating the reactants of different polarities and to concentrate the products in an organic phase by a volume effect. Under these conditions, the concentration of compound i in the aqueous phase is calculated from the equation:

$$[\mathrm{i}] = S_i^{\mathrm{hexane}} k_i^{\mathrm{hexane}} \Phi_i$$

in which S_i^{hexane}, k_i^{hexane}, and Φ_i represents the counting surface, the response and distribution coefficients of i between both phases. This last parameter depends on the temperature and the amount of sodium hydroxide.

The imine standard solutions are prepared by weighing the pure product into hexane. Aqueous solutions of **5** are quantified by UV. The distribution study shows that the substituted chloramine is quasi completely transferred to the hexane provided that the concentration of NaOH in the aqueous phase is greater than 0.1 M. On the other hand, the more polar imine only partially goes into the hexane. The Φ_i coefficients were determinated at the pH where the kinetics are studied. The wavelength, fixed at 240 nm, results from a compromise between the absorptions of the above compounds and those of the mobile phase.

The imine and ClAZA solutions were analysed by UV spectrophotometry. Due to spectral interference, the optical measurements were taken at two wavelengths $\lambda_1 = 225$ nm and $\lambda_2 = 280$ nm. The imine absorption at λ_2 being zero, the concentrations of **4** and **5** were calculated from the following equations (l = 1 cm):

$$[\mathrm{ClAZA}] = \frac{A(\lambda_1, t)}{\epsilon_{\mathrm{ClAZA}}{}^{\lambda_1}}$$

$$[\mathrm{Imine}] = \frac{[A(\lambda_2, t)\epsilon_{\mathrm{ClAZA}}{}^{\lambda_1} - \epsilon_{\mathrm{ClAZA}}{}^{\lambda_2} A(\lambda_1, t)]}{\epsilon_{\mathrm{ClAZA}}{}^{\lambda_1}\epsilon_{\mathrm{Imine}}{}^{\lambda_1}}$$

where $\epsilon_{\mathrm{Imine}}{}^{\lambda_1} = 172\ \mathrm{M^{-1}\ cm^{-1}}$, $\epsilon_{\mathrm{ClAZA}}{}^{\lambda_1} = 118\ \mathrm{M^{-1}\ cm^{-1}}$ et $\epsilon_{\mathrm{ClAZA}}{}^{\lambda_2} = 209\ \mathrm{M^{-1}\ cm^{-1}}$.

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