

Synthesis of Pyrazolidine by Intramolecular Raschig Amination: Modelling and Optimization

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This paper described a new synthesis of pyrazolidine from 1,3-diaminopropane and sodium hypochloride. A global process was developed, involving the characterization of the reaction mechanisms, kinetics and the optimization of the synthesis parameters. The rate constants were determined as function of the reagent concentrations ($2 \cdot 10^{-3}$ – $2 \cdot 10^{-2}$ mol.l⁻¹), the pH (12.89 – 14.64) and the temperature (283-318K). The overall reaction, of first order for the both reagents, is the result of two successive mechanisms: the first being pH independent, the second accelerated by increasing pH. The bimolecular rate constant was modeled as a function of the hydroxide ions activity. The enthalpy and entropy of activation of the molecular process were established at 298K. The yield of the reaction reaches 80% for the following conditions $[DAP]_0 / [OCl]_0 = 8$; pH = 12.89 ; T = 298K.

1. Introduction

This work is a part of a complete study involving the preparation, by the Raschig way, of an endocyclic hydrazine, the pyrazolidine (PYRZ, C₃H₈N₂), used in the pharmaceutical and cosmetical industries. Currently, the method used for the preparation of pyrazolidine, developed by Crawford (1966) and Hasegawa et al. (1998), involves reaction between 1,3-dibromopropane and hydrazine, leading thus to expensive synthesis. To avoid these inconveniences, we have implemented the Raschig way (Raschig (1907a and 1907b), Omietanski et al. (1956) and Jain et al. (1985)), which consists of an oxidation of the amine reagent by sodium hypochloride as shown in figure 1.

This synthesis is carried out in two steps:

Step 1: oxidation of 1,3-diaminopropane (**I**, DAP, C₃H₁₀N₂) by sodium hypochloride (**II**, OCl) and formation of N,chloro-1,3-diaminopropane (**III**, C₃H₉N₂Cl).

Step 2: cyclization of N,chloro-1,3-diaminopropane (**III**) leading to pyrazolidine (**IV**).

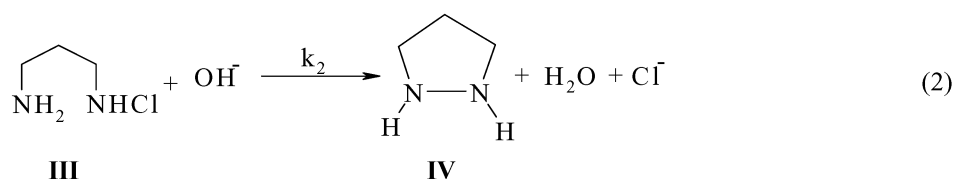
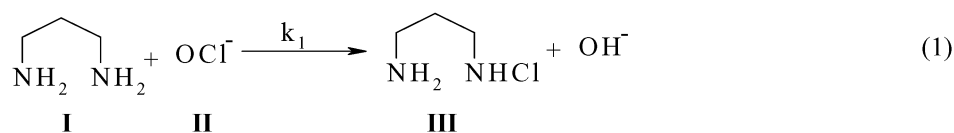


Figure 1: Reaction mechanism of the formation of pyrazolidine by the Raschig way

This synthesis requires an excess of the diaminopropane (DAP) reagent, in comparison to sodium hypochlorite, in order to increase the yield in pyrazolidine to 80%. The optimization of the preparation conditions requires thus the knowledge of the kinetic parameters that govern each reaction.

2. Experimental sections

The synthesis was performed with the following conditions: $T = 298\text{K}$; $[\text{DAP}]_0 / [\text{OCl}^-]_0 = 20$, ratio which greatly promotes the formation of N,chloro-1,3-diaminopropane with a yield of 90%.

2.1. Products used and analytical methods

1,3-diaminopropane: supplied by Acros® ; Sodium hypochlorite: supplied by Arkema® ; Water was purified by circulation on an ion-exchange resin.

The N,chloro-1,3-diaminopropane presents a UV absorption band at $\lambda = 252 \text{ nm}$ (figure 2). We deduce then, from the Beer-Lambert law, an experimental molar extinction coefficient ϵ for N,chloro-1,3-diaminopropane of $364 \text{ l.mol}^{-1}.\text{cm}^{-1}$

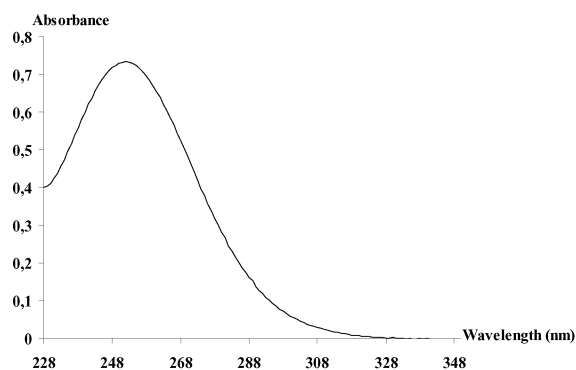


Figure 2: UV absorption spectrum of N,chloro-1,3-diaminopropane; $[\text{N,chloro-1,3-DAP}]_0 = 2.10^{-3} \text{ mol.l}^{-1}$

The standard solutions of pyrazolidine, used for the development of analytical methods and standardization, were prepared by neutralization of pyrazolidine dihydrochloride (PZRZ.2HCl), provided by the ISO-CHEM Company, by sodium hydroxide.

The pyrazolidine was detected and quantified by gas chromatography coupled to mass spectrum (GC/MS). The measurements were performed using an Agilent Technologies 6890N gas chromatograph equipped with an automatic injector (76826B). This chromatograph is coupled to a mass spectrum Agilent Technology 5970. The column used is a HP-Polyethylene glycol Innovax 19091N-133 Agilent Technologies.

3. Experimental results

3.1. Partial orders

The reaction of formation of N,chloro-1,3-DAP (1) is very fast compared to the formation of the pyrazolidine (2). This reaction (1) is quantitative and the rate constants are extremely fast. Also, the rate of formation of NH_2Cl , CH_3NHCl and $(\text{CH}_3)_2\text{NCl}$ from HOCl and the appropriate amine were studied by Weil and Morris (1949). The reactions are second global order with respect to the concentrations of each reactant, but the rates show a marked dependence according to the pH of the solution. The average rate constant ($k_{\text{NH}_2\text{Cl}}$) at 298K is equal to $3.7 \cdot 10^8 \text{ l} \cdot \text{mol}^{-1} \cdot \text{min}^{-1}$ therefore; our rate constant k_1 must have a similar value. The kinetic study was thus focused on the second reaction step ((2), formation of the PZRZ, k_2). The rate laws were established, for the transformation of N,chloro-1,3-diaminopropane in pyrazolidine, at $\text{pH} = 12.89$ ($[\text{NaOH}]_0 = 0.1 \text{ mol l}^{-1}$), $T = 298\text{K}$ and a molar ratio $[\text{DAP}]_0 / [\text{OCl}^-]_0 = 20$ in order to limit the side reactions. Denoting by x the instantaneous concentration of N,chloro-1,3-diaminopropane, its rate of disappearance is thus obtained by the following equation:

$$-\frac{dx}{dt} = v_1 k_2 x^\alpha \quad (3)$$

With α , the partial order and v_1 the corresponding stoichiometric coefficient. In these conditions, it is possible to follow the reaction by recording UV spectra curves $x = f(t)$ as function of the reaction time. The kinetic parameters were thus determined by degeneration of the partial order.

To evaluate α , four sets of measurements were carried out with OCl^- concentrations ranging from $2 \cdot 10^{-2}$ to $2.5 \cdot 10^{-3} \text{ mol} \cdot \text{l}^{-1}$, as shown in Table 1. In these conditions, the equation (3) becomes:

$$-\frac{dx}{dt} = \Psi x^\alpha \quad (4)$$

The curves $\log(x_0/x) = f(t)$ are, in all cases, straight-lines crossing through the origin and with the same slope (Ψ). The reaction is then of first order for each reagent and the average rate constant at 298K and $\text{pH} = 12.8$ is equal to $0.113 \text{ l} \cdot \text{mol}^{-1} \cdot \text{min}^{-1}$.

Table 1: Experimental results: $[DAP]_0/[OCl]_0 = 20$; $T = 298K$; $pH = 12.89$

$[DAP]_0$ mol.l^{-1}	$[OCl]_0$ mol.l^{-1}	Ψ min^{-1}	k_2 $\text{l.mol}^{-1}.\text{min}^{-1}$
0.05	$2.5.10^{-3}$	$0.3.10^{-3}$	0.107
0.1	5.10^{-3}	$0.63.10^{-3}$	0.112
0.2	1.10^{-2}	$1.21.10^{-3}$	0.113
0.4	2.10^{-2}	$2.40.10^{-3}$	0.118

3.2. Influence of pH

The measurements were performed at 298 K for pH ranging from 12.89 to 14.64; the pH value is obtained by addition of sodium hydroxide. Overall results are reported in Table 2. The values of the first three columns give the initial molar concentrations of DAP, OCl^- and NaOH. The fourth column shows the corresponding pH values at $T = 298K$, calculated from the work of A. Kertof and Kegeles (1940), on the determination of activity coefficients of sodium hydroxide in concentrated solution, and the last column gives the values of the rate constants k_2 .

Table 2: Kinetics of formation of pyrazolidine; evolution of k_2 versus pH

$[DAP]_0$ mol.l^{-1}	$[OCl]_0$ mol.l^{-1}	$[NaOH]_0$ mol.l^{-1}	pH	k_2 $\text{l.mol}^{-1}.\text{min}^{-1}$
0.2	0.01	0.1	12.89	0.146
0.2	0.01	0.5	13.53	0.147
0.2	0.01	1	13.83	0.164
0.2	0.01	2	14.18	0.241
0.2	0.01	3	14.42	0.391
0.2	0.01	4	14.64	0.601

Figure 3 shows that the rate constant k_2 varies with the alkalinity of the medium. When $pH < 13.53$, k_2 is nearly constant and equal to $0.147 \text{ l.mol}^{-1}.\text{min}^{-1}$. For higher pH values, k_2 increases rapidly.

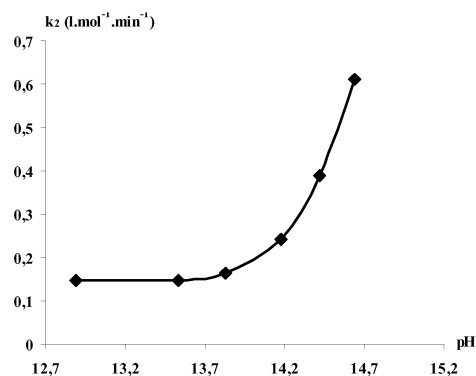
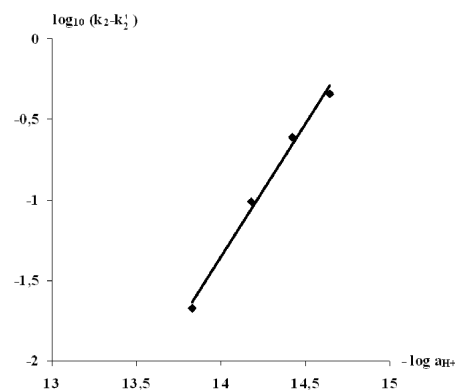
Figure 3: Evolution of k_2 versus pH

Figure 4: Relation between the ionic mechanism and pH.

These phenomena can be modeled by the following equation:

$$k_2 = k_2' + \frac{k_2''}{a_{H^+}} \quad (5)$$

with k_2' and k_2'' , empirical constants, and a_{H^+} , the activity of H^+ ions in the reaction medium. Using the logarithms, we obtain:

$$\log(k_2 - k_2') = \log k_2'' - \log a_{H^+} \quad (6)$$

If this formula is applicable, it is thus possible to find a pair of values (k_2' , k_2'') such that the curve $\log(k_2 - k_2') = f(\text{pH})$ becomes a straight line with a slope equals to unity. We obtain thus a straight line, with a correlation coefficient $r^2 = 0.992$ (figure.4) for the two following values:

$$k_2' = 0.143 \text{ l.mol}^{-1}.\text{min}^{-1}$$

$$k_2'' = 3.01.10^{-16} \text{ l.mol}^{-1}.\text{min}^{-1}$$

We notice that k_2' is very close to the value of k_2 determined experimentally at $\text{pH} = 12.89$ ($k_2 = 0.147 \text{ l.mol}^{-1}.\text{min}^{-1}$). We deduce then the general expression of the rate of formation of pyrazolidine at 298K, as function of the activity of H^+ ions, a_{H^+} :

$$\frac{d[\text{PYRZ}]}{dt} = (k_2' + \frac{k_2''}{a_{H^+}})[N, \text{chloro} - 1,3 - \text{DAP}] \quad (7)$$

It underlines the existence of two competitive reactions of global order 2, one of which being pH independent.

3.3 Influence of the temperature

The influence of temperature was studied at $\text{pH} = 12.89$, in the pH range where the reaction is pH independent. The rate constants were measured between 298 K and 318 K for initial molar concentrations of DAP and OCl^- respectively equal to 0.1 mol l^{-1} and $5.10^{-3} \text{ mol l}^{-1}$. The activation parameters are thus: $\Delta H^{0\#} = -2.41 \text{ kJ.mol}^{-1}$; $\Delta S^{0\#} = -79.3 \text{ J.K}^{-1}.\text{mol}^{-1}$ and $\Delta G^{0\#} = 21.22 \text{ kJ.mol}^{-1}$

Following the Arrhenius law, k_2 is then expressed by the following equation

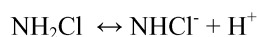
$$k_2 (\text{l.mol}^{-1}.\text{min}^{-1}) = 7.3.10^{10} \exp(-68.3/RT)$$

4. Conclusions

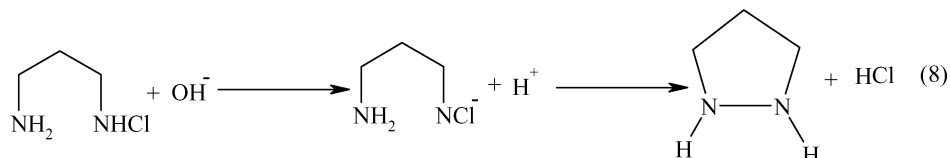
The overall reaction, of first order for the both reagents, is the result of two successive mechanisms:

- The first being pH independent: for $\text{pH} < 13.53$, k_2 is almost constant and equal to $0.146 \text{ M}^{-1}.\text{min}^{-1}$

- The second being accelerated by increasing the pH: for $\text{pH} > 13.53$, k_2 increases rapidly with pH. This mechanism can be interpreted from the hypothesis of Anbar and Yagil (1962), by the fact that chloramine in basic medium is partially dissociated into chloramide NHCl^- ions according to the following rapid pre-equilibrium:



Thus, the reaction mechanism is as follows:



By a kinetic approach, we have shown that it is possible to prepare the pyrazolidine in aqueous media, by action of sodium hypochlorite on 1,3-diaminopropane. This new process requires an excess of amine at least ≥ 8 and a pH value of 13.5. This method is more suitable for use on an industrial scale and can be implemented in batch or continuously processes.

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