

N-Chlorination rate of five-membered heterocyclic nitrogen compounds

Cristina Pastoriza^{a*}, Juan Manuel Antelo^a, Francisco Andrés Amoedo^a and Mercedes Parajó^a

The kinetics of *N*-chlorination reaction of pyrrolidine, pyrrolidone, succinimide, 5,5-dimethyloxazolidine-2,4-dione, 5,5-dimethylhydantoin and 1-hydroxymethyl-5,5-dimethylhydantoin with HOCl in aqueous solution were studied at 25 °C, constant ionic strength and under isolation conditions in a wide pH range. The set of compounds studied in this paper is characterized by having different functional groups and the same cyclic structure, consisting of a five-member ring with a nitrogen atom in the ring, which is susceptible to be chlorinated. This series of compounds covers nine p*K*_a units, and the kinetic studies allow us to know, like, the presence of an amino, amide or imide group modify the reactivity of nitrogenous compound.

Experimental data were fitted to the first-order kinetic equation. All reactions were found to be of first order in both HOCl and nitrogenous compound concentration. Kinetics studies demonstrate that some of these compounds are hydrolyzed in alkaline medium. In each case, reaction mechanism in agreement with the experimental results is proposed. The results were compared with other compounds with similar cyclic structure (2-oxazolidinone and proline). Copyright © 2016 John Wiley & Sons, Ltd.

Keywords: *N*-chlorination; heterocyclic nitrogen compounds; hydantoins; pyrrolidine; pyrrolidone

INTRODUCTION

The need to develop new biocides that improve their effectiveness against a wide range of microorganisms and reduce their adverse effects have been one of the reasons why the study of *N*-halamine compounds has been of great interest. These compounds have shown excellent biocidal capabilities because they act as oxidizing agents. It has been shown that the biocidal properties such as persistence in the medium and effectiveness are related to the structure and ionization constant of the *N*-halamine compounds.^[1,2] The stability of these *N*-halamines in aqueous solution provides a general idea of the type of biocide compound.

Worley *et al.* have studied novel heterocyclic biocidal *N*-halamine derivatives, such as oxazolidinones, imidazolidinones, hydantoins and spirocyclic amines, which have long-term stabilities in contact with aqueous solution and in dry storage.^[3] The stability of heterocyclic biocidals in aqueous solution not only depends of the nature of the nitrogen bonded to halogen but it also depends on a steric hindrance factor.^[1]

In the present work, a study of *N*-chlorination reaction of different heterocyclic nitrogen compounds with HOCl has been carried out. It has chosen a set of six compounds with different functional groups. However, all of them have in common the same cyclic structure consisting of a five-member ring with a nitrogen atom in the ring. The simplest compound selected with these characteristics is the pyrrolidine with an amino group. From this compound, we have been choosing other compounds in which the amino group has been replaced by others. Pyrrolidone (amide group), succinimide (imine group), 5,5-dimethyloxazolidine-2,4-dione (oxazolidinedione group), 5,5-dimethylhydantoin (hydantoin group) and 1-hydroxymethyl-5,5-dimethylhydantoin (hydantoin group) were the other

compounds chosen for investigation. Figure 1 shows all the compounds studied in this work.

This set of heterocyclic organic compounds of five atoms (Fig. 1) and their derivatives, very different chemically but with similar structures, is very interesting from the point of view pharmacologically because of their activity like antiepileptic and anti-convulsants.^[4–9] It is interesting to indicate that the type of substituent at C(5) appears to be extremely important in determining the physiological properties of these compounds.^[10]

Moreover, these heterocyclic compounds and their derivatives are of great interest because they possess other interesting characteristics. They are biologically active compounds^[8,11–20] and industrially useful compounds.^[7,8,20–30]

In addition, the *N*-chloro compounds formed in the *N*-chlorination reactions of these nitrogen compounds are of great importance in organic synthesis and in the chemistry of natural compounds. *N*-chloro compounds can act as halogenating, hydroxyhalogenating, oxidizing and condensing agents.^[31] The mechanism of formation of the N–Cl bond in different heterocyclic groups and the nature of the substituents around the nitrogen, which is chlorinated, are important aspects in their activity as biocide compounds.^[32]

In spite of the importance of the compounds selected in this paper, to study their *N*-chlorination reaction and of the products

* Correspondence to: C. Pastoriza, Departamento de Química Física, Facultad de Química, Universidad de Santiago de Compostela, 15782 La Coruña, Spain. E-mail: cinecris@gmail.com

a C. Pastoriza, J. M. Antelo, F. A. Amoedo, M. Parajó
Departamento de Química Física, Facultad de Química, Universidad de Santiago de Compostela, 15782, La Coruña, Spain

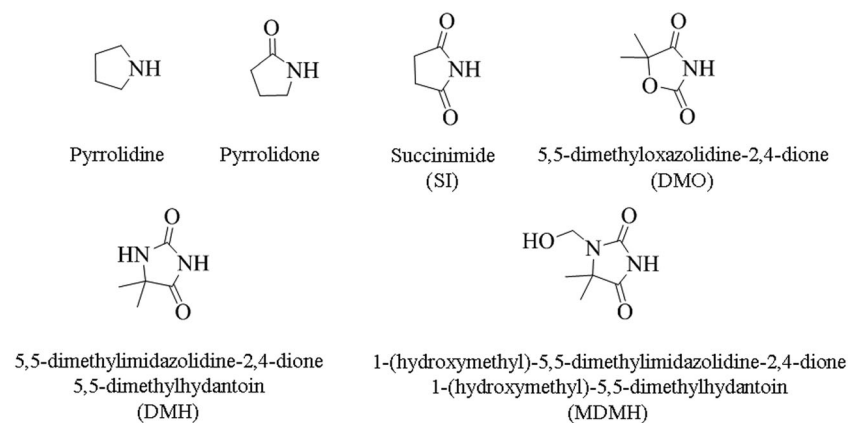


Figure 1. Heterocyclic organic compounds studied

formed, there are only very few studies with some of them.^[33–35] Therefore, we present the kinetic results obtained in the study of the *N*-chlorination reaction of six heterocyclic compounds of five-members containing at least one nitrogen atom in the ring with HOCl. These compounds were specifically selected based on their structural similarity of the cyclic ring and their extensive use, both in medicine and as industrially. Hence, it is possible that these compounds or their residues, which are important intermediates in environmental chemistry and biochemistry, may appear as contaminants emergent in water. As a consequence, if this water is subsequently subject to chlorination processes, there is the possibility that the *N*-chloro compounds are formed.

EXPERIMENTAL

Reagents

Sodium hypochlorite was obtained by passing a stream of chlorine through a solution of NaOH. The product obtained was stored at 0 °C, pH higher than 11 and in a topaz flask to avoid the decomposition by action of light. Its concentration was determined iodometrically. The solution used in the kinetic experiments was prepared every day from ClO[−] synthesized in the laboratory; its concentration having been previously checked spectrophotometrically.^[36]

Aqueous solutions of nitrogenous compounds were prepared using commercial products of P. A. grade quality: pyrrolidine (Merck), pyrrolidone (Merck), succinimide (Merck), 5,5-dimethyloxazolidine-2,4-dione (Aldrich), 5,5-dimethylhydantoin (Aldrich) and 1-(hidroximethyl)-5,5-dimethylhydantoin (Lancaster). They were prepared every day.

All reactions were carried out under conditions such that the pH value was maintained constant during the reaction; for this, we used different buffer solutions trying that the total concentration of external buffer was the same for all experiences performed with each amino compound. The buffer solutions used were as follows: CH₃COOH/CH₃COO[−] (pK_a = 4.54), H₂PO₄[−]/HPO₄^{2−} (pK_a = 6.8), H₃BO₃/H₂BO₃[−] (pK_a = 9.27), HCO₃[−]/CO₃^{2−} (pK_a = 10.3) and CF₃CH₂OH/CF₃CH₂O[−] (pK_a = 12.8).

A NaClO₄ solution was also prepared and used to control the ionic strength of the medium.

Instrumental

A Varian Cary 1 Bio spectrophotometer (Agilent Technologies, Santa Clara, CA, USA) was used for the previous studies, equipped with a thermostated cell holder and quartz cells with a 1 cm path length and a capacity of 3 cm³. This spectrophotometer was also used to check the concentration of ClO[−] solution and to monitor the reactions with *t*_{1/2} > 2 min. For the following of the faster reactions, a stopped flow spectrophotometer, Applied Photophysics (Leatherhead, UK) DX.17MV, was used. A system of mixed symmetric was used to monitor the reactions in aqueous solutions.

The thermostat used, a Selecta Frigiterm S-382 (Barcelona, Spain), ensured a consistency in temperature of ±0.1 °C. A workstation

allowed us to obtain the absorbance-time data that were sent to a computer equipped with a programme to analyse the data.

The pH measurements were made with a pH metre, PHM 82 Standard, radiometer Copenhagen (Radiometer Copenhagen, Denmark), equipped with a combined GK2401C electrode, thermostated at 25 °C. The pH metre was calibrated with standard solutions of pH 2.00 (Panreac), 4.01, 7.02 and 9.21 supplied by Crison, Barcelona, Spain.

The data treatment was performed using a spreadsheet (Grafit 5.0), which has allowed us to obtain the different magnitudes from the experimental data.

Kinetics

All studies were performed under isolation conditions using the nitrogenous compound as reagent in excess, with a [nitrogenous compound]/[HOCl] mole ratio higher than 10. Therefore, the concentration of the nitrogenous compound can be considered practically constant during the reaction, and it can be included in the rate constant (*k*_{obs}). Moreover, the concentration of protons is a parameter that has a great influence on the reaction rate; for this reason, it was necessary to maintain its constant concentration in each experiment using buffer solutions. All the experiments were carried out at 25 ± 0.1 °C, and the ionic strength was adjusted with NaClO₄.

The spectrophotometric method used to monitor the reactions allows us to know the variation of absorbance with time. The pseudo-first-order rate constants were obtained from the fit of the absorbance-time data, at a selected wavelength, to the first-order integrated rate equation.

All experiments were repeated between four and seven times. The values for the rate constants of pseudo-first order included in the tables are the average value of all the values obtained experimentally. The deviations obtained in each case were less than 5%. In those cases where the deviations were greater, the experiment was rejected and repeated.

RESULTS AND MECHANISM

All compounds studied are heterocyclic compounds (Fig. 1) with different functional groups but all containing an N–H group susceptible to be chlorinated. In this paper, the results obtained in the kinetic study of the *N*-chlorination reaction of each one with

HOCl are shown separately. The order in the presentation of these results is based on the complexity of the heterocyclic structure, which depends on the functional group. Therefore, and according to Fig. 1, the pyrrolidine is the first compound presented because it is the simplest of the six compounds that have been studied.

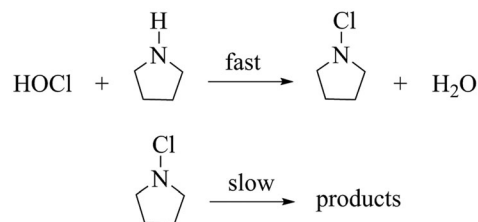
N-chlorination reaction of pyrrolidine

The kinetic study of the *N*-chlorination reaction of pyrrolidine with hypochlorite was performed using a spectrophotometric method. In order to find the most appropriate experimental conditions for monitoring the reaction, previous spectrophotometric studies of each of the reactants and of the reaction mixture were carried out. The superposition of these absorption spectra allows us to prove that when the mixture reaction occurs, the band at 292 nm, corresponding to hypochlorite, disappears and simultaneously appears a band at 260 nm, which corresponds to *N*-chloropyrrolidine (Fig. 2). This is a fast process; and therefore, the kinetic study of the formation reaction of *N*-chloropyrrolidine is carried out using a stopped-flow spectrophotometer. Subsequently, a slow disappearance of the absorption band of *N*-chloropyrrolidine is observed because of the decomposition of this product. The different rates between these processes allow us to study the formation reaction of the *N*-chloropyrrolidine and their reaction of decomposition independently (Scheme 1).

Considering the existing information on the chlorination processes involving organic nitrogenous compounds, the reaction between HOCl and these compounds could be described by the following rate equation (Eqn 1).

$$v = \frac{d[\text{N-chloropyrrolidine}]}{dt} = k [\text{Pyrrolidine}]^a [\text{HOCl}]^b [\text{H}^+]^c \quad (1)$$

A set of experiments was designed to determine the orders of reaction (*a*, *b* and *c*) and the rate constant (*k*). The kinetic experiments were carried out by the isolation method, being the hypochlorite the limiting specie (concentration of hypochlorite at least 10 times lower than pyrrolidine concentration). Moreover, the study was carried out using buffer solutions or high concentrations of sodium hydroxide solution to assure us that the proton concentration is maintained constant during the reaction. In these conditions, it was verified that the reaction is first order with respect to hypochlorite concentration, and the equation earlier can be expressed as (Eqn 2)



Scheme 1. General equation of the *N*-chlorination reaction of pyrrolidine with HOCl

$$v = k_{\text{obs}}[\text{HOCl}] \quad (2)$$

The reaction monitoring can be carried out following the variation of absorbance with time at 292 nm or at 260 nm. In all cases, the experimental results fulfil the kinetic equation of first order, which allow us to obtain the pseudo-first-order rate constant (k_{obs}). Each experience was repeated between 6 and 10 times, verifying the reproducibility of the experimental results. The values of the first-order kinetic constants, shown in this work, are the average values of all values obtained experimentally.

With the purpose of obtaining kinetic information about the *N*-chlorination reaction of pyrrolidine, a set of experiments was designed to verify the influence of different parameters on the rate constant. Parameters such as pyrrolidine concentration, ionic strength, buffer solutions concentration, temperature and pH were studied.

On the one hand, it was found that the reaction is first order with respect to pyrrolidine concentration. However, significant influences of buffer concentration or ionic strength on the experimental rate constant were not found. Furthermore, the variation of the rate constant with temperature allows us to verify that the experimental results fulfil the Arrhenius equation and Eyring equation and calculate the apparent activation parameters for this reaction. The values obtained for these parameters are as follows: $E_a = (79 \pm 1) \times 10^3 \text{ J mol}^{-1}$, $\Delta H^\ddagger = (76 \pm 1) \times 10^3 \text{ J mol}^{-1}$ and $\Delta S^\ddagger = (49 \pm 5) \text{ J mol}^{-1} \text{ K}^{-1}$ at pH = 9.25.

On the other hand, the experimental results show a complex dependency between the rate constant and the pH (Fig. 3). The study of the influence of pH on the rate constant in the range of pH3–12 was carried out using buffer solutions, whereas the experiments in a strong alkaline medium were carried out using different concentrations of NaOH solution. In strong alkaline medium, the acidity of the medium is expressed by the acidity function (H_-), calculated from sodium hydroxide concentration using bibliographic data.^[37]

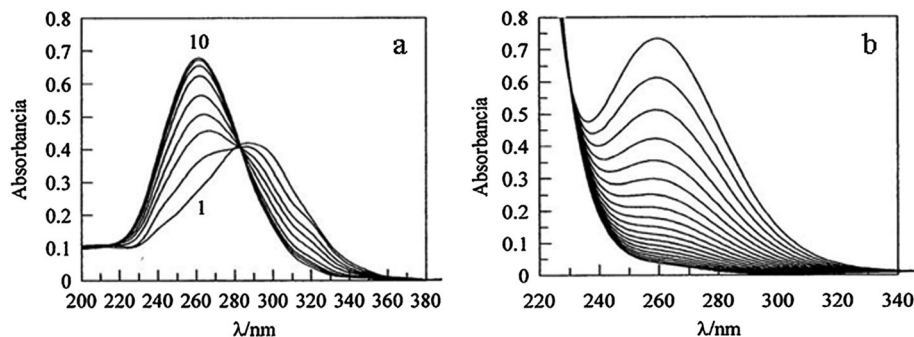


Figure 2. Absorption spectrum of reaction mixture. $[\text{ClO}^-] = 0.002 \text{ M}$, $[\text{Pyrrolidine}] = 0.02 \text{ M}$, $[\text{OH}^-] = 0.10 \text{ M}$, $I = 1 \text{ M}$. (a) *N*-chloropyrrolidine formation reaction, $\Delta t = 0.01 \text{ s}$; (b) *N*-chloropyrrolidine decomposition reaction, $\Delta t = 40 \text{ min}$

Reaction mechanism of *N*-chloropyrrolidine formation

The existence of a complex dependency between the rate constant and the pH can only be interpreted on the basis of the acid–base equilibria of the reactive species. Therefore, it is expected that the reaction can take place through some of the four possible combinations of species present in the medium when the mix of the reaction occurs.

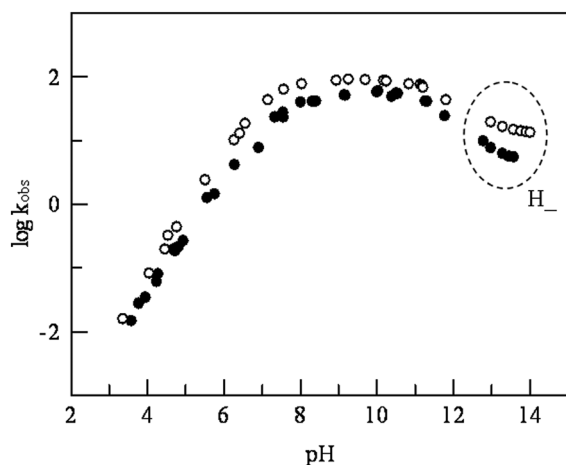
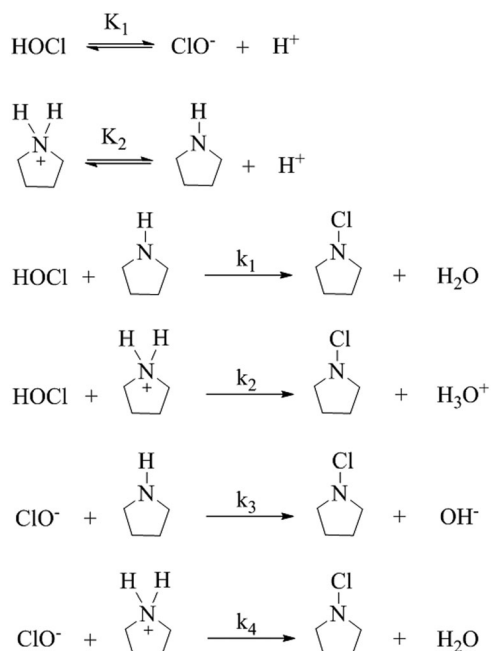


Figure 3. Influence of pH on pseudo-first-order rate constant (k_{obs}). \circ , [Pyrrolidine] = 0.01 M, $[\text{ClO}^-] = 0.001$ M, $I = 0.5$ M; \bullet , [Pyrrolidine] = 0.02 M, $[\text{ClO}^-] = 0.002$ M, $I = 1.0$ M

The acid-base equilibria of the reactive species and the four possible determining steps of the reaction rate are shown in Scheme 2. According to this scheme, it can obtain the overall reaction rate expression for the formation reaction of *N*-chloropyrrolidine (Eqn 3).

$$v = \frac{\left(\frac{k_1 [\text{H}^+] K_2 + k_2 [\text{H}^+]^2 + k_3 K_1 K_2 + k_4 [\text{H}^+] K_1}{(K_1 + [\text{H}^+]) (K_2 + [\text{H}^+])} \right) [\text{Pyrrolidine}]_{\text{T}} [\text{HOCl}]_{\text{T}}}{[\text{Pyrrolidine}]_{\text{T}} [\text{HOCl}]_{\text{T}}} \quad (3)$$



Scheme 2. Reaction mechanism proposed for the formation reaction of *N*-chloro-pyrrolidine with HOCl

$$k_{\text{obs}} = \frac{\left(\frac{(k_1 K_2 + k_4 K_1) [\text{H}^+] + k_2 [\text{H}^+]^2 + k_3 K_1 K_2}{(K_1 + [\text{H}^+]) (K_2 + [\text{H}^+])} \right) [\text{Pyrrolidine}]_{\text{T}}}{[\text{Pyrrolidine}]_{\text{T}}} \quad (4)$$

In accordance with Scheme 2, step 2 is very important in strongly acidic medium, whereas step 3 will be important especially in basic medium. Steps 1 and 4 are kinetically indistinguishable. Therefore, it is possible to obtain a value for a rate constant that includes the rate constants k_1 and k_4 or assume, according to bibliographic information, that the reaction only takes place through step 1 (k_1).

To calculate the values of the kinetic constants for the reaction of *N*-chlorination of pyrrolidine, a nonlinear fit of the experimental results obtained in the influence of the pH on the second-order rate constant ($k_{2\text{nd}} = k_{\text{obs}}/[\text{Pyrrolidine}]_{\text{T}}$) was carried out according to Eqn 4. For this, it was necessary to consider the values for ionization constants of HOCl and pyrrolidine at ionic strength 0.5 and 1 M, so ionic strength changes in this range have little effect on the $\text{p}K_{\text{a}}$. In the case of HOCl, we have considered the values $7.50^{[38]}$ and $(7.47 \pm 0.1)^{[39]}$ at ionic strength 0.5 and 1 M, respectively. However, in the literature, no experimental values were found for the $\text{p}K_{\text{a}}$ of the pyrrolidine at these ionic strengths.^[40–42] Thus, in the present work, we have determined the value of its ionization constant under the same conditions of concentration, temperature and ionic strength that were used in the kinetic experiments.

Table 1 summarizes the values of the rate constant of the second order obtained from the nonlinear fit to Eqn 4.

N-chlorination reaction of pyrrolidone

Spectrophotometric studies of the reaction mixture allow us to verify that when the mixture of reactants occurs, there is a disappearance of the absorption band at 292 nm, which is characteristic of ClO^- , and the simultaneous appearance of a band at 250 nm. This band corresponds to the formation of *N*-chloropyrrolidone.

The progress of the formation reaction of *N*-chloropyrrolidone was monitored using a conventional spectrophotometer, because previous studies have shown that the half-life for this reaction is greater than 2 min. Moreover, it was found that the process of formation and decomposition of the *N*-chloro compound can take place with very similar rates under certain conditions. So, in order to study independently both reactions, it is necessary to choose properly the experimental conditions.

Kinetic results allow us to confirm that the reaction is first order with respect to the ClO^- and pyrrolidone concentration. Furthermore, it was proved that neither the buffer concentration,

Table 1. Second-order rate constants for the formation reaction of *N*-chloropyrrolidine with HOCl

Pyrrolidine + HOCl	$I = 0.5$ M	$I = 1.0$ M
$k_1/\text{M}^{-1} \text{s}^{-1}$ (HOCl + RNH)	$(3.7 \pm 0.2) \times 10^7$	$(4.2 \pm 0.3) \times 10^7$
$k_2/\text{M}^{-1} \text{s}^{-1}$ (HOCl + RNH_3^+)	(1.6 ± 0.4)	(0.5 ± 0.3)
$k_3/\text{M}^{-1} \text{s}^{-1}$ (ClO^- + RNH)	$(6.0 \pm 0.8) \times 10^2$	$(7.0 \pm 0.9) \times 10^2$
$k_4/\text{M}^{-1} \text{s}^{-1}$ (ClO^- + RNH_3^+)	$(6.3 \pm 0.3) \times 10^3$	$(6.4 \pm 0.4) \times 10^3$
$\text{p}K_2$ ($\text{RNH} \rightleftharpoons \text{RN}^- + \text{H}^+$)	11.28 ± 0.01	11.29 ± 0.07

used to maintain the protons concentration constant in the reaction medium, nor the ionic strength have any appreciable influence on the rate constant.

The study of the influence of temperature on the rate constant for the formation reaction of *N*-chloropyrrolidone was carried out in a range of temperature between 22 and 40 °C at pH = 8–10, determining the apparent-activation thermodynamic parameters for this process. These values can be calculated using Arrhenius equation and Eyring activated complex theory. The values obtained from these equations are as follows: $E_a = (49 \pm 2) \times 10^3 \text{ J mol}^{-1}$, $\Delta H^\ddagger = (46 \pm 2) \times 10^3 \text{ J mol}^{-1}$ and $\Delta S^\ddagger = (-108 \pm 7) \text{ J mol}^{-1} \text{ K}^{-1}$ at pH 8.10 ($\text{H}_3\text{BO}_3/\text{H}_2\text{BO}_3^-$).

On the other hand, the reaction has been studied in a wide range of pH. The reaction was studied between pH 6–10 by using buffer solutions of phosphate and boric acid, whereas, at values of pH > 12, the study was carried out using NaOH solutions directly. In this range of pH, pH > 12, the acidity of the medium is expressed by acidity function (H_-) (Fig. 4).

Reaction mechanism of *N*-chloropyrrolidinone formation

The chlorination reaction of pyrrolidone shows a complex dependence of pH on the rate constant (Fig. 4). This same behaviour has been found in the kinetic study of the *N*-chlorination reaction of 2-oxazolidinone with HOCl.^[43]

The study of *N*-chlorination of 2-oxazolidinone was also performed under isolations conditions and was found that the reaction is first order with respect to the concentration of each reactant. Hence, the reaction mechanism that allow us to justify the experimental results for the *N*-chlorination reaction of pyrrolidone should be the same as that proposed in the *N*-chlorination reaction of 2-oxazolidinone.

According to the mechanism proposed in the formation reaction of *N*-chloro-2-oxazolidinone, the following overall rate equation (Eqn 5) can be used to describe the kinetics and therefore allows us to justify the experimental results for the *N*-chlorination reaction of pyrrolidone: the order to reaction with respect to reagents concentration and the complex dependence between k_{obs} and pH. Thus, it allows us to calculate the rate constants for each step by nonlinear fit of the experimental results.

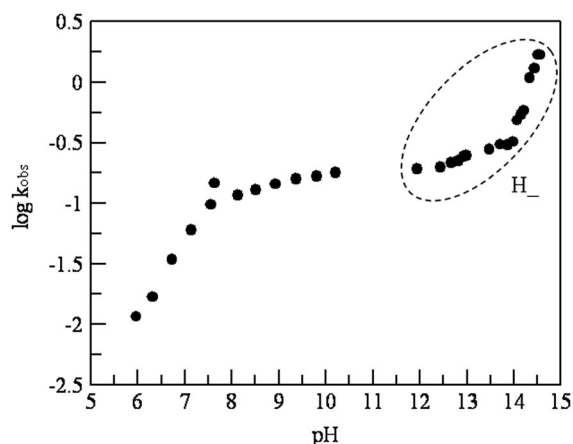


Figure 4. Influence of pH on pseudo-first-order rate constant (k_{obs}). $[\text{Pyrrolidinone}] = 0.01 \text{ M}$; $[\text{ClO}^-] = 0.001 \text{ M}$; $I = 0.5 \text{ M}$

$$k_{\text{obs}} = \frac{k_1 [\text{H}^+]^2 + k_2 [\text{H}^+] K_2 + k_3 [\text{H}^+] K_1 + k_4 K_1 K_2}{(K_1 + [\text{H}^+]) (K_2 + [\text{H}^+])} [\text{Pyrrolidone}]_T \quad (5)$$

In this equation, the nomenclature used for the rate constants is the same as that used in the reaction mechanism proposed in the reaction of pyrrolidone with HOCl. It refers to the reaction between the two neutral species (k_1), the combinations between one anionic species and another neutral species (k_2 and k_3) or the two anionic species (k_4). This equation (Eqn 5) also reflects the importance of the ionization equilibrium of each reactive species.

In the literature, no experimental values were found for the pK_a of the nitrogenous compound although we found a theoretical value for pyrrolidone: $pK_a = 16.62 \pm 0.20$ (calculated using Advanced Chemistry Development (ACD/Labs) Software V11.02). For the HOCl, experimental values of pK_a were found. Therefore, we have considered the value of pK_a of HOCl to be constant ($pK_a = 7.50$)^[38] in Eqn 5, whereas the pK_a for the nitrogenous compound has been evaluated by nonlinear fit of the experimental results according to this equation.

Table 2 summarizes the values of the rate constants of the second order obtained from nonlinear fit to Eqn 5 for the *N*-chlorination reaction of pyrrolidone with HOCl. Moreover, these values are compared with the literature values for the *N*-chlorination reaction of the 2-oxazolidinone with HOCl.^[43]



N-chlorination reaction of succinimide

N-chlorosuccinimide (NCS) can be obtained easily in aqueous solution by mixing solutions of succinimide (SI) and hypochlorite. However, it is only available of partial kinetic information on this process.

Higuchi *et al.*^[35] have studied the kinetic for this reaction in the range of pH between 1.96 and 4.92, and subsequently Matté *et al.*^[34] studied the kinetic of the formation reaction of NCS in acid medium (pH < 5) and in alkaline medium (pH > 9).

In the present work, the kinetic of this reaction was studied in a range of pH between 1.61 and 11.23. The study was performed under isolations conditions, being the hypochlorite concentration at least 10 times lower than the SI concentration. Monitoring of the reaction was carried out by measuring the absorbance of

Table 2. Second-order rate constants for the formation reaction of *N*-chloropyrrolidone and *N*-chloro-2-oxazolidinone with HOCl

	Pyrrolidone	2-oxazolidinone
		
Pyrrolidone + HOCl		
$k_1/\text{M}^{-1} \text{ s}^{-1}$ (HOCl + RNH)	0.012 ± 0.003	0.18 ± 0.02
$k_2/\text{M}^{-1} \text{ s}^{-1}$ (HOCl + RN ⁻)	$(1.29 \pm 0.02) \times 10^7$	$(1.5 \pm 0.4) \times 10^7$
$k_3/\text{M}^{-1} \text{ s}^{-1}$ (ClO ⁻ + RNH)	0.2 ± 0.1	20 ± 5
$k_4/\text{M}^{-1} \text{ s}^{-1}$ (ClO ⁻ + RN ⁻)	$(0.47 \pm 0.2) \times 10^2$	$(2.9 \pm 0.7) \times 10^2$
pK_2 (RNH \rightleftharpoons RN ⁻ + H ⁺)	15.93 ± 0.08	13.5 ± 0.2

the mixture reaction against time. The measurements were carried out to 292 nm, which corresponds to the maximum of the absorption band of hypochlorite.

In order to determine the order of the reaction, different experiences using buffer solutions of acetate ($pK_a = 4.58$) and phosphate ($pK_a = 6.8$) were carried out. These experimental results allow us to verify the first order with respect to concentration of each reactant, hypochlorite and SI. Moreover, a significant change was not observed on the rate constants by modifying the ionic strength or the concentration of buffer solutions.

The first-order pseudo-rate constants were evaluated in a wide range of pH, using different buffer solutions (acetate, phosphate and borate). The results are shown in Fig. 5, where we can see three different areas: (i) up to $pH = 7.50$, (ii) between $7.50 < pH < 9.62$ and (iii) from $pH = 9.62$. The values 7.50 and 9.62 correspond to the pK_a of HOCl and SI, respectively.^[38,44]

To values of pH lower than the pK_a (HOCl), the logarithm of k_{obs} fits linearly to the pH, with a slope close to 1. To values of pH between pK_a (SI) and pK_a (HOCl), the rate constant is practically constant, whereas to values of pH higher than the pK_a (SI), the rate constant decreases with a slope close to -1 .

When the reaction is studied at $pH > 11$, using NaOH solutions to reach the desired pH, the rate constants are difficult to evaluate because the absorbance variation against time, at 292 nm, shows the existence of two different processes for the disappearance of ClO^- . These two processes have close rates, so they cannot be studied independently. To $pH > 12$, it only observed the second reaction process.

Under the experimental conditions in which only the second process is observed ($pH > 12$), it was verified that the reaction is first order with respect to the ClO^- concentration and first order with respect to the SI concentration. On the other hand, the kinetic experiments show that there is no appreciable influence of the ionic strength on the rate constant, and furthermore, it evaluated the activation parameters at NaOH concentration of 0.4 M.

The values of the experimental rate constants obtained to different concentrations of NaOH are included in Fig. 6. To these values, the acidity of the medium is expressed by acidity function (H_-). In this graph, we can see a linear dependence between

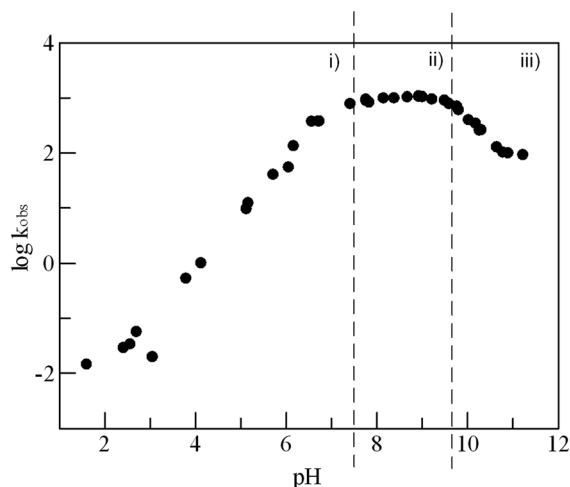


Figure 5. Influence of pH on pseudo-first-order rate constant (k_{obs}). [SI] = 0.01 M; $[ClO^-] = 0.001$ M; $I = 0.5$ M. (i) $pH < 7.50$, pK_a (HOCl) = 7.50; (ii) $7.50 < pH < 9.62$; (iii) $pH > 9.62$, pK_a (SI) = 9.62. SI, succinimide

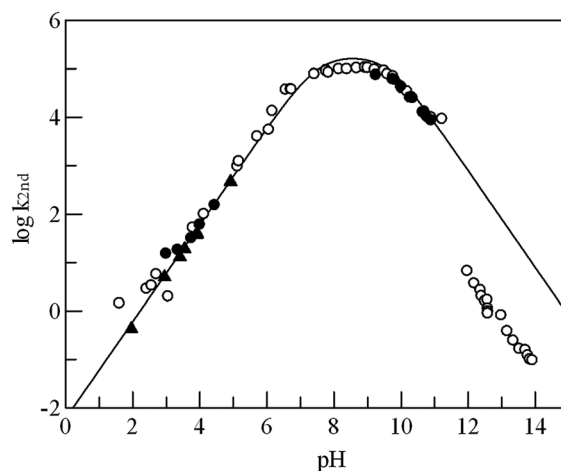


Figure 6. Experimental values and theoretical curve deduced from reaction mechanism with HOCl ($pH < 12$). \circ , this work; \bullet , Matté *et al.*; \blacktriangle , Higuchi *et al.*

both variables $\log k_{2nd}$ and pH, which seems to indicate that there is a linear relationship with a slope approximately -1 .

Reaction mechanism of *N*-chlorosuccinimide formation

In order to interpret the behaviour of the reaction to different values of pH, it is necessary to take into account the acid–base equilibria in which it may involve the reagent species in solution. And, the possibility of that the reaction takes place through four possible steps resulting in the combination of the possible acid or basic forms of these reagents.

In the same way as that in the aforementioned proposed mechanisms, it is possible to obtain a complex rate equation for the *N*-chlorination reaction of SI from this general scheme. The rate equation will be a sum of four terms like Eqn 5. Two of them, steps 2 and 3, are kinetically indistinguishable. Step 1, in which the two acid species are involved, only has importance in a strongly acid medium. On the contrary, step 4, in which the two basic species are involved, has only importance in alkaline medium.

The values of the kinetic constants for this mechanism can be calculated by fitting the experimental results obtained to study the influence of the pH on the rate constant ($pH = 1.26$ – 11.23) to the equation deduced of the reaction mechanism (Eqn 5). This adjustment was carried out in two ways: (a) by assuming that the reaction occurs only through steps 1, 2 and 4 or (b) by assuming that the reaction occurs only through steps 1, 3 and 4. Table 3 summarizes the rate constants obtained by nonlinear fit in each case.

In this table (Table 3), the rate constants for the *N*-chlorination reaction of SI with HOCl obtained by Matté and Higuchi are also included. The values of the rate constants obtained in the present work are in agreement with literature values. All the values summarized in this table are shown in Fig. 6, where it also included the nonlinear fit obtained considering only step 2. In this figure, it can be observed that the adjustment reproduces quite well the experimental results, although it has observed a deviation at $pH < 2.42$ and $pH > 11.20$.

Steps 2 and 3 cannot be distinguished by kinetic studies, and only a quantum treatment can help to clarify the reaction path

Table 3. Second-order rate constants for the formation reaction of *N*-chlorosuccinimide with HOCl

Succinimide + HOCl	298°K $pK_a(\text{HOCl}) = 7.50$, $pK_a(\text{SI}) = 9.62$		293°K $pK_a(\text{HOCl}) = 7.58$ $pK_a(\text{SI}) = 9.71$	298°K $pK_a(\text{HOCl}) = 7.53$ $pK_a(\text{SI}) = 9.62$
	(a) Steps 1, 2 and 4	(b) Steps 1, 3 and 4	Matte <i>et al.</i> ^[34]	Higuchi <i>et al.</i> ^[35]
$k_1/\text{M}^{-1} \text{s}^{-1}$ (HOCl + SI)	1.2 ± 0.4	1.2 ± 0.4	—	—
$k_2/\text{M}^{-1} \text{s}^{-1}$ (HOCl + SI ⁻)	$(2.2 \pm 0.1) \times 10^7$	—	$(2.2 \pm 0.4) \times 10^7$	2.14×10^7
$k_3/\text{M}^{-1} \text{s}^{-1}$ (ClO ⁻ + SI)	—	$(1.6 \pm 0.1) \times 10^5$	$(1.6 \pm 0.3) \times 10^5$	—
$k_4/\text{M}^{-1} \text{s}^{-1}$ (ClO ⁻ + SI ⁻)	$(2 \pm 2) \times 10^3$	$(2 \pm 2) \times 10^3$	—	—

SI, succinimide.

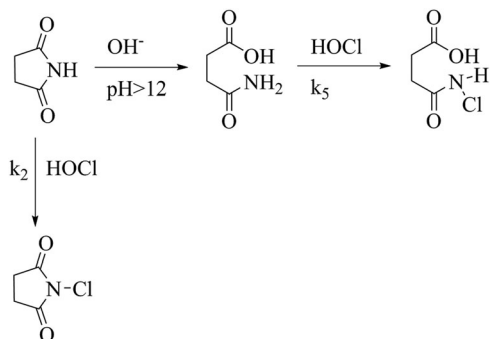
that leads to a transition state of minimum energy.^[33] All studies seem to indicate that step 2 would be the most probable and that, in aqueous medium, the transition state is assisted by at least two molecules of water.^[45–47]

At pH > 11.20, the experimental results are deviated of the behaviour expected by the mechanism indicated earlier, such as shown in Fig. 6.

In the literature, we have found information about the behaviour of aqueous solutions of SI in alkaline medium. It reveals the existence of a hydrolysis process of the SI with irreversible ring-cleavage and formation of succinamic acid.^[8,44,45,48–50] The hydrolysis process is delayed until the pH values is above the pK_a of succinimide.^[46] The specie formed, succinamic acid, can react with the ClO⁻ to give an *N*-chloro compound (Scheme 3).

According to Scheme 3, the ClO⁻ disappears in the reaction medium by two different processes: forming the NCS and forming the *N*-chlorosuccinamide. The rate of both processes depends on the HOCl concentration, and on the values of the rate constants for k_2 and k_5 , and of the concentration of species SI ion and succinamic acid. These concentrations are conditioned by the dependence of the hydrolysis rate of SI with pH.

Indeed, theoretical studies and experimental studies were found in the literature on the hydrolysis reaction of SI as much in alkaline medium as in neutral medium. In these studies, it showed that the hydrolysis in alkali medium is preferable to the same reaction in neutral medium both kinetically and thermodynamically.^[45] Some values of the rate constant found for the hydrolysis process at 25 °C are as follows: $1.8 \times 10^{-3} \text{ min}^{-1}$ and $2.4 \times 10^{-3} \text{ min}^{-1}$ at values of pH close to pK_a of SI, pH = 9.32 and 9.92, respectively,^[44] and $2.13 \text{ M}^{-1} \text{ s}^{-1}$ at pH = 10.5.^[46] Under these experimental conditions, the hydrolysis process is slower than the chlorination process of SI because

**Scheme 3.** Aqueous solutions of succinimide in alkaline medium, hydrolysis and *N*-chlorination

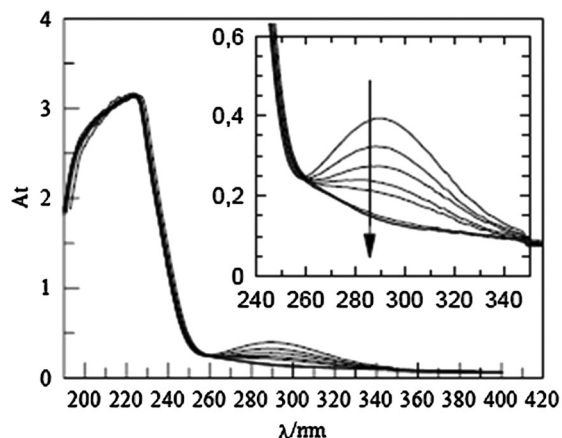
the concentration of the formed succinamic acid is very small and the process k_5 does not compete with the process k_2 . However, in the range of pH = 11–12, the rate of the hydrolysis process increases with decreasing the rate of chlorination process of SI. In this pH range, the two processes of chlorination (k_2 and k_5) are going to take place with similar rates, making difficult the kinetic study of both processes separately.

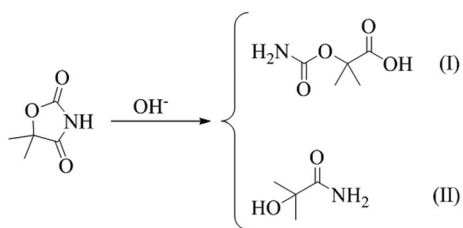
To values of pH > 12 (Fig. 5), the experimental results seem to indicate that the reaction occurs entirely through the chlorination of succinamic acid. So, taking into account the variation of the second-order rate constant with the acidity function, a value for the rate constant of this process can be evaluated. The second-order rate constant for the *N*-chlorination of succinamic acid is $k_5 = (1.8 \pm 0.1) \times 10^5 \text{ M}^{-1} \text{ s}^{-1}$.

***N*-chlorination reaction of dimethadione (5,5-dimethyloxazolidine)**

Reaction of dimethadione (DMO) with HOCl has been studied in the range of pH from 8 to 11.25. It studied the influence on the rate constant of different parameters such as reagents concentration (HOCl and DMO), buffer solution concentration, pH, ionic strength and temperature. These studies were carried out under isolation conditions ([DMO]/[ClO⁻]; mole ratio higher than 10), following the disappearance band of ClO⁻ at 292 nm (Fig. 7).

Kinetic studies showed that an *N*-chlorination reaction occurs. Experimental results showed a first order with respect to each reactant, and that there is no influence of buffer concentration or

**Figure 7.** Absorption spectrum of reaction mixture to 1, 20, 40, 60, 80, 180, 380 and 680 min. [DMO] = 0.01 M, [ClO⁻] = 0.001 M, [H₃BO₃/H₂BO₃] = 0.33 M, I = 0.5 M, pH = 9.30. DMO, dimethadione



Scheme 4. Alkaline hydrolysis of DMO

ionic strength on the rate constant. However, an influence of the temperature on the rate constant was found. Furthermore, it was found that there is a linear decrease in the $\log k_{\text{obs}}$ with increasing pH.

In spite of that, we cannot propose a reaction mechanism that allows us to justify the experimental results. Because, the information found in the literature, about the dimethadione ($\text{p}K_{\text{a}} = 6.35^{[51]}$) in solution, indicates us that this nitrogenous compound in alkaline medium is rapidly hydrolyzed. In this hydrolysis process takes place the ring-cleavage, giving rise to two new nitrogenous compounds by two different ways (Scheme 4) to form carbamoyloxyacids and α -hydroxy amides. The new compounds are capable of being chlorinated.^[52–54]

As a result of this hydrolysis, both compounds 2-[(aminocarbonyl)oxy]-2-methyl-propanoic acid (I) and 2-hydroxy-2-methylpropanamide (II) can be formed, although the literature indicates that there is a greater preference for the formation of compound II.^[52]

Therefore, despite the fact that experimental results provide evidence of a chlorination process, we cannot propose a reaction mechanism for this process because we have no evidence that this is the chlorinated molecule.

N-chlorination reaction of 5,5-dimethylhydantoin and 1-hydroxymethyl-5,5-dimethylhydantoin

Other processes studied in the present work are the chlorination reactions of 5,5-dimethylhydantoin (DMH) and of 1-hydroxymethyl-5,5-dimethylhydantoin (MDMH) with ClO^- .

The DMH contains two nitrogen atoms with quite different properties, amide nitrogen and imide nitrogen in positions 1 and 3, respectively. Both nitrogens can be chlorinated. In the literature, several studies were found on the *N*-halogenation reaction of hydantoins as on the stability of *N*-halamine formed.

The information available for the *N*-chlorination reaction of hydantoins indicates that, in the reaction of *N*-chlorination of DMH, the formation of the 3-chloro-dimethylhydantoin occurs in the first place and, subsequently, the 1-chloro-dimethylhydantoin also appears in the reaction medium. According to the literature, in the beginning, the reaction is kinetically controlled. However, after a while, there is a thermodynamic control that determines the reaction products. Moreover, the formation of 1,3-dichloro-dimethylhydantoin is also going to take place when there is an excess of chlorinating agent.^[32,55–57]

In the case of MDMH, the molecule cannot be chlorinated in positions 1 or at positions 1 and 3 at the same time.

Therefore, in order to carry out the kinetic study of formation reaction of the 3-chloro-5,5-dimethylhydantoin, reaction mixtures with ClO^- concentration 10 times lower than DMH concentration were prepared. Under these experimental conditions of isolation, a spectrophotometric study of the reaction mixture was performed. This study allowed us to demonstrate that a very fast process of disappearance of ClO^- occurs. So, the measurements of absorbance at 292 nm at different times can be used to the kinetic monitoring of the reaction.

Analysis of data absorbance versus time allows us to prove that there is a fast first decrease of absorbance followed by a slower decrease. Each one of these process shows a good fit to a kinetic of first order, being the half-life of 6 ms for the first process and 5.4×10^4 ms for the second at $\text{pH} = 6.01$. This result indicates that it is possible to study both processes independently. The kinetic constants for the first process are identified as formation constants of 3-chloro-dimethylhydantoin, whereas the rate constants for the slower process correspond with the inverse process, which is the hydrolysis process of 3-chloro-dimethylhydantoin formed.

Kinetic study of the formation of 3-chloro-5,5-dimethylhydantoin was carried out in a range of pH between 5 and 11, using different buffer solutions to reach the desired pH. In these experiments, the concentrations of HOCl and DMH and the temperature and the ionic strength were maintained constant, and only the concentration of the buffer solution was modified.

Experimental results are fitted to a first-order kinetic model, which allow us to determine the pseudo-first-order rate constant (k_{obs}). A set of experiments was carried out to prove that the reaction is first order with respect to the DMH concentration and independent of buffer concentration and of the ionic strength. Moreover, a complex dependence between the rate constant and pH was found for both processes (Fig. 8).

Analogous study was performed with the nitrogenous compound MDMH showing a similar behaviour (Fig. 8).

Reaction mechanism of 3-chloro-hydantoins

In order to propose a reaction mechanism, it is necessary to consider the different acidities of the nitrogen atoms and thus, according to the bibliographic information, it assumes that only the nitrogen at the 3 is ionized. Based on this, the mechanism for the formation reaction of the 3-chloro-5,5-dimethylhydantoin is identical to that proposed for the case of the SI (Eqn 5). As a

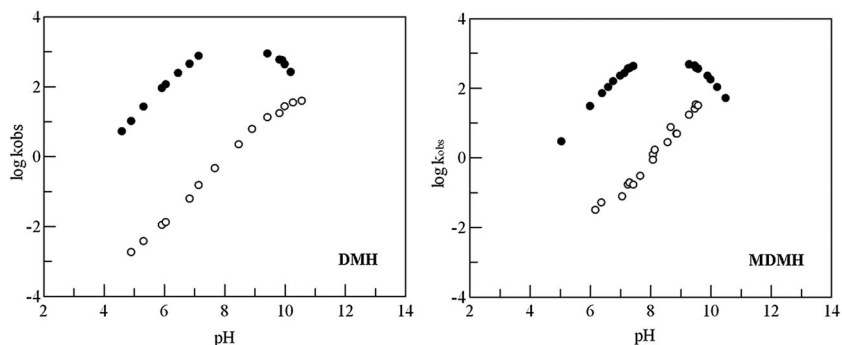


Figure 8. Influence of pH on $\log k_{\text{obs}}$. ●, *N*-chlorination reaction; ○, Hydrolysis reaction. k_{obs} , pseudo-first-order rate constant; DMH, 5,5-dimethylhydantoin; MDMH, 1-hydroxymethyl-5,5-dimethylhydantoin

Table 4. Second-order rate constants for the formation reaction of 3-chloro-5,5-dimethylhydantoin and 3-chloro-1-hydroxymethyl-5,5-dimethylhydantoin with HOCl

	DMH	MDMH
Hydantoins + HOCl		
$k_2/M^{-1} s^{-1}$ (HOCl + RN ⁻)	$(7.5 \pm 0.4) \times 10^6$	$(10.1 \pm 0.2) \times 10^6$
$k_3/M^{-1} s^{-1}$ (ClO ⁻ + RNH)	$(1.53 \pm 0.08) \times 10^5$	$(1.27 \pm 0.02) \times 10^5$
pK_2 (RNH \rightleftharpoons RN ⁻ + H ⁺)	9.16 ± 0.08	9.37 ± 0.2

DMH, 5,5-dimethylhydantoin; MDMH, 1-hydroxymethyl-5,5-dimethylhydantoin.

result, from the combination of the four species implied in the equilibria of the reactive species, four possible determining steps of the reaction rate are proposed.

Analyzing each step of the reaction mechanism proposed and considering that the kinetic studies were performed in the range of pH between 5 and 11, we can say that the rate constants for steps 1 and 4 will be very small compared with the corresponding values for steps 2 and 3. Hence, steps 1 and 4 can be discarded in the data analysis.

Thus, the reaction rate could be written by Eqn 6:

$$k_{\text{obs}} = \left(\frac{k_2 [\text{H}^+] K_2 + k_3 [\text{H}^+] K_1}{(K_1 + [\text{H}^+]) (K_2 + [\text{H}^+])} \right) [\text{DMH}]_{\text{T}} \quad (6)$$

Steps 2 and 3 are kinetically indistinguishable. However, most of the information for *N*-chlorination reaction of nitrogenous compounds with HOCl indicates that the reaction takes place through

step 2, the reaction between the neutral species of the hypochlorous acid and the ionic species of DMH. These two constants can be evaluated independently, by nonlinear fit of the experimental results to Eqn 6. For this, it was necessary to consider the values for ionization constants of HOCl, DMH or MDMH at the same ionic strength at which the experimental results were obtained, at ionic strength 1 M. In the literature, we have found experimental values for the HOCl at different ionic strengths, whereas the pK_a values for the nitrogenous compounds, DMH and MDMH, have been necessary to evaluate by nonlinear fit of the experimental results according to Eqn 6. The value for the pK_a of the HOCl considered was 7.47 at ionic strength 1 M.^[39] These values are included in Table 4 along with the second-order rate constants obtained by nonlinear fit of the experimental data using Eqn 6.

As can be seen in Fig. 8, the experimental results obtained in the influence of pH on the rate constants, corresponding to the *N*-chlorination reaction of DMH or MDMH, present a bell-shaped profile. The rate maximum occurs at a pH value, $\text{pH}_{\text{max}} = (pK_1 + pK_2)/2$, midway between the pK_a of the HOCl and that of the nitrogenous compound. This same profile, bell-shaped curve, has been observed in the *N*-chlorination reaction of SI with ClO⁻.

On the other hand, another study was carried out to determine the ionization constants of the DMH and the MDMH. Potentiometric and spectrophotometric measurements were performed at different ionic strengths. Table 5 summarizes the results obtained in both methods. In the case of DMH, the potentiometric titration shows that there is a second process of dissociation whose value could not be determined accurately by either method. In the case of DMH, the values of the ionization constants obtained both experimentally as by nonlinear fit agree fairly well with those found in the literature. In the case of MDMH, despite that we have not found literature values for pK_a , the experimental values agree with that obtained by nonlinear fit.

Hydrolysis of *N*-chloro-hydantoins formed

The following absorbance variation, at 292 nm, with the time for the two processes were observed with half-lives very differently

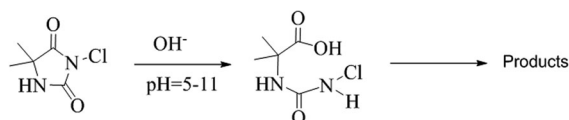
Table 5. Experimental values of pK_a for 5,5-dimethylhydantoin and 1-hydroxymethyl-5,5-dimethylhydantoin

Nitrogenous compound	Spectrophotometric method (I = 0.5 M)	Potentiometric method (I = 0 M)	Ref
 DMH	H in position 3 8.83 ± 0.02	9.08 ± 0.02	8.93^2 $9.03^{[32]}$ $9.00^{[58]}$ $9.19^{[59,60]}$ $9.20^{[61]}$ $14^{[58]}$
 MDMH	H in position 1 14.9 ± 0.1^1	—	Values were not found
		9.25 ± 0.05	9.16 ± 0.02

DMH, 5,5-dimethylhydantoin; MDMH, 1-hydroxymethyl-5,5-dimethylhydantoin.

¹This value is not accurate.

²Calculated using Advanced Chemistry Development (ACD/Labs).



Scheme 5. Hydrolysis of 3-chloro-5,5-dimethylhydantoin

so they can be studied separately. The data, absorbance versus time, were fitted to first-order kinetic equation in each case.

Experimental results showed that the rate constant, for the slower process observed, increases with increasing the DMH concentration. However, there is no dependence of first order with respect to DMH concentration. Besides, the values of the pseudo-rate constants determined are independent of buffer concentration and of ionic strength.

Moreover, the slower process (Fig. 7) shows a linear relation between the logarithm of the first-order rate constant and the pH in the range between 5 and 11, with a slope practically equal to 1. The results obtained for the two hydantoin are reasonably coincident.

On the other hand, according to the literature available, the hydantoin in aqueous solution can be hydrolyzed. In this process, in which ring-opening occurs to give the ureido acids as intermediate, which can hydrolyze to α -amino acids (Scheme 5),^[62,63] it was observed that the rate constant increase with increasing pH.^[64–68] It suggests that the second process observed corresponds with the hydrolysis reaction of the 3-chlorohydantoin formed. The mechanism for this hydrolysis reaction should be analogous to that of the hydantoin proposed in the literature.

Nevertheless, experimental results are not enough to assess the rate constant of the determining step and can establish the kinetics characteristics of this second process.

DISCUSSION

The set of compounds studied in this paper is characterized by having different functional groups. However, all of them have in common the same cyclic structure consisting of a five-membered ring with a nitrogen atom in the ring (Fig. 1). In this paper, the kinetics results obtained from the study of the *N*-chlorination reaction of these compounds with HOCl are shown.

Therefore, it would be interesting to compare these results with other bibliography; whether they are for the formation reaction of the *N*-halo compounds studied with other chlorinating agents or for the reaction of similar compounds with the same chlorinating agent. However, only kinetic studies for the reaction of two similar compounds to those studied, 2-oxazolidinone (OXA)^[43] and proline,^[69] with HOCl, were found in the literature.

The theoretical profiles, $\log k_{2nd}$ against pH, for each compound studied are plotted in Fig. 9. In each case, the profile was obtained from the reaction mechanism proposed and using the rate constants obtained by nonlinear fit. Moreover, the theoretical profiles for the OXA and proline are also shown in this figure (for 2-oxazolidinone, see Table 2 in this paper, and for proline: $k = 2 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$ and $pK_a = 10.65$ ^[69]).

This figure allows us to compare the kinetic behaviour of these seven heterocyclic compounds in the range of pH of interest, biological and environmental. Two different types of profiles can be distinguished: a profile with S-shaped and another with bell-shaped. The first one corresponds to the compounds OXA

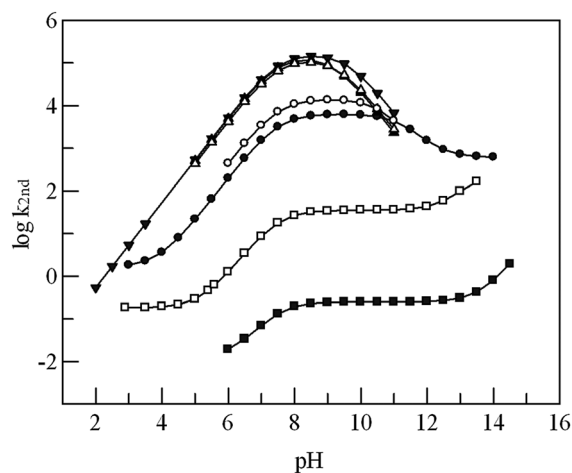


Figure 9. Theoretical profiles obtained from the mechanism proposed. \blacktriangledown , succinimide (SI); \blacktriangle , 5,5-dimethylhydantoin (DMH); \triangle , 1-hydroxymethyl-5,5-dimethylhydantoin; \circ , proline; \bullet , pyrrolidine; \square , 2-oxazolidinone (OXA); \blacksquare , pyrrolidinone

and pyrrolidinone and the second corresponds with the compounds SI, DMH, MDMH, proline and pyrrolidine.

The OXA and pyrrolidinone, which have the highest pK_a value, present a very different behaviour with respect to other compounds studied. They have an amide bond characterized by its strong resonance, and they are remarkably stable to hydrolysis, with the half-life for neutral hydrolysis at room temperature counted in hundreds of years.^[70] Moreover, according to kinetics results, these compounds are chlorinated more slowly than others.

Another compound studied is SI, for which there is available bibliographic information about its *N*-chlorination reaction. It is characterized by having an imide bond. The kinetics results shown in the present work, in the range of pH between 1.61 and 11.23, are in total agreement with those reported by Matté^[34] and also by Higuchi.^[35] However, at $pH > 11.20$, this compound shows an anomalous behaviour that it was attributed to a hydrolysis process with ring-cleavage.

The hydrolysis of imide and amide group depends on the pK_a value. Thus, these groups are hydrolyzed more easily at lower pK_a value.^[70] For this reason, we can say that the two amides studied, OXA and pyrrolidinone, do not undergo a process of hydrolysis because they have a pK_a value higher than 14. However, the succinimide with $pK_a = 9.62$ undergoes an important process of hydrolysis from $pH = 10$, and the hydantoin, with a lower pK_a than SI but close, are hydrolyzed more easily. In addition, the DMO with a $pK_a = 6.38$ is much more easily hydrolyzed. In this case, the rate constants for the formation reaction of *N*-chloro dimethadione could not be assessed, because the formed species in the hydrolysis process interfere with the process of *N*-chlorination of DMO.

Regarding the hydantoin, it is important to emphasize the total agreement on their experimental results. On the one hand, the DMH contain two *N* atoms in the ring that can be chlorinated, one of which is an amide nitrogen, in position 1, whereas in position 3 is an imide nitrogen. Both of them can be chlorinated, but according to what was mentioned earlier, the chlorination in position 3 (imide nitrogen) is easier than in position 1 (amide nitrogen), and also, it takes place at a higher rate. Therefore, the chlorination occurs in the position of the imide nitrogen.^[32,55–57] On the other hand, the MDMH has a substituent in

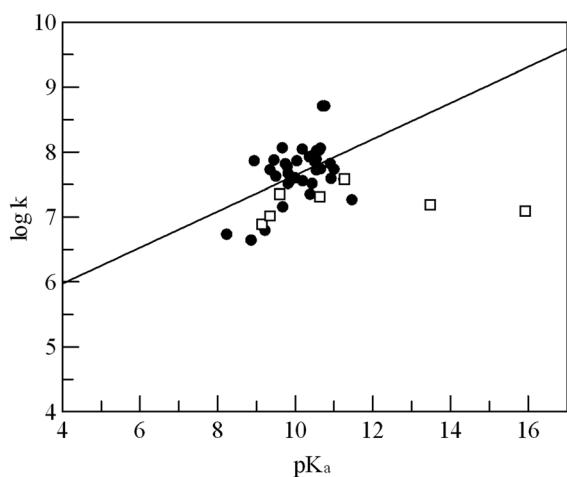


Figure 10. Brønsted relationship, $\log k$ versus pK_a . ●, Bibliographic values and □, values presented in this work

position 1, so, in this case, *N*-chlorination only is possible in position 3 (Fig. 9). This fact supports that *N*-chlorination takes place in position 3.

Finally, proline and pyrrolidine, which do not contain functional groups in the C-alpha to the nitrogen atom in the cyclic structure, exhibit a behaviour similar to that found in the literature for other secondary amines, which shows a bell-shaped profile, and its shape depends on the ionization constant of the HOCl and of the nitrogenous compound. These amino compounds are more stable than amide and imide compounds.

On the other hand, being able to prove the existence of structure-reactivity relationships is a common practice in kinetic studies owing to its relatively good correlation between the results obtained for homologous series. In our case, the only compound that could be compared with secondary amines is pyrrolidine because we do not have structural data neither for the compounds studied nor other similar compounds. Hence, the Brønsted relationship is the only one which we have been able to establish given that it is only necessary to have the pK_a values for the HOCl and for the nucleophiles studied.

Literature available provided us sufficient information about the *N*-chlorination reaction of nitrogenous compounds with HOCl to establish the Brønsted relationship. It found information for nitrogenous compounds such as primary and secondary amines and straight-chain amino acids. In total, 38 values were found for different compounds of this type. These values are represented in Fig. 10 and the trend line of these bibliographic data. Moreover, the values obtained in the present work along with OXA and proline were also included in this figure, but they are not included in the adjustment.

In Fig. 10, it can be seen that the pyrrolidinone and OXA compounds present a considerable deviation with regard to the other nucleophiles. However, pyrrolidine is in good accordance with the trend line drawn, showing an identical behaviour to secondary amines. Additionally, it can be seen that the results obtained with the other cyclic compounds studied, SI, DMH and MDMH, do not show a deviation of the behaviour of the corresponding nitrogenous compounds of straight chain, in spite that in these cases the nitrogen chlorinated is an imide nitrogen.

It is interesting to emphasize the importance of the pK_a values of the nucleophile compound in the chlorination process because there is an increase almost in the linear of $\log k$ with

increasing pK_a , being the only exceptions in the amide compounds.

In the literature, we have found very few kinetic studies for the chlorination reaction of amides with HOCl, in which the rate constants refer to the reaction step of HOCl with the ionic species (RN^-). Nevertheless, it found values for the reaction of aliphatic amides with HOCl corresponding to the reaction step of ClO^- with the neutral species (RNH). The values found, in those cases, are of order of those obtained in this work for the same steps.^[71,72] It has observed a decrease of the rate constant with increasing the ionization constant (pK_a). Despite this fact, the Brønsted relation has not been established because of the great uncertainty in the ionization constant values.

All compounds studied in this paper are of the extensive interest in different fields of application, not only because of their direct application but also because they are part of structure of other more complex compounds conferring interesting properties for their application.^[73–78] Consequently, it is quite probable that these compounds are in contact with chlorinated aqueous solutions, both in the human digestive system and the natural environment. Thus, the *N*-chlorination process shown in this paper may take place in both systems.

In the case of *N*-chlorination of compounds with amino or imide groups, for millimolar solutions, the half-life ranges between 0.7 and 20 s at $pH=4$, whereas the reactions are much faster at $pH=7$ decreasing the half-life about 1000 times with respect to the corresponding values at $pH=4$. However, in the case of the compounds with an amide group, the *N*-chlorination reactions are much slower varying the half-life, between 6 and 95 min at $pH=4$ and between 0.13 and 6 min at $pH=7$.

Additionally, it should be noted that the *N*-chloramines formed are highly reactive compounds, which may be involved in *N*-chlorination reactions exchanging chloro, Cl^+ , with other nitrogenous compounds present in the medium. So, these processes need to be considered when similar situations are studied both in the digestive system and the natural environment, where it is possible to find a large number of nitrogenous compounds.

REFERENCES

- [1] A. Akdag, S. Okur, M. L. McKee, S. D. Worley, *J. Chem. Theory Comput.* **2006**, *2*, 879–884.
- [2] K. Barnes, J. Liang, R. Wu, S. D. Worley, J. Lee, R. M. Broughton, T. S. Huang, *Biomaterials*. **2006**, *27*, 4825–4830.
- [3] A. Akdag, M. L. McKee, S. D. Worley, *J. Phys. Chem. A*. **2006**, *110*, 7621–7627.
- [4] R. Gitto, L. D. Luca, G. D. Sarro, Anticonvulsants. *Burger's Medicinal Chemistry and Drug Discovery*. **2010**, 121–160. (DOI:10.1002/0471266949.bmc099.pub2).
- [5] D. A. Coulter, J. R. Huguenard, D. A. Prince, *Br. J. Pharmacol.* **1990**, *100*, 800–806.
- [6] J. X. Shen, J. Brodbelt, *J. Mass Spectrometry*. **1996**, *31*, 1389–1398.
- [7] E. S. Stratford, R. W. Curley Jr., *J. Med. Chem.* **1983**, *26*, 1463–1469.
- [8] M. K. Hargreaves, J. G. Pritchard, H. R. Dave, *Chem. Rev.* **1970**, *70*, 439–469.
- [9] Y.-F. Zhang, J. W. Gibbs III, D. A. Coulter, *Epilepsy Res.* **1996**, *23*, 15–36.
- [10] A. Carmeman, N. Carmeman, in: *Molecular and Quantum Pharmacology. Proceedings of the 7th Jerusalem Symposium on Quantum Chemistry and Biochemistry*(Eds: D. Reidel), Springer Netherlands, Dordrecht-Holland, **1974** Vol. 7, Chapter 16, 213–228.
- [11] L. J. Yves, *Bioorg. Med. Chem.* **2007**, *15*, 2479–2513.
- [12] W. B. Im, S. H. Choi, J.-Y. Park, S. H. Choi, J. Finn, S.-H. Yoon, *Euro. J. Med. Chem.* **2011**, *46*, 1027–1039.

- [13] T. N. Bansode, J. V. Shelke, V. G. Dongre, *Eur. J. Med. Chem.* **2009**, *44*, 5094–5098.
- [14] M. L. Curtin, R. B. Garland, H. R. Heyman, R. R. Frey, M. R. Michaelides, J. Li, L. J. Pease, K. B. Glaser, P. A. Marcotte, S. K. Davidsen, *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2919–2923.
- [15] D. A. Brown, J. Garthwaite, *J. Physiol.* **1979**, *297*, 597–620.
- [16] J. Zweens, H. Frankera, *J. Clin. Chem. Clin. Biochem.* **1984**, *22*, 641–645.
- [17] B. R. Danielsson, C. Danielsson, M. F. Nilsson, *Reprod. Toxicol.* **2007**, *24*, 42–56.
- [18] Z. Rajic, B. Zorc, S. Raic-Malic, K. Ester, M. Kralj, K. Pavelic, J. Balzarini, E. De Clercq, M. Mintas, *Macromolecules.* **2006**, *11*, 837–848.
- [19] J. Lin, C. Winkelmann, S. D. Worley, J. Kim, C.-I. Wei, U. Cho, R. M. Broughton, J. I. Santiago, J. F. Williams, *J. Appl. Polym. Sci.* **2002**, *85*, 177–182.
- [20] V. Shankarananth, D. Ranganayakulu, C. Sridhar, K. K. Rajasekhar, *J. Pharm. Res.* **2012**, *5*(3), 1633–1635.
- [21] V. Singh, R. Saxena, S. Batra, *J. Org. Chem.* **2005**, *70*, 353–356.
- [22] F. Bellina, R. Rossi, *Tetrahedron.* **2006**, *62*, 7213–7256.
- [23] S. S. Purohit, D. Kumar, *All Res. J. Chem.* **2014**, *5*, 1–11.
- [24] Y. H. Li, L. Zhang, P. Tseng, Y. Zang, Y. Jin, J. Shen, *Tetrahedron Lett.* **2009**, *50*, 790–792.
- [25] N. P. Shetgiri, B. K. Nayak, *Indian J. Chem. B.* **2005**, *44 B*, 1933–1936.
- [26] O. Merino, B. M. Santoyo, L. E. Montiel, H. A. Jiménez-Vázquez, L. G. Zepeda, J. Tamariz, *Tetrahedron Lett.* **2010**, *51*, 3738–3742.
- [27] S. F. Hojati, M. Gholizadeh, M. Haghdoost, F. Shafiezhadeh, *Bull. Korean Chem. Soc.* **2010**, *31*(11), 3238–3240.
- [28] V. Kumar, M. P. Kaushik, A. Mazumdar, *Eur. J. Org. Chem.* **1910–1916**, 2008.
- [29] H. B. Kocer, S. D. Worley, R. M. Broughton, O. Acevedo, T. S. Huang, *Ind. Eng. Chem. Res.* **2010**, *49*, 11188–11194.
- [30] D. C. Whitehead, R. J. Staples, B. Borhan, *Tetrahedron Lett.* **2009**, *50*, 656–658.
- [31] I. V. Koval', *Russ. J. Org. Chem.* **2002**, *38*(3), 301–337.
- [32] A. Akdag, S. D. Worley, O. Acevedo, M. L. McKee, *J. Chem. Theory Comput.* **2007**, *3*, 2282–2289.
- [33] J. M. Antelo, F. Arce, J. Cruegeiras, M. Parajó, *J. Phys. Org. Chem.* **1997**, *10*, 631–636.
- [34] D. Matte, B. Solastiouk, A. Merlin, X. Deglise, *Can. J. Chem.* **1992**, *70*, 89–99.
- [35] A. Hussain, T. Higuchi, A. Hurwitz, I. H. Pitman, *J. Pharm. Sci.* **1972**, *61*(3), 371–374.
- [36] J. Carrell Morris, *J. Phys. Chem.* **1996**, *70*(12), 3798–3805.
- [37] G. Yagil, *J. Phys. Chem.* **1967**, *71*(4), 1034–1044.
- [38] K. Kumar, R. A. Day, D. W. Margerum, *Inorg. Chem.* **1986**, *25*, 4344–4350.
- [39] C. M. Gerritsen, D. W. Margerum, *Inorg. Chem.* **1990**, *29*(15), 2757–2762.
- [40] S. Searles, M. Tamres, F. Block, L. A. Quaterman, *J. Am. Chem. Soc.* **1956**, *78*, 4917–4920.
- [41] D. D. Perrin, B. Dempsey, E. P. Serjeant, *pKa Prediction for Organic Acids and Bases*. Chapman & Hall, London, **1981**.
- [42] D. R. Lide, *CRC Handbook of Chemistry and Physics, Internet Version 2005*, <http://www.hbcpnetbase.com> (CRC Press, Boca Raton, FL, **2005**).
- [43] C. Pastoriza, J. M. Antelo, F. A. Amoedo, M. Parajó, *J. Phys. Org. Chem.* **2015**, *28*, 602–611.
- [44] H. F. Walton, A. A. Schilt, *J. Am. Chem. Soc.* **1952**, *74*(20), 4995–4996.
- [45] F. A. Konuklar, V. Aviyente, M. F. R. Lopez, *J. Phys. Chem. A.* **2002**, *106*, 11205–11214.
- [46] R. W. Huffman, *J. Org. Chem.* **1982**, *47*, 3687–3691.
- [47] O. Takahashi, K. Kobayashi, A. Oda, *Chem. Biodiversity.* **2010**, *7*, 1349–1356.
- [48] M. Niyaz Khan, A. Khan, *J. Org. Chem.* **1975**, *40*(12), 1793–1794.
- [49] F. A. S. Knonuklar, V. Aviyente, *Org. Biomol. Chem.* **2003**, *1*, 2290–2297.
- [50] N. Banjac, N. Trisovic, N. Valentinc, G. Uscumlic, S. Petrovic, *Hem. Ind.* **2011**, *65*(4), 439–453.
- [51] S. Addanki, F. D. Cahill, J. F. Sotos, *J. Biol. Chem.* **1968**, *243*(9), 2337–2348.
- [52] S. L. Shapiro, I. M. Rose, F. C. Testa, E. Roskin, L. Freedman, *J. Am. Chem. Soc.* **1959**, *81*(24), 6498–6504.
- [53] S. Y. Szeto, N. E. Burlinson, J. E. Rahe, P. C. Oloffs, *J. Agri. Food Chem.* **1989**, *37*, 523–529.
- [54] R. F. Rekler, W. T. Nauta, *Recueil des Travaux Chimiques des Pays-Bas et de la Belgique.* **1951**, *70*, 241–253.
- [55] R. A. Corral, O. O. Orazi, *J. Org. Chem.* **1963**, *28*, 1100–1104.
- [56] I. Naquib, T.-C. Tsao, P. K. Sarathy, S. D. Worley, *Ind. Eng. Chem. Res.* **1991**, *30*, 1669–1671.
- [57] B. W. McCann, H. Song, H. B. Kocer, I. Cerkez, O. Acevedo, S. D. Worley, *J. Phys. Chem. A.* **2012**, *116*, 7245–7252.
- [58] I. Markish, O. Arrad, *Ind. Eng. Chem. Res.* **1995**, *34*, 2125–2127.
- [59] M. Zief, J. T. Edsall, *J. Am. Chem. Soc.* **1937**, *59*, 119, 2245–2248.
- [60] R. van Zelm, G. Stam, M. A. J. Huijbregts, D. Van de Meebt, *Chemosphere.* **2013**, *90*(2), 312–317.
- [61] H. Fujioka, T. Tan, *J. Pharm. Dyn.* **1981**, *4*, 759–770.
- [62] E. Ware, *Chem. Rev.* **1950**, *46*(3), 403–470.
- [63] C. Avendaño, J. C. Menéndez, In Kirk-Othmer encyclopedia chemical technology, 4th edn, **2000**, pp. 1–21 (DOI:10.1002/0471238961.0825040101220514.a01)
- [64] M. Bergon, J.-P. Calmon, *J. Chem. Soc. Perkin Trans. 2.* **1978**, *5*, 493–497.
- [65] J. Taillades, I. Beuzelin, L. Garrel, V. Tabacik, C. Bied, A. Commeyras, *Orig. Life Evol. Biosph.* **1998**, *28*, 61–77.
- [66] J. Kaneti, A. J. Kirby, A. H. Koedjikov, I. G. Pojarlieff, *Org. Biomol. Chem.* **2004**, *2*, 1098–1103.
- [67] R. C. Petterson, U. Grzeskowiak, *J. Org. Chem.* **1959**, *24*(10), 1414–1419.
- [68] G. R. Stark, D. G. Smith, *J. Biol. Chem.* **1963**, *238*, 214–226.
- [69] X. L. Armesto, M. Canle, J. A. Santaballa, *Tetrahedron.* **1993**, *49*(1), 275–284.
- [70] M. Szostak, J. Aubé, *Chem. Rev.* **2013**, *113*, 5701–5765.
- [71] M. Deborde, U. von Gunten, *Water Res.* **2008**, *42*, 13–51.
- [72] J. M. Antelo, F. Arce, M. Parajó, A. I. Pousa, J. C. Pérez-Moure, *Int. J. Chem. Kinet.* **1995**, *27*, 1021–1031.
- [73] R. Li, P. Hu, X. Rena, S. D. Worley, T. S. Huang, *Carbohydr. Polym.* **2013**, *92*, 534–539.
- [74] D. Gupta, S. Bhaumik, *Indian J. & Fibre Textile Res.* **2007**, *32*, 254–263.
- [75] L. Qian, G. Sun, *Ind. Eng. Chem. Res.* **2005**, *44*, 852–856.
- [76] V. Shankarananth, D. Ranganayakulu, C. Sridhar, K. K. Rajasekhar, *J. Pharm. Res.* **2012**, *5*(3), 1633–1635.
- [77] N. Pandit, R. K. Singla, B. Shrivastava, *Int. J. Med. Chem.* **2012** ID 159285. DOI:10.1155/2012/159285.
- [78] N. Banjac, N. Trišović, N. Valentinc, G. Ušćumlić, S. Petrović, *Hem. Ind.* **2011**, *65*(4), 439–453 DOI: DOI:10.2298/HEMIND110224030B.

SUPPORTING INFORMATION

Additional supporting information can be found in the online version of this article at the publisher's website.