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Research paper



Kinetics studies of phytomedicine mathesia - γ-butyrolactone interaction

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Abstract

Kinetic studies of the interaction between γ-Butyrolactone and one of the phytomedecines such as Mathesia used for Buruli ulcer treatment were investigated by conductimetry. γ-Butyrolactone which is the simplest form of lactone was used as probe in order to fully understand how a cyclic ester, such as lactone, could behave in a basic environment. It was observed that for the Mathesia solution at pH 11 the minimal apparent rate constant was around 3.54636 compare to sodium hydroxyde solution at pH 12 where the minimal apparent rate constant was around 3.12295. The apparent rate constants of successive diluted solutions of Phytomedicine Mathesia show up the dilution factor 1: 4. A plot of apparent rate constant versus dilution factor gave a curve with a correlation coefficient of 0.99831.

Keywords: *Mycobacterium Ulcerans; Mycolactone; Γ-Butyrolactone; Buruli Ulcer; Mathesia.*

1. Introduction

Infection with Mycobacterium ulcerans called "Buruli ulcer," better known as "MBASU" is an infection of Mycobacteria whose reservoir is in the environnement[1]. This infection is rampant in swampy areas in tropical and subtropical regions of Africa, Latin America, Asia, Oceania, and Pacific Occidental [2-7]. Recent studies [5-9], made in Health centers both in Kimpese and Songololo in Democratic Republic of the Congo have shown that ulcerated and mixed forms are the most frequent (80%) because of late consultations due to the attribution of the origin of the disease to "bad luck." The lack of good understanding of this disease by the population is the leading cause of late consultations. The synergic use of antibiotics or association of antibiotics for the treatment of Buruli ulcer have shown some limitations and resistence. The Combination of anti-tuberculosis drugs such as Rifampicin and Streptomycin allowing healing in one or two cases without the need for surgery [8]. Antibiotic treatment alone is not always enough for the complete cure of patients and the repair is the responsibility of surgery (pansement, graft, necrotizing tissue debris, etc.). The association of Chloramine - Metronidazole - Nitrofurantoin is used as an antiseptic for budding and sterilization of the wound [9]. Impervious Mycolactone to antibiotics, causes tissue ulceration when injected only with the mouse [10], [11]. In our laboratory, "Mathesia" was used as a phytomedecine and tested on thirty patients reported after direct examination in the hospital. It was reported that a regeneration of tissue, epithelialization of the wound, causing arresting the development of the disease and a complete cure could be reached. The results appear to be interesting and deserve a thorough review. This suggests that active substances in MATHESIA kill microorganisms where is the causative agent of Buruli ulcer [12]. Taking in account that γ-Butyrolactone is the simple model of the lactone and destroys body tissues in the same way as Mycolactone produced by M. ulcerans, we believe that the basic hydrolysis of the γ-Butyrolactone will have the same action like Mathesia on Mycolactone in treating Buruli ulcer [13], [14] Also, Mathesia likely proceeds by the same mechanism of hydrolysis of lactones like the one initiated by sodium hydroxyde. Saponification of the ethyl acetate by Mostafa et al (2018) [15] where studying the hydrolysis of Ethyl acetate using sodium hydroxide solutions showed a rate constant around 0, 0712L/mol.min) which is close to the observed rate constant was found for the kinetic hydrolysis of the lactone. In this study, we show the kinetics of basic hydrolysis using the conductivity of Phytomedicine Mathesia with γ-Butyrolactone and sodium hydroxide with γ-Butyrolactone to check the mode of action of Mathesia in the destruction of Mycolactone.

2. Experimental

2.1. Materials and equipments

NaOH (Merck) for analysis, γ-Butyrolactone (Merck), Mathesia was obtained from Kinshasa drugstore in Democratic Republic of Congo (A.M.M/A.M/A.V.No MS 1253/10/01/0034/2010). Conductivity of solutions were measured using radiometer Copenhagen 219537.

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2.2. Methods

Conductimetry evaluates the concentration of the constituents in ionized medium such as mineral ions and organiques [15].
Conductivity will track the interaction between sodium hydroxide and γ-Butyrolactone and between Mathesia and γ-Butyrolactone, and to determine the rate constants of both hydrolysis reactions.
Let assume the following model of hydrolysis reaction:

$A + B \xrightarrow{k} C$

The relationship gives the rate of this reaction:

$$V = -\frac{dC_A}{dt} = -\frac{dC_B}{dt} = -k.C_A.C_B$$

The variation of the conductivity of the medium as a function of time can be deduced. The order of the reaction and the rate of the reaction is a computer-based statistics program.

3. Experimental procedure

In a 60 mL cylinder, 20 mL of NaOH (0.02 M) or Mathesia solution and 20 mL of γ-Butyrolactone were added in the same concentration. The resulting solutions were stirred vigorously, and conductivity was measured after each five minutes. The reaction was completed when the conductivity values were constant.

4. Results and discussion

4.1. Conductimetry

Conductimetry followed the kinetics of hydrolysis of γ- Butyrolactone by NaOH and by the MATHESIA. Data and curves for the variation of the conductivity of the γ- Butyrolactone solution are shown in Figures 1-4

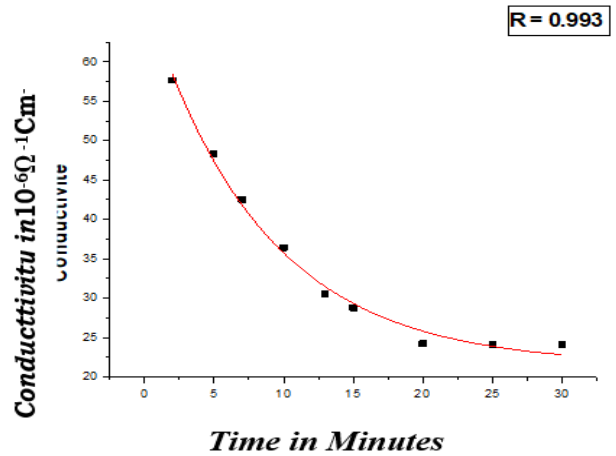


Fig. 1: Evaluation of the Conductivity of the 0.02 M Solution of Γ-Butyrolactone in the Presence of 0.02 M NaOH at Different Time.

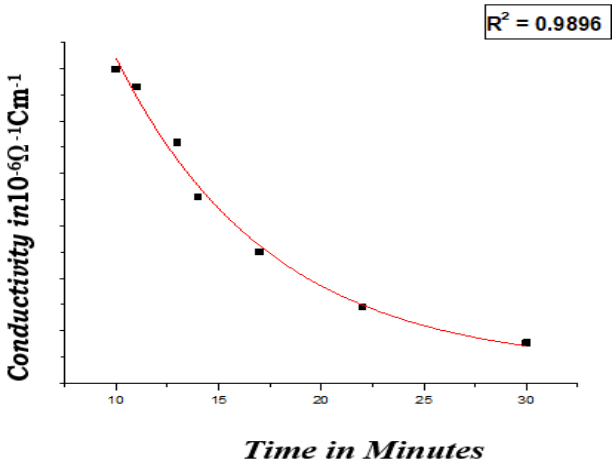


Fig. 2: Evolution of the Conductivity of the 0.02 M Solution of Γ-Butyrolactone in the Presence of Undiluted Mathesia at Different Time.

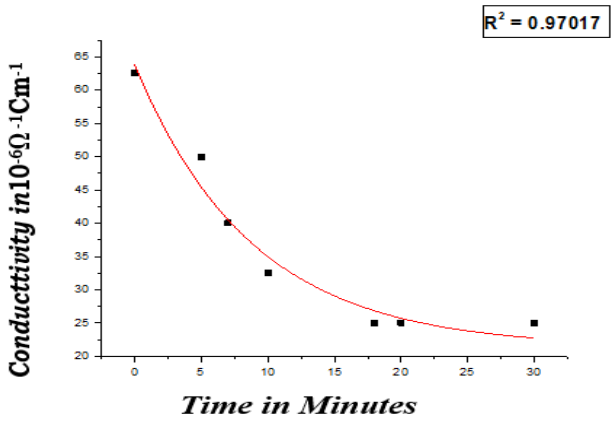


Fig. 3: Evolution of the Conductivity of 0.02 M Solution of γ-Butyrolactone in the Presence of MATHESIA Diluted 1:1.

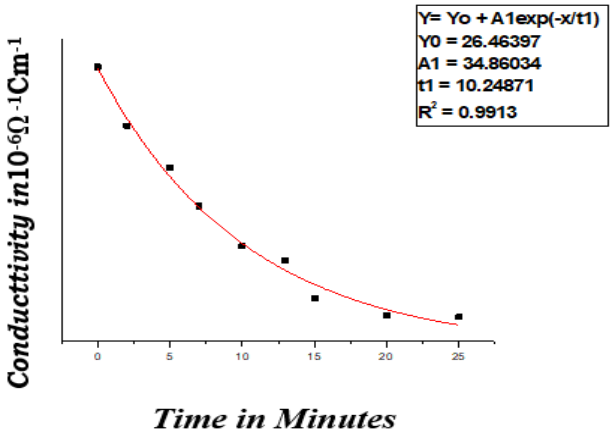


Fig. 4: Evolution of the Conductivity of 0.02M Solution of γ -Butyrolactone in the Presence of MATHESIA Diluted 1:2.

From Figure 1 to 4 it can be seen that the change in conductivity of γ-Butyrolactone solutions in the presence of either NaOH or MATHESIA (concentrated or diluted) at different time, decreases exponentially. The various linearization attempts concentration versus time or conductivity versus time resulted in a linear equation of the following form:

$$\frac{1}{C} = \frac{1}{Co} + kt \text{ or } \frac{1}{\chi_B} = \frac{1}{\chi_B^0} + k_{app}.t$$

These equations are consistent with a two-order response, and rate constants such as the apparent rate constant of hydrolysis of γ-Butyrolactone can be deduced as slope as shown in Figure 5 and 6.

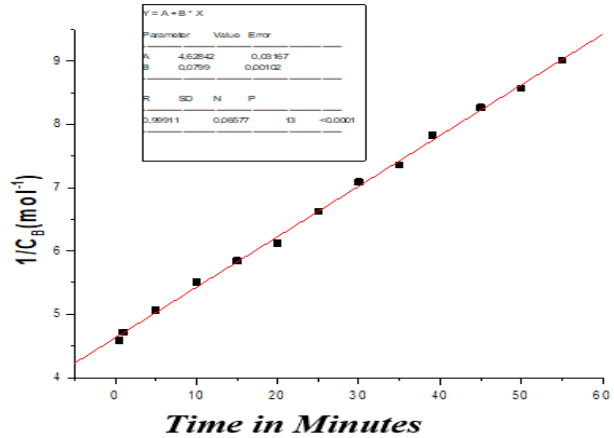


Fig. 5: Evolution of $1/C_B$=F (T) Of γ -Butyrolactone Solution in the Presence of A Different Concentration of NaOH.

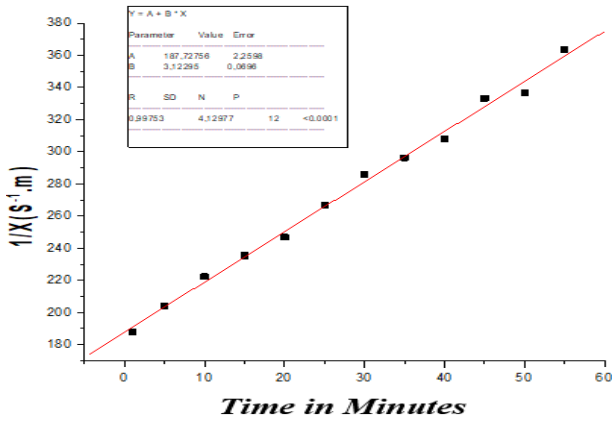


Fig. 6: Evolution of 1/χ=F (T) of the **γ** -Butyrolactone Solution in the Presence of Different Concentrations of NaOH

It was noticed that the rate constant k divided by the sum of different ion mobility of sodium hydroxyde (0.0248) gives a value of kapp following the relationship:

$$K_{app} = (\frac{k}{\lambda_{Na^+} + \lambda_{OH^-}})^{\cdot}$$

This follows that:

$\frac{1}{\chi_B} = \frac{1}{\chi_B^0} + (\frac{k}{\lambda_{Na^+} + \lambda_{OH^-}}).t$ in comparison with the expression $\frac{1}{C_B} = \frac{1}{C_B^0} + k.t$ and with $\lambda_{Na^+} + \lambda_{OH^-} = 0{,}0248 S.m^2.mol^{-1}$ and the mobility of sodium and hydroxide ions are: $\lambda_{Na^+} = 50.10^{-4} S.m^2 mol^{-1} and \lambda_{OH^-} = 198.10^{-4} S.m^2.mol^{-1}$

Unlike ion mobility of the NaOH solution whichenters the composition of Mathesia are not known,and assuming that theMathesia reacts withγ-Butyrolactone by the same mechanism as NaOH, the comparison between the NaOH rate constants and different dilutions of Mathesia will be based on the apparent rate constant, Kapp. The summary of experimental data obtained from the relations: 1/X=F (t) from which different parameters are found is given in Table 1. The rate constants k and k_{app} were found to be around 0, 0799 and 3.12295 respectively. Comparing the value of the slope obtained from the interaction of γ -Butyrolactone - NaOH above with that obtained with the saponification of ethyl acetate by Mostafa Ghobashy *et al* where studying the hydrolysis of ethyl acetate using caustic soda (k = 0,0712 $L.mol^{-1}.min^{-1}$), with some differences due to the use of acetate in place of lactone, the order of magnitude of the constant remains acceptable[15].

Table 1: Summary of Experimental Data Obtained from the Relations: 1/X=F (T)

N°	Product	1/X	$1/X_0$	R	a	K_{app}	pH
1	NaOH	364	187.728	0.99753	0.0200	3.12295	12.0
2	Mathesia 0	250	166.446	0.99950	0.1000	3.54636	11.0
3	Mathesia1:1	400	167.655	0.99949	0.0500	6.81876	10.5
4	Mathesia1:2	326	169.450	0.99983	0.0300	8.69996	10.0
5	Mathesia1:3	1000	168.312	0.99992	0.0250	9.78772	9.5
6	Mathesia1:4	400	167.315	0.99987	0.0200	10.05306	9.0
7	Mathesia1:5	200	164.239	0.99968	0.0170	9.87665	8.7
8	Mathesia1:6	208	162.864	0.99979	0.0140	8.69269	8.5
9	Mathesia1:7	222	168.229	0.99971	0.0125	7.13093	8.3

It emerges that the mathematical processing of experimental dataleads tolinear correlations having almost the same correlation coefficients (R=0.99). The calculated rate constants are apparent because of the impossibility of determining the ionic mobility of Mathesia λ_i in solution. The Mathesia apparent rate constants are greater than those of NaOH and increase with the dilution.

Indeed, γ -Butyrolactone causes tissue ulceration and more particularly of the skin. This effect, however, is stopped by the application of a base such as NaOH and happens to be much faster dimmed by applying diluted 1:4 solution of Mathesia. Above the 1:4 dilution, the apparent rate constant of Mathesia become smaller. The plot of the apparent rate constants as a function of dilution factor is obtained as Gaussian curve with a correlation coefficient around 0.99831.

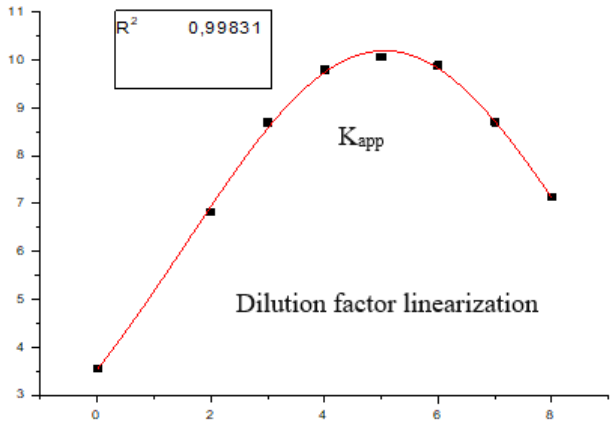


Fig. 7: Evolution of Dilution Factors Compared to Apparent Rate Constants.

This curve shows a maximum between dilution factors 4 and 6 corresponding to a greater rate of hydrolysis of γ-Butyrolactone by Mathesia. This maximum is the same approximation of the dilution of Mathesia dose in the treatment of the effect of Mycolactone. The Mathesia pH between 9 and 10 is a base hydrolysis mechanism factor of the γ -Butyrolactone similar to NaOH. The opening of the chain of γ-Butyrolactone and the Mycolactone is made by a hydrolysis reaction emitted by the essential component of Mathesia. Dilution causes a decrease in pH. It is 11 at the beginning and 9.0 to 1:4 dilutions.

Compared to streptomycin, the Mikacine, and other antibiotics, Mathesia proves to be an excellent drug in the treatment of Buruli ulcer, since other antibiotics have limited effects in the destruction of microorganisms that cause disease without preventing the devastation of tissues, which makes the disease difficult to treat. [11] Treatment of UB based on two oral antibiotics, rifampicin and clarithromycin, whose goal is to kill the bacteria, M. ulcerans [16]. In the WHO publication in 2009 for the treatment of Buruli ulcer, streptomycin is against-indicated during pregnancy.[17]

5. Conclusion

It this study, we started with γ- Butyrolactone as a product probe with the known molecular weight, density, and concentration. Assuming that γ- Butyrolactone reacts in the same mechanism as the more devastating the tissue Mycolactone secreted by Mycobacterium ulcerans, it was noticed that: Diluting Mathesia increases the rate of hydrolysis of γ -Butyrolactone with a maximum observed at the 1:4 dilutions and a decrease in pH 11 at the start and 9.0 for the dilution 1:4.

The comparison of the different apparent rate constants of Mathesia concentrated or diluted to the caustic solutions show that the rate constant of the NaOH is still lower than Mathesia confirming its high activity on the γ -Butyrolactone.

The mechanism of action of Buruli ulcer (BU), goes through basic hydrolysis of Mycolactone with stopping his destructive action of tissue. The primary component of the Mathesia solution stops the devastating effects of tissue Mycolactone, while its organic substances act as antibacterial agents. In any event, one would conclude that Mycolactones lose their devastating power of tissues through ring opening mechanism.

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