

Kinetics and mechanism of oxidation of gabapentin by N-bromosuccinimide in aqueous alkaline medium. Comparing to the kinetics of oxidation by N-bromosuccinimide in aqueous acid medium

ABSTRACT

The kinetics of oxidation of gabapentin (GBP) by N-bromosuccinimide (NBS) in an alkaline medium has been investigated over (7.40-8.70) pH range, (25-40°C) for a range of [NBS] and [GBP]. The oxidation reaction showed unique kinetics that greatly differed on going from acid medium to base medium. In an acid medium (pH=2.52), the reaction rate showed first order kinetics with respect to [NBS], fractional order dependence on both [GBP] and $[H^+]$ and increased with temperature over (303–321°K) range. In an alkaline medium, the oxidation reaction shows first order dependence on [GBP], fractional order on $[H^+]$ over (1.99-39.80) $\times 10^{-9}$ range and zero order dependence on [NBS]. It is noteworthy that the reaction rate decreased with increasing temperature over the range studied. On addition of acrylonitrile to the reaction mixture, polymerization was observed after a day.

Keywords: Kinetics of oxidation, oxidation of gabapentin, oxidation with N-bromosuccinimide, reaction mechanism

1. INTRODUCTION

N-bromosuccinimide (NBS) is an acid imide which considered as a source of positive halogen (Br^+) and this reagent has been exploited as an oxidant for a variety of substrates [1-5] in both acidic and basic solutions. The use of NBS as an oxidant is extensive in the determination of a number of organic compounds [6-9]. In this case the oxidation proceeded via the bromium ion (Br^+) [10-12] in polar media, or through a free radical path involving homolytic dissociation of NBS [13, 14]. However, little information existed in the literature on NBS reactions with respect to the oxidation kinetics of pharmaceuticals [15,16] which may throw some light on the mechanism of metabolic conversions in biological systems [17]. Gabapentin (GBP), 1-amino-methyl cyclohexanecarboxylic acid is a neuroleptic drug and is important due to its biological significance and selectivity towards the oxidant. Gabapentin

has been used as anti-convulsant agent that is useful in the treatment of epileptic seizures [18]. It has also been shown to be a potential drug for treatment of neurogenic pain [19-21]. GBP was designed as γ -aminobutyric acid analogue [22], but has subsequently been shown not to interact with any of the enzymes on the GBP metabolic pathway [23]. Furthermore, GBP has been used for the treatment of some mood disorders, anxiety and tardive dyskinesia. Kinetic study of oxidation of gabapentin by chloramine-T in HClO_4 medium has been reported [24]. The reaction rate was first order dependent on $[\text{CAT}]_0$, fractional order on $[\text{GP}]_0$ and inverse fractional order on $[\text{H}^+]$. Moreover, the kinetics of oxidation of gabapentin by bromamine-T in NaOH medium was also studied [25]. The reaction rate exhibited first order kinetics with respect to $[\text{BAB}]$ and fractional order in both $[\text{GBP}]$ and $[\text{NaOH}]$. The kinetics of oxidation of gabapentin anion by alkaline diperiodatonickelate (IV) was studied spectrophotometrically [26]. The reaction was first order with respect to $[\text{DPN}]$, an apparent less than unit order, each in $[\text{GBP}]$ and $[\text{alkali}]$. The rate constants were found to increase with increasing temperature over (298–313°K). A mechanism involving the formation of a complex between the oxidant and substrate has been proposed. Additionally, the Kinetics of oxidation cleavage of gabapentin with N-bromosuccinimide in acid medium was investigated [27]. The experimental rate law was $-\text{d}[\text{NBS}]/\text{dt} = k[\text{NBS}][\text{GBP}]^x [\text{H}^+]^y$, where x and y are less than unity and the oxidation reaction was increased with temperatures over the (303–321°K) range.

In the present work, there was an intension to study the kinetics of oxidation of gabapentin by NBS in alkaline medium and comparing to the kinetics of its oxidation by N-bromosuccinimide in acid medium[27].

2. MATERIAL AND METHODS

Gabapentin (GBP) solid was obtained as a gift sample from Pfizer Company, Egypt. Stock solution of gabapentin was prepared by dissolving an appropriate amount of the solid in doubly distilled water. The required concentrations of GBP were prepared from the stock solution by suitable dilution. An aqueous solution of gabapentin was stable at least 20 days at room temperature. N-bromosuccinimide (NBS) was prepared afresh each day from GR Merk sample of the reagent. All other reagents used were of analytical grade. Buffer solutions were prepared from NaH_2PO_4 and borax of known molarity. NaCl solution was used to adjust the ionic strength in the different buffered solutions. Doubly distilled water was used in all preparations and experiments.

2.1. KINETIC PROCEDURE

Appropriate amounts of gabapentin, NaCl and water in the required buffer to keep the total volume constant at 30ml were thermostated in water bath at the required temperature for ca.20min. A measured amount of NBS solution also thermostated separately at the same

69 temperature was rapidly added to the mixture and thoroughly mixed. The progress of the
70 reaction was monitored spectrophotometrically by measuring the decrease in the
71 absorbance of gabapentin at $\lambda = 290$ nm versus time (Figure1) using a Shimadzu 1700UV-
72 vis spectrophotometer.

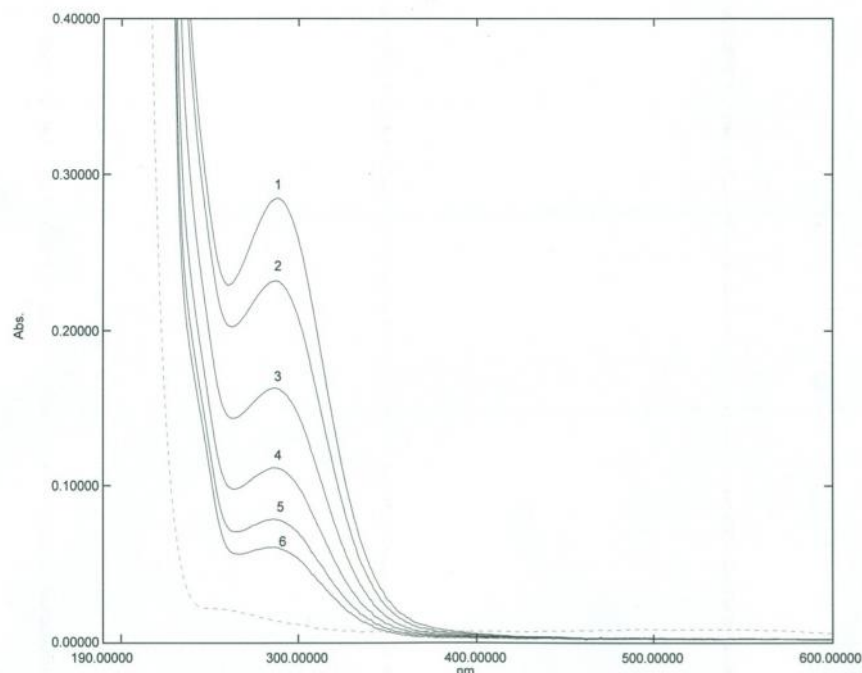


Fig. 1. Absorption spectra of the reaction mixture at different times. Peaks (1-6) were recorded at 1, 2, 5, 10, 15, and 20 min. from the time of initiation of reaction respectively. The dashed curve for aqueous solution of gabapentin alone. pH = 8.50, T= 25°C , [GBP] = 0.001 mol dm⁻³ , [NBS] = 0.01 mol dm⁻³

73
74 The pH of the reaction mixture was measured using a 3505 Jenway pH-meter. The
75 oxidation reaction was carried out under pseudo-first order conditions by using a large
76 excess (at least 10 fold) of [NBS] over [GBP].

77 2.2. STOICHIOMETRY

78 The stoichiometry of the reaction was ascertained by carrying out several sets of
79 experiments with varying amounts of NBS concentration largely in excess (at least twice)
80 over gabapentin concentration in the required buffer, and the mixtures were allowed to stand
81 until completion. 5ml aliquot of each of the reaction mixture was withdrawn and transferred
82 to a titrating flask containing 5ml of 4% KI. The liberated iodine was estimated by standard
83 Na₂S₂O₃ solution using starch as indicator. The results showed that, one mol of NBS
84 consumed one mol of gabapentin and the reaction is thus represented stoichiometrically as,
85 $\text{RCH}_2(\text{NH}_2)\text{CH}_2\text{COOH} + \text{NBS} \longrightarrow \text{products}$

2.3. PRODUCTS ANALYSIS

For identification of the oxidation products, the reaction mixture containing excess concentration of gabapentin was kept aside until completion. The main reaction products were extracted with ether and subjected to spot tests. The main reaction product was identified as 1-(hydroxymethyl) cyclohexane acetic acid by spot test for carboxylic and OH-groups [28].

3. RESULTS AND DISCUSSION

Kinetics of oxidation of GBP by NBS was studied over the (7.4-8.7) pH range and (25-40°C) over a range of GBP and NBS concentrations. The rate of the oxidation was measured at the start of the slow reaction. Plots of A_t versus time where A_t is the absorbance at time t , were curved. Plots of $\ln(A_\infty - A_t)$ and $1/(A_\infty - A_t)$ versus time, where A_∞ and A_t are the absorbance at infinity and time t , respectively, showed marked deviations from linearity. The initial rate method was thus employed to calculate the rate of oxidation reaction from the slopes of the initial tangents of absorbance versus time plots at $\lambda=290$ nm using the appropriate molar absorptivity of gabapentin at the pHs used. The main advantage of the initial rate method is, to avoid problems in tackling reversible equilibria, which should be unimportant during the early stages of the forward reaction when the products have not accumulated. The effect of [NBS] on the rate of oxidation was studied by varying [NBS] over the $(2.0-20.0) \times 10^{-3}$ mol dm⁻³ range and keeping other parameters at constant values. The constancy of the initial rates at different concentrations of NBS over the range studied (Table 1) and (Figure 2) were indicated that the reaction was zero order dependent on [NBS].

The rate equation depending on [NBS] is thus represented as,

$$(-d[\text{GBP}]/dt) = k_1 \quad (1)$$

For zero order reaction, variation of the absorbance with time at different [NBS] should be linear along the progress of the oxidation reaction, but (Figure 2) indicated that, the linear relation existed only through the initiation of the reaction which may supports a zero order dependence on [NBS] for a limited period of time. Increasing of [NBS] may increase the rate of the fast step and has no effect on the rate determining step (slowest step). When the concentration of N-bromosuccinimide decreased enough, the rate of the fast step also decrease to the point where both steps have similar rates. At that point, the rate of oxidation will be affected by the concentration of N-bromosuccinimide and the absorbance versus time plots may deviate from linearity.

121 **Table1. Dependence of the reaction rate on [GBP], [NBS], and temperature at pH =**
 122 **7.40**

T °C	$10^4[\text{GBP}]$ (mol dm ⁻³)	$10^2[\text{NBS}]$ (mol dm ⁻³)	$10^4 \times \text{initial rate}$ (mol ⁻¹ dm ³ s ⁻¹)	k_1 s ⁻¹
25	0.80	2.00	1.03	1.28
25	2.00	2.00	2.57	1.28
25	8.00	2.00	10.35	1.29
25	10.00	2.00	12.90	1.29
30	0.40	2.00	0.37	0.93
30	0.60	2.00	0.55	0.92
30	0.8	2.00	0.75	0.93
30	1.00	2.00	0.93	0.93
30	2.00	2.00	1.84	0.92
30	4.00	2.00	3.72	0.93
30	8.00	2.00	7.32	0.92
30	10.00	2.00	9.06	0.91
30	20.00	2.00	18.50	0.92
30	2.00	0.20	1.30	1.30
30	2.00	0.30	1.28	1.28
30	2.00	0.40	1.29	1.29
30	2.00	0.50	1.31	1.31
30	2.00	0.60	1.31	1.31
30	2.00	0.70	1.30	1.30
30	2.00	0.8	1.29	1.29
30	2.00	0.9	1.30	1.30
30	2.00	1.00	1.32	1.32
35	0.80	2.00	0.45	0.56
35	2.00	2.00	1.15	0.57
35	8.00	2.00	4.40	0.55
35	10.00	2.00	5.45	0.55
40	0.80	2.00	0.25	0.31
40	2.00	2.00	0.64	0.32
40	8.00	2.00	2.44	0.31
40	10.00	2.00	3.04	0.30

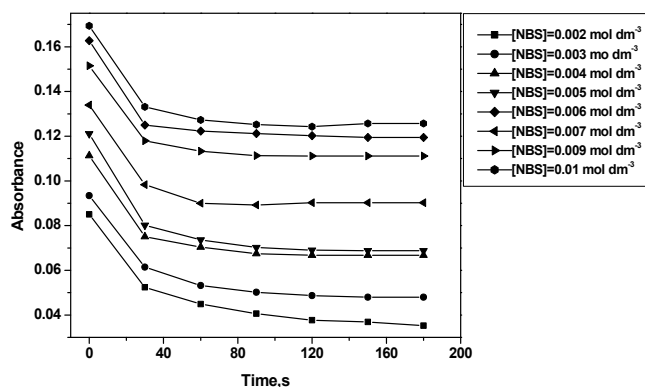


Fig. 2. Absorbance versus time at different [NBS].

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157 The effect of gabapentin concentrations on the oxidation rate were examined over the
 158 concentrations range $(0.40\text{--}20.0) \times 10^{-4} \text{ mol dm}^{-3}$. Values of the initial rates (Table 1)
 159 indicated that, the initial rates increased with increasing [GBP] over the range studied. Plot
 160 of log initial rate versus log initial [GBP] was linear with slope $=1.0 \pm 0.1$, indicating that the
 161 reaction was first order dependent on [GBP] and the rate equation is represented as,

162 $(-d[\text{GBP}]/dt) = k_1[\text{GBP}]$ (2)

163 The effect of pH on the rate of oxidation was investigated by varying the pH values over the
 164 (7.40–8.70) range and keeping other parameters constant. Kinetics data in (Table 2) and
 165 (Figure 3) indicated that the values of the oxidation rates increased as pH decreased over
 166 the range studied and supported the involvement of the protonated form of gabapentin in the
 167 rate determining step.

168 **Table 2. Effect of pH on the initial rates at [NBS] = 0.02 mol dm^{-3} , $T=30^\circ\text{C}$, $\lambda=290\text{nm}$**

169

pH		$10^4 \times \text{initial rates}$ ($\text{mol}^{-1} \text{dm}^3 \text{s}^{-1}$)			
	$10^4[\text{GBP}]$ (mol dm^{-3})	0.80	2.00	8.00	10.00
7.40		0.75	1.93	7.32	9.06
7.70		0.62	1.77	7.00	8.78
8.20		0.44	1.51	6.12	7.67
8.70		0.31	1.35	5.51	6.91

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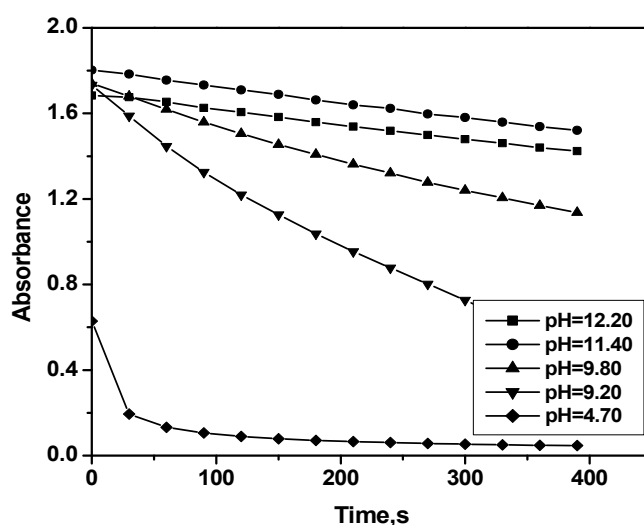


Fig. 3. Variation of absorbance versus time at different pH's. [GBP] = 0.01 mol dm⁻³, [NBS] = 0.1 mol dm⁻³, and T = 20 °C

173

174 This observation may be explained in terms of the protonation behavior of GBP in aqueous
 175 media via the lone pair of the nitrogen atom of amino group. Plot of log initial rate versus log
 176 [H⁺] was linear with slope less than unity indicating, fractional order dependence on [H⁺]. The
 177 rate is thus represented as,

178
$$(-d[\text{GBP}]/dt) = k_1[\text{H}^+]^x \quad (3)$$

179 Where x is less than unity. Plots of the initial rates versus [GBP] at different pHs over (7.40-
 180 8.70) range were linear with zero intercept (Figure 4) with correlation coefficients $r_1=0.99993$
 181 $r_2=0.99995$, $r_3=0.99988$ and $r_4=0.9997$ at pHs, 7.40, 7.70, 8.20, and 8.70 respectively.

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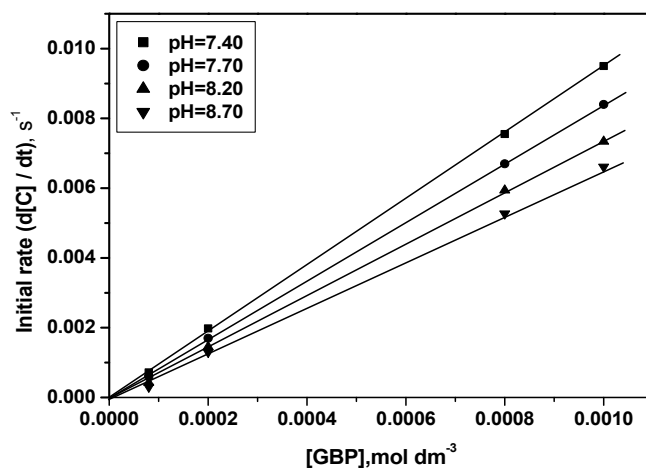


Fig. 4. Plots of initial rates versus [GBP] at different pHs

183

184 From Eqs. 1, 2 and 3, the rate law is represented as,

185 $(-d[\text{GBP}]/dt) = k_1 [\text{GBP}][\text{H}^+]^x$ (4)

186 The effect of temperatures on the rate of oxidation were also studied over the range (25-
 187 40°C) at constant pH, [GBP], [NBS] and ionic strength. The kinetics data (Table1) indicated
 188 that, the rate of oxidation decreased with increasing temperature over the range studied.
 189 This phenomenon may support a multistep reaction in which a highly exothermic process
 190 (slowest step) preceding the electron transfer step is encountered. Plots of the initial rates
 191 versus [GBP] at different temperatures were linear with zero intercept (Figure 5) with
 192 correlation coefficients, $r_{25} = 0.99985$, $r_{30} = 0.9999$, $r_{35} = 0.99993$, and $r_{40} = 0.99996$ at
 193 temperatures 25, 30, 35, and 40°C respectively.

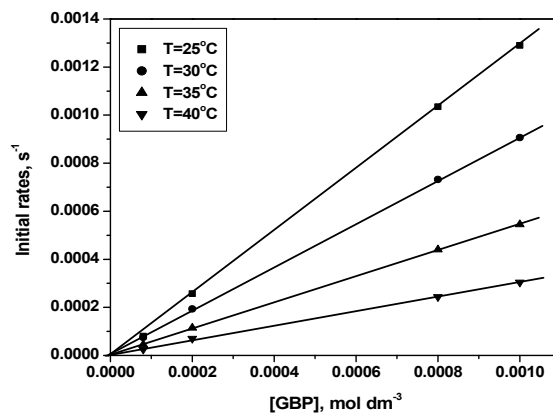


Fig. 5. Plots of initial rates versus [GBP] at different temperatures

194

195 Values of the rate constant k_1 were calculated from the slopes of the plots at different
196 temperatures (Table 3).

197 **Table 3. Values of k_1 at different temperatures**

198

T(°C)	$k_1(s^{-1})$
25	1.30
30	0.90
35	0.54
40	0.30

199

200 Thermodynamic activation parameters including the enthalpy $\Delta H^\ddagger$ and entropy $\Delta S^\ddagger$
201 associated with k_1 were calculated using a least squares fit to the transition state theory
202 equation as $-78.6 \text{ kJ mol}^{-1}$ and $-505.5 \text{ J K}^{-1} \text{ mol}^{-1}$ respectively. The rate determining step is
203 exothermic as indicated by the negative value of $\Delta H^\ddagger$. The composite negative value of $\Delta S^\ddagger$
204 may be largely the result of substantial mutual ordering of the solvated water molecules [29]
205 of the equilibrium reactions and intramolecular electron transfer step. The effect of ionic
206 strength on the oxidation reaction was studied by varying the ionic strength of the reaction
207 medium using an aqueous solution of NaCl of known concentration and maintaining other
208 parameters constant. The experimental results indicated that, there is no significant effect of
209 the ionic strength on the oxidation rates and supported that the reaction took place between
210 charged and non charged species. The effect of dielectric constant (D) of the medium on
211 the rate of oxidation was investigated by using different MeOH-H₂O solvent mixtures over 0-
212 40 wt% range at T = 30°C, at constant pH, ionic strength, [GBP] and [NBS]. The values of
213 the dielectric constants for various weight percentage composition of MeOH-H₂O were
214 abstracted as reported [30]. Values of the oxidation rate were decreased when MeOH
215 percentage increased (Table 4).

216 **Table 4. Kinetics data for the oxidation of [GBP] by NBS at different MeOH-**
217 **H₂O solvent mixtures; [GBP] = $1.0 \times 10^{-3} \text{ mol dm}^{-3}$, [NBS] = 0.02 mol dm^{-3} and**
218 **T= 30°C**

MeOH W%t	$10^4 \times \text{initial rates}$ (d[C]/dt)	log initial rate	D	1/D
0	9.06	-3.04	76.73	0.013
10	7.56	-3.12	72.37	0.014
20	6.45	-3.19	67.48	0.015
30	5.23	-3.28	62.71	0.016
40	4.05	-3.39	58.06	0.017

219

220 Plot of log initial rate versus 1/D was linear with negative slope (Figure 6).

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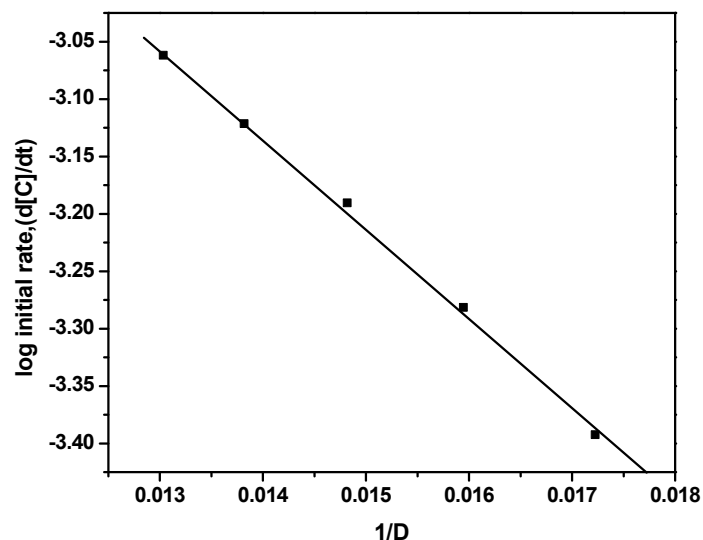
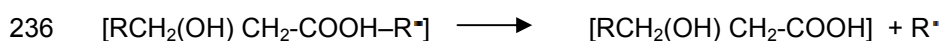
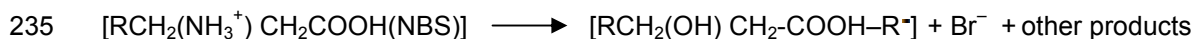
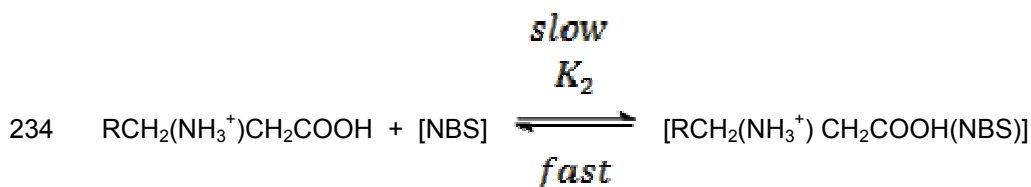
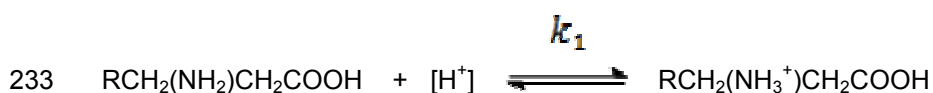


Fig. 6. Plot of log initial rate versus 1/D

222

223 The intervention of free radicals in the reaction was examined by addition of acrylonitrile to
 224 the reaction mixture under the reaction conditions and kept aside for 24h. On diluting the
 225 reaction mixture with MeOH, a copious precipitate was observed suggesting, the free
 226 radicals intervention. An experiment was performed to check the polymerization of the
 227 reaction mixture in absence of acrylonitrile but, no polymerization was observed indicating
 228 that the polymerization is attributed to the acrylonitrile by the effect of succinimyl radicals.

229 Since, NBS is capable to coordinates the substrate through the carbonyl group [31]. The
 230 observed kinetics of oxidation of gabapentin by N-bromosuccinimide in an alkaline medium
 231 may therefore described by the following reaction scheme that includes a first reversible
 232 slow step which is the rate determining step, followed by another three fast steps.



Where $R^\cdot$ is the succinimidyl radical. The succinimidyl radical may prefer to abstract a hydrogen atom from the aqueous medium to form succinimide rather than dimerize to give bisuccinimide [32, 33].

240

241 4. CONCLUSION

242 The kinetics of oxidation of gabapentin (GBP) by N-bromosuccinimide (NBS) in an alkaline
243 medium has been studied spectrophotometrically. In acid solutions, the oxidation reaction of
244 gabapentin by N-bromosuccinimide exhibited classical kinetics, where the reaction rate was
245 first order dependent on [NBS], fractional order on both [GBP] and $[H^+]$ and increased with
246 increasing temperatures over (303-321°K) range. In an alkaline medium (the presented
247 work), the reaction exhibited a unique kinetics, where the reaction rate was first order
248 dependent on [GBP], fractional order on $[H^+]$ and zero order dependent on [NBS]. It is
249 noteworthy that the reaction rate decreased with increasing temperatures over (25-40°C)
250 range. This may be explained in the light of a multistep reaction mechanism in which, the
251 slowest step is highly exothermic. A free radical mechanistic pathway supported by
252 polymerization of acrylonitrile was suggested.

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