

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

Alaa Eldin Mokhtar Abdel-Hady

Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Sinai University, Arish City, Cairo Egypt, P.O. Box 45518

ABSTRACT

The kinetics of oxidation of gabapentin (GBP) by N-bromosuccinimide (NBS) in an alkaline medium has been investigated. The oxidation reaction showed unique kinetics that greatly differed on going from acid to base medium. In an acid medium (pH=2.52), the reaction rate showed first order dependence on [NBS], fractional order dependence on both [GBP] and $[H^+]$ and increased with temperature over (303–321°K) range. In an alkaline medium, the rate showed 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 temperature over the range studied. An inner-sphere mechanism for the oxidation pathway supported by free radicals intervention was proposed.

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

E-mail: alaaeldin60@yahoo.com

Tel no: +20.68.3336852

Fax no: +20.68.3336847

1. INTRODUCTION

N-bromosuccinimide (NBS) is acid imides which considered as a source of positive halogen (Br^+) and this reagent has been exploited as an oxidant for a variety of substrates [1-3] in both acid and alkaline solutions. The use of NBS as an oxidant is extensive in the determination of a number of organic compounds [4-6]. In this case the oxidation proceeded via the bromium ion (Br^+) [7-9] in polar media, or through a free radicals path involving homolytic dissociation of NBS [10, 11]. However, little information existed in the literatures on NBS reactions with respect to the oxidation kinetics of pharmaceuticals [12,13] which may throw some light on the mechanism of metabolic conversions in biological systems [14]. Gabapentin (GBP), 2-[1-(aminomethyl)cyclohexyl]acetic 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 [15-17]. It has also been shown to be a potential drug for treatment of neurogenic pain [18,19]. GBP was designed as γ -aminobutyric acid, but has subsequently been shown not to interact with any of the enzymes on the GBP metabolic pathway [20]. 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 [21]. The reaction rate was first order dependence on chloramine-T $[\text{CAT}]_0$, fractional order on gabapentin $[\text{GP}]_0$ and inverse fractional order on $[\text{H}^+]$. Moreover, the kinetics of oxidation of gabapentin by bromamine-T in NaOH medium was also studied [22]. The reaction rate exhibited first order kinetics with respect to bromamine-T $[\text{BAB}]$ and fractional order in both $[\text{GBP}]$ and $[\text{NaOH}]$. The kinetics of oxidation of gabapentin anion by alkaline diperiodatonickelate (IV) was studied spectrophotometrically [23]. The reaction was first order with respect to diperiodatonickelate $[\text{DPN}]$ and 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 an acid medium was investigated [24]. 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.

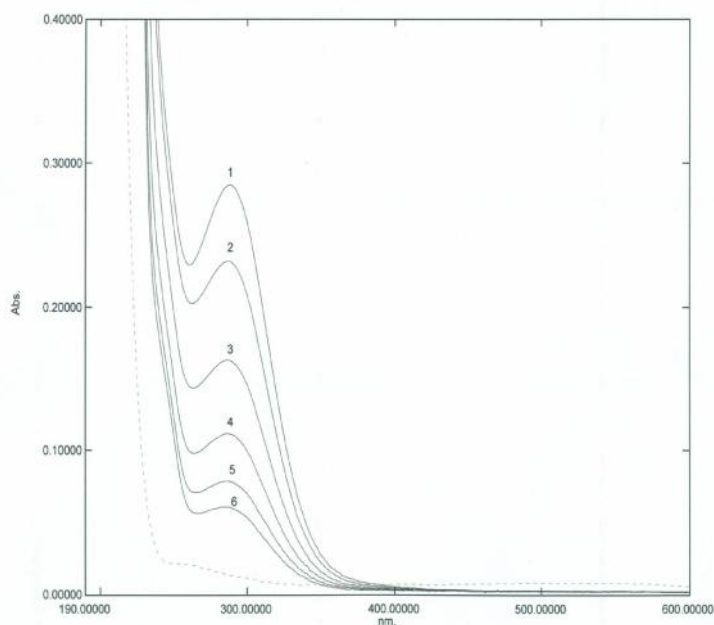
In the present work, there was an intension to study the kinetics of oxidation of gabapentin by NBS in an alkaline medium and comparing to the kinetics of its oxidation by N-bromosuccinimide in an acid medium [24].

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 Merck 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

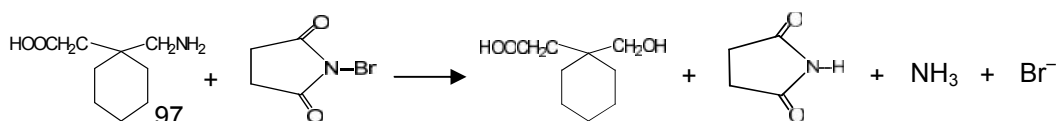
73 A Shimadzu 1700UV-vis spectrophotometer was used to follow the progress of the oxidation
 74 reaction by measuring the decrease in the absorbance of gabapentin at $\lambda = 290$ nm versus
 75 time (Figure1). N-bromosuccinimide and gabapentin solutions in the required buffers were
 76 allowed to equilibrate separately for 20 min in a water bath before the reaction was initiated.
 77 The NBS solution was then added quickly to the reaction mixture and a sample was then
 78 transferred to an absorption cell. The pH of the reaction mixture was measured using a 3505
 79 Jenway pH-meter. The reaction was carried out under pseudo-first order conditions with
 80 NBS concentrations always in a large excess (at least 10 fold) over gabapentin
 81 concentrations.



82
 83 **Fig. 1. Absorption spectra of the reaction mixture at different times. Peaks (1-6) were**
 84 **recorded at 1, 2, 5, 10, 15, and 20 min. from the time of initiation of reaction**
 85 **respectively. The dashed curve for aqueous solution of gabapentin alone. pH = 8.50,**
 86 **T= 25°C , [GBP] = 0.001 mol dm⁻³ , [NBS] = 0.01 mol dm⁻³**
 87

88 2.2. STOICHIOMETRY

89 The stoichiometry of the reaction was ascertained by carrying out several sets of
 90 experiments with varying amounts of NBS concentration largely in excess (at least twice)
 91 over gabapentin concentration in the required buffer, and the mixtures were allowed to stand
 92 until completion. 5ml aliquot of each of the reaction mixture was withdrawn and transferred
 93 to a titrating flask containing 5ml of 4% KI. The liberated iodine was estimated by standard
 94 Na₂S₂O₃ solution using starch as indicator. The results showed that, one mol of NBS
 95 consumed one mol of gabapentin and the reaction is thus represented stoichiometrically as,



98

99 **2.3. PRODUCTS ANALYSIS**

100 For identification of the oxidation products, the reaction mixture containing excess
 101 concentration of gabapentin was kept aside until completion. The main reaction products
 102 were extracted with ether and subjected to spot tests. The main reaction product was
 103 identified as 1-(hydroxymethyl) cyclohexane acetic acid by spot test for free carboxylic and
 104 OH- groups [25]. The product was also confirmed by IR spectra where, the presence of
 105 absorption band at 1681 cm⁻¹ and 1394 cm⁻¹ indicates the free -COO- group and there is
 106 a broad valley in the region 3098–3500 cm⁻¹ indicating the presence of -OH group as well
 107 as carboxylic -OH group. There is C-O stretching frequency of alcoholic -OH group
 108 (hydroxy methyl group) at 1066 cm⁻¹ indicating the formation of -CH₂-OH group, which
 109 was absent in gabapentin, and -OH deformation bands occur at 1329–1320 cm⁻¹.

110 **3. RESULTS AND DISCUSSION**

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

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

126 $(-d[\text{GBP}]/dt) = k_1$ (1)

127 For zero order reaction, variation of the absorbance with time at different [NBS] should be
 128 linear along the progress of the oxidation reaction, but (Figure 2) indicated that, the linear
 129 relation existed only through the initiation of the reaction which may support a zero order
 130 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 decreased 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.

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

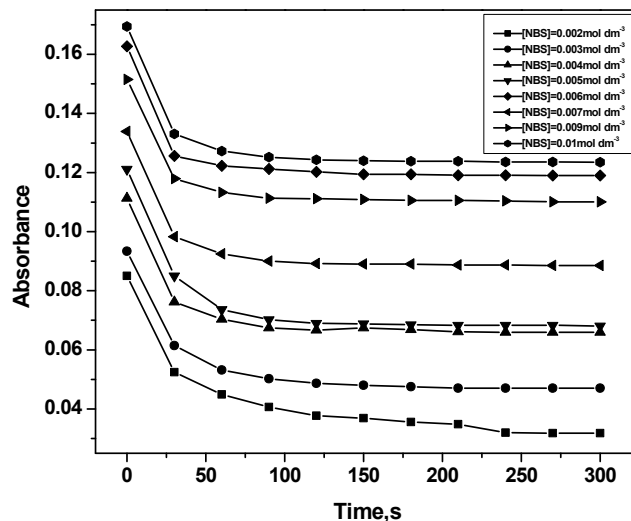


Fig. 2. Absorbance versus time at different [NBS]. pH= 8.60, [GBP]= 2.0×10^{-4} mol dm⁻³, T =30°C

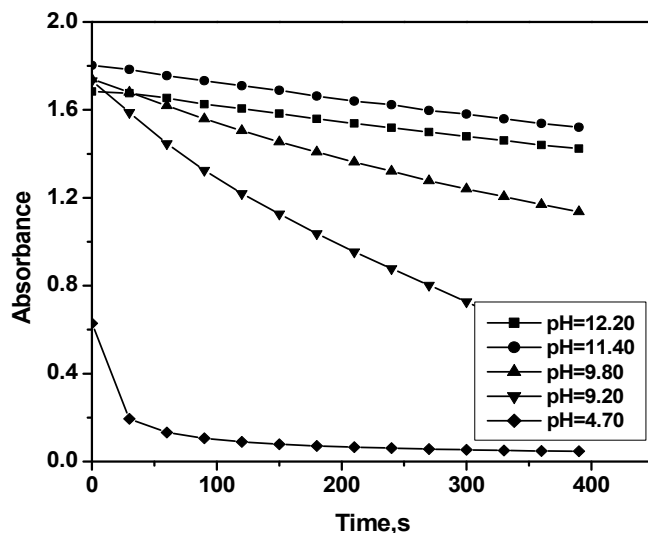
The effect of gabapentin concentrations on the oxidation rate were examined over the concentrations range $(0.40\text{--}20.0) \times 10^{-4}$ mol dm⁻³. Values of the initial rates (Table 1) indicated that, the initial rates increased with increasing [GBP] over the range studied. Plot of log initial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

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

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

Table 2. Effect of pH on the initial rates at [NBS] = 0.02 mol dm⁻³, T=30°C, λ =290nm

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



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

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

194
$$(-d[\text{GBP}]/dt) = k_1[\text{H}^+]^x \quad (3)$$

195 Where x is less than unity. Plots of the initial rates versus [GBP] at different pHs over (7.40-
 196 8.70) range were linear with zero intercept (Figure 4) with correlation coefficients $r_1=0.99993$
 197 $r_2=0.99995$, $r_3=0.99988$ and $r_4=0.9997$ at pHs, 7.40, 7.70, 8.20, and 8.70 respectively.

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

199
$$(-d[\text{GBP}]/dt) = k_1 [\text{GBP}][\text{H}^+]^x \quad (4)$$

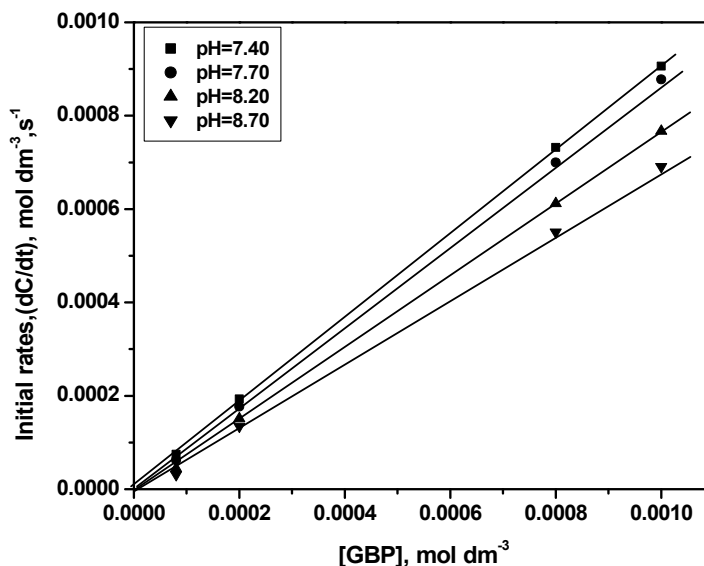


Fig. 4. Plots of initial rates versus [GBP] at different pHs

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

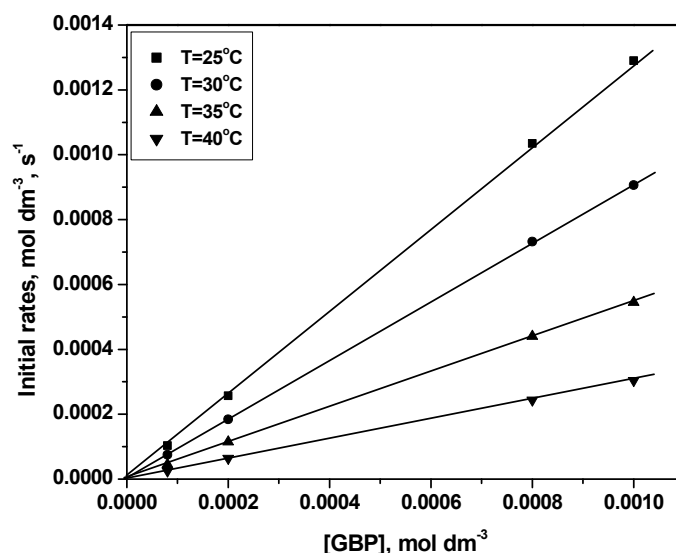


Fig. 5. Plots of initial rates versus [GBP] at different temperatures.

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

Table 3. Values of k_1 at different temperatures

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

Thermodynamic activation parameters including the enthalpy $\Delta H^{\ddagger}$ and entropy $\Delta S^{\ddagger}$ associated with k_1 were calculated using a least squares fit to the transition state theory equation as $-78.6 \text{ kJ mol}^{-1}$ and $-505.5 \text{ J K}^{-1} \text{ mol}^{-1}$ respectively. The rate determining step is an exothermic as indicated by the negative value of $\Delta H^{\ddagger}$. The composite negative value of $\Delta S^{\ddagger}$ may be largely the result of substantial mutual ordering of the solvated water molecules [26] of the equilibrium reactions and intramolecular electron transfer step. The effect of ionic strength on the oxidation reaction was studied by varying the ionic strength of the reaction medium using an aqueous solution of NaCl of known concentration and maintaining other parameters constant. The experimental results indicated that, there is no significant effect of the ionic strength on the oxidation rates and supported that the reaction took place between charged and non charged species. The effect of dielectric constant (D) of the medium on the rate of oxidation was investigated by using different MeOH-H₂O solvent mixtures over 0-40 wt% range at $T = 30^{\circ}\text{C}$, at constant pH, ionic strength, [GBP] and [NBS]. The values of

the dielectric constants for various weight percentage composition of MeOH-H₂O were abstracted as reported [27]. Values of the oxidation rates were decreased when MeOH percentage increased (Table 4).

Table 4. Kinetics data for the oxidation of [GBP] by NBS at different MeOH-H₂O solvent mixtures; [GBP] = 1.0x10⁻³ mol dm⁻³, [NBS] = 0.02 mol dm⁻³ and T= 30°C

MeOH Wt. %	10 ⁴ x initial rates (d[C]/dt),mol dm ⁻³ ,s ⁻¹	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

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

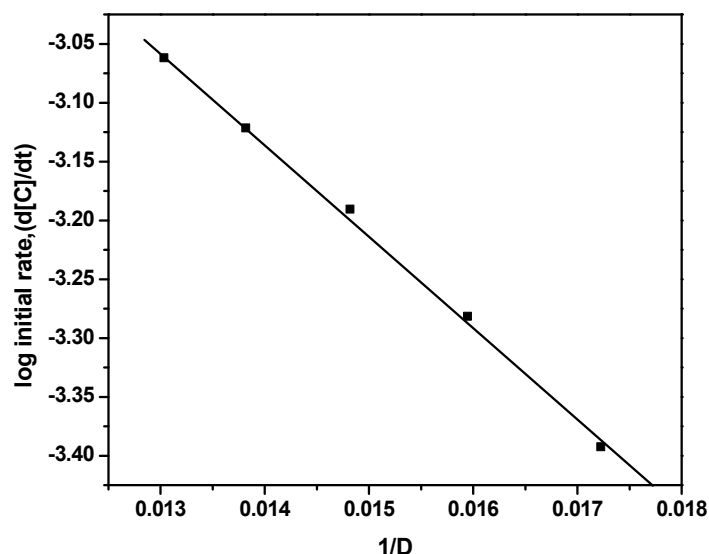
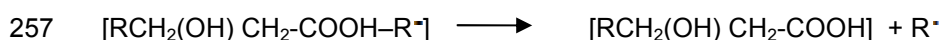
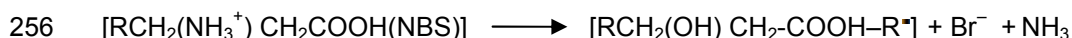
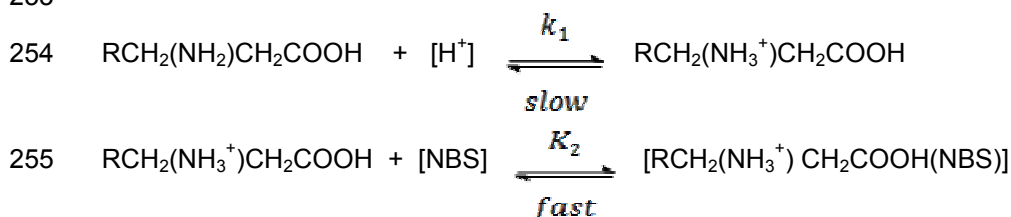


Fig. 6. Plot of log initial rates versus 1/D

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

249 Since, NBS is capable to coordinates the substrate through the carbonyl group [28]. The
 250 observed kinetics of oxidation of gabapentin by N-bromosuccinimide in an alkaline medium
 251 may therefore described by the following reaction scheme that includes a first reversible
 252 slow step which is the rate determining step, followed by another three fast steps.

253



258 Where R is cyclohexane group and R^* is the succinimidyl radical. The succinimidyl radical
 259 may prefer to abstract a hydrogen atom from the aqueous medium to form succinimide
 260 rather than dimerize to give bisuccinimide [29, 30].

261 4. CONCLUSION

262 The kinetics of oxidation of gabapentin (GBP) by N-bromosuccinimide (NBS) in an alkaline
 263 medium has been studied spectrophotometrically. In acid solutions, the oxidation reaction of
 264 gabapentin by N-bromosuccinimide exhibited classical kinetics, where the reaction rate was
 265 first order dependence on [NBS], fractional order on both [GBP] and $[\text{H}^+]$ and increased with
 266 temperatures over (303-321°K) range. In an alkaline medium (the presented work), the
 267 reaction exhibited a unique kinetics, where the reaction rate was first order dependence on
 268 [GBP], fractional order on $[\text{H}^+]$ and zero order for a limited period of time dependence on
 269 [NBS]. It is noteworthy that the reaction rate decreased with increasing temperatures over
 270 (25-40°C) range. This may be explained in the light of a multistep reaction mechanism in
 271 which, the slowest step is highly exothermic. An inner-sphere mechanism for the oxidation of
 272 gabapentin by N-bromosuccinimide in an alkaline aqueous solution supported by free radical
 273 intervention was proposed.

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