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Acidic Permanganatic Oxidation of Benzocaine: a Kinetic Study

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Abstract

Permagnetic oxidation of Benzocaine has been studied at different temperatures using spectrophotometer under acidic conditions. The effect of variation of substrate Benzocaine (BZC), oxidant ($KMnO_4$) and acid H_2SO_4 was studied under pseudo first order reaction conditions. The effect of different salts and solvents on oxidation of BZC was also studied. The reaction was found to be first order with respect to oxidant, substrate and acid H_2SO_4 .

Key words: Benzocaine (BZC), $KMnO_4$, permanganatic oxidation, acidic media.

Introduction

Benzocaine is a local anesthetic drug and commonly used as topical pain relive. It is also used in cough drops. BZC is used for painless killing of animals and aquatic species during scientific experimentation[1] or it is used for anesthesing fishes[2]. Local anesthesia is used to prevent nociception (the transmission of noxious stimuli) either as a sole agent in conscious organisons, or more usually during sedation or general anesthesia.[3] It is widely used in intensive aquaculture systems to control stress during handling and confinement operations[4] sometimes BZC is also present in cocaine as adulterant[5, 6] BZC is a oxidizing agent. It convert heame iron from ferrous (Fe^{2+}) into ferric (Fe^{3+}), which forms methemoglobin. The new compound, methamoglobin, cannot bind oxygen and hence mortality level increases.[7] There are various reports for the oxidation of drugs and organic compounds using permanganate[8 – 12]. Therefore we decided to investigate oxidation kinetics of Benzocaine in acidic media.

Experimental

For the present study distilled water was prepared in the laboratory using all quick fit glass assembly distillation units. A pinch of KOH and $KMnO_4$ was added during distillation, the pH of the distilled water was monitored. All solutions were prepared in double distilled water. A stock solution 0.01M $KMnO_4$ was prepared and standardized using oxalate solution. A thermostat of locally assembled Dinesh make was used to Benzocaine. BZC was purchased from local Chemical traders. All kinetic runs were carried out in thermostat by champing the reaction vessel and the conditions such as variation in oxidant, variation in substrate, variation in H_2SO_4 effect of temperature, effect of salt and effect of solvent were studied. All kinetic runs were monitored using spectrophotometer (ELICO SL 210) at 525 nm.

Result and Discussion

1. Effect of variation of Substrate (BZC) :

To find out effect of substrate variation, the concentration of BZC was varied from 1×10^{-3} to 9×10^{-3} M, keeping constant concentration of $[KMnO_4] = 1 \times 10^{-3}$ M, $[H_2SO_4] = 1$ M . As the reaction has been studied under pseudo first order condition pseudo first order rate constants were calculated.

Table 1: Psuedo first order rate constant at = 25^0C ± 0.5^0C keeping variation in substrate (BZC)

[BZC]	[$KMnO_4$]	[H_2SO_4]	k
1×10^{-3}	1×10^{-3}	1M	2.11×10^{-2}
2×10^{-3}	1×10^{-3}	1M	1.87×10^{-2}
3×10^{-3}	1×10^{-3}	1M	1.98×10^{-2}
4×10^{-3}	1×10^{-3}	1M	2.18×10^{-2}
5×10^{-3}	1×10^{-3}	1M	2.16×10^{-2}
6×10^{-3}	1×10^{-3}	1M	2.30×10^{-2}
7×10^{-3}	1×10^{-3}	1M	2.66×10^{-2}
8×10^{-3}	1×10^{-3}	1M	4×10^{-2}
9×10^{-3}	1×10^{-3}	1M	4.62×10^{-2}

The following equation was used for the calculation of first order rate constants.

$$k = \frac{2.303}{t}\log\frac{(OD)_{\infty} - (OD)_0}{(OD)_{\infty} - (OD)_t}$$

Where k is rate constant, t is time , O.D. –Optical Density

The rate constants are a represented in the tabular form (table 1). At low concentration of BZC (below 5×10^{-3}M], the rate constants seems to be constant with slight positive or negative deviations, but above the concentration of 5 x 10 – 3M, the rate constant increases. This indicate that strong concentration oxidant is required for the oxidation of BZC.

2. Effect of variation of oxidant :

In the another set of experiments, oxidant was varied in the range of 1×10^{-3}M to 9×10^{-3}M. The concentration of substrate [BZC] was selected at 1×10^{-3} M and concentration of H_2SO_4 1M and temperature was kept constant 25°C ± 0.5°C in thermostat. It is clear seen that initially pseudo first order rate increases with increasing the concentration of $KMnO_4$ but at higher concentration of oxidant the rate decreases (Table 2). Hence the rate of reaction under pseudo first order rate of reaction depends on the concentration of oxidant.

Table 2: Psuedo first order rate constant at = 25^0C ± 0.5^0C keeping variation in oxidant ($KMnO_4$).

[BZC]	[$KMnO_4$]	[H_2SO_4]	k
1×10^{-3}	1×10^{-3}	1M	2.10×10^{-2}
1×10^{-3}	2×10^{-3}	1M	2.84×10^{-2}
1×10^{-3}	3×10^{-3}	1M	3.02×10^{-2}
1×10^{-3}	4×10^{-3}	1M	3.85×10^{-2}
1×10^{-3}	5×10^{-3}	1M	4.9×10^{-2}
1×10^{-3}	6×10^{-3}	1M	5.34×10^{-2}
1×10^{-3}	7×10^{-3}	1M	5.86×10^{-2}
1×10^{-3}	8×10^{-3}	1M	4.36×10^{-2}
1×10^{-3}	9×10^{-3}	1M	4.85×10^{-2}

3. Effect of variation of H_2SO_4 concentration:

To study the effect of variation of concentration of sulphuric acid H_2SO_4, in the experimental sets the concentration of H_2SO_4 was varied in the range of 1×10^{-1} to 9×10^{-1} M, keeping constant concentration i.e. [BZC]= 1×10^{-3} and [$KMnO_4$] = 8×10^{-3} M, at the $25^0C \pm 0.5^0C$ constant temperature.(Table 3)As the reaction has been studied under pseudo first order condition for varying [H_2SO_4] was made and pseudo first order rate constants were calculated. It is clear from that pseudo first order rate constants increases with increases in concentration of H_2SO_4 confirming the first order dependence with respect to acid. Hence the reaction under pseudo order rate depends on the concentration of acid. We plot initial rate with conc. of H_2SO_4. The trend line is linear with negative slope. (Fig.4.4.3)

Table 3: Psuedo first order rate constant at = $25^0C \pm 0.5^0C$ keeping variation in H_2SO_4:

[BZC]	[$KMnO_4$]	[H_2SO_4]	k
1×10^{-3}	8×10^{-3}	1×10^{-1}	2.76×10^{-2}
1×10^{-3}	8×10^{-3}	2×10^{-1}	2.89×10^{-2}
1×10^{-3}	8×10^{-3}	3×10^{-1}	2.67×10^{-2}
1×10^{-3}	8×10^{-3}	4×10^{-1}	4.11×10^{-2}
1×10^{-3}	8×10^{-3}	5×10^{-1}	4.59×10^{-2}
1×10^{-3}	8×10^{-3}	6×10^{-1}	4.6×10^{-2}
1×10^{-3}	8×10^{-3}	7×10^{-1}	5.02×10^{-2}
1×10^{-3}	8×10^{-3}	8×10^{-1}	4.71×10^{-2}
1×10^{-3}	8×10^{-3}	9×10^{-1}	4.28×10^{-2}

4. Effect of variation of temperature:

The effect of temperature was studied keeping constant concentration of all reactants such as [$KMnO_4$] = 8×10^{-3} M, [BZC] = 1×10^{-3} M and [H_2SO_4] = 9×10^{-3}. The temperature variation was done in the range of 25°C to 50 °C. (Table. 4) The energy of activation was calculated by plotting graph between log k versus 1/T, a straight line was obtained. (Table. 5) The temperature dependence of rate constant can be given as;

$$k = \frac{k_B}{T} e^{\frac{\Delta Ea^{\#}}{RT}} e^{\frac{\Delta S^{\#}}{R}}$$

In the above equation T is Temperature in Kelvin ΔS is change in Entropy, ΔH is change in Enthalpy & ΔG Gibb's free energy change

The modest enthalpy of activation and higher rate constant of slow step indicate that the oxidation presumably occurs by an inner sphere mechanism. The free energy change (ΔG), enthalpy changes (ΔH) and entropy change (ΔS) was determined.

Table 4: Psuedo first order rate constant at different temperatures:

Temp.	[BZC]	[$KMnO_4$]	[H_2SO_4]	k
25°C	1×10^{-3}	8×10^{-3}	9×10^{-1}	5.07×10^{-2}
30°C	1×10^{-3}	8×10^{-3}	9×10^{-1}	5.23×10^{-2}
35°C	1×10^{-3}	8×10^{-3}	9×10^{-1}	4.12×10^{-2}
40°C	1×10^{-3}	8×10^{-3}	9×10^{-1}	7.17×10^{-2}
45°C	1×10^{-3}	8×10^{-3}	9×10^{-1}	6.8×10^{-2}
50°C	1×10^{-3}	8×10^{-3}	9×10^{-1}	6.47×10^{-2}

The energy of activation was calculated to be -11672.09 J/mole. This activation energy was used to calculate the enthalpy of activation (ΔH) using equation

$$\Delta H = \Delta E — RT$$

The value of (ΔH) decreases with increase with increase temperature.The average (ΔH) was found -14253.59 J/mole.with a range -14149.66 to -14357.51 J/mole. Then from this, we calculated entropy of activation

Table 5: Thermodynamic parameter of the kinetic oxidation process:

T	k	$\Delta H^{\#}$ ($J\ mole^{-1}$)	$\Delta S^{\#}$ ($J\ mole^{-1}$)	$\Delta G^{\#}$ ($J\ mole^{-1}$)
298	0.0507	-14149.66	-137.74	26899.17
303	0.0523	-14191.23	-137.41	27445.51
308	0.0412	-14232.80	-138.06	28290.87
313	0.0717	-14274.37	-135.85	28249.37
318	0.068	-14315.94	-135.85	28885.15
323	0.0647	-14357.51	-135.84	29519.36

There was no regular trend of entropy change, it varies from the range of -137.74 to -135.84 J/mole. The average entropy of activation was found to be -136.79 J/mole which is negative and indicates that the transition state is highly organized due to loss of number of degrees of freedom. The average free energy (ΔG) was then calculated using (ΔH) and (ΔS) as per the equation,

$$\Delta G = \Delta H - T\Delta S$$

It was observed that (ΔG) increases with increase in temperature. The average (ΔG) was found to be 28214.91 J/mol and it changes in the range of 26899.17 J/mole to 29519.36 J/mole (Fig.4.4.5) A plot of (ΔH) verses (ΔS) is linear which is followed by this equation.

$$(\Delta H) = \beta \Delta S$$

Where β is called isokinetic temperature, for BZC it was = 104.20k.

5. Effect of variation of solvent concentration:

The reaction was monitored in four different solvents, namely1,4 dioxane ,acetic acid, DMF acetone. The rate constants for acetone was found to be less compaired to other solvent. In acetone rate constant decreases with increase in percentage of solvent. In DMF rate constant increases with increases in percentage of solvent. For acetic acid also rate constant decreases, but no regular trend was observed for 1,4 dioxane. (Table. 6).

Table 6: Psuedo first order rate constant at = 25°C ± 0.5°C keeping variation in solvent concentration: [BZC] = 1 X10^{-3}; [$KMnO_4$] = 8 X 10^{-3}; [H_2SO_4] = 9 X 10^{-3}; [Temp.] = 25°C ± 0.5°C

Percentage of	Rate constant (sec^{-1})			
Solvent	1,4 dioxane	Acetic Acid	DMF	Acetone
10 %	6.68×10^{-1}	2.33×10^{-2}	6.47×10^{-2}	2.4×10^{-2}
20 %	9.89×10^{-1}	2.72×10^{-2}	6.61×10^{-2}	2.12×10^{-2}
30 %	9.29×10^{-2}	2.74×10^{-2}	6.42×10^{-2}	2.22×10^{-2}
40 %	11.29×10^{-2}	2.67×10^{-2}	6.79×10^{-2}	2.33×10^{-2}
50 %	3.5×10^{-2}	2.9×10^{-2}	5.58×10^{-2}	2.23×10^{-2}
60 %	3.31×10^{-2}	3.25×10^{-2}	6.15×10^{-2}	2.09×10^{-2}

6. Effect of variation of salts:

To study the effect of variation of salts, the concentration of salts was varied from 1 x 10^{-2} to 9 x 10^{-2} M, keeping constant concentration of reactants such as [$KMnO_4$] = 8 x 10^{-3} M; [BZC] = 1 x 10^{-3} M; [H_2SO_4] = 9 X 10^{-3}; (Table.4.1) From the obtained results, it is clear that pseudo first order rate constant k_{obs} decreases with the increase in concentration of salts. A plot of log k_{obs} vs $\sqrt{\mu}$, according to extended Bronsted -Debye-Huckel equation was found to be linear with positive slopes (NaCl, $CaCl_2$, $AlCl_3$, Na_2SO_4, Na_3PO_4 and $MnSO_4$) indicating positive salt effect. (Fig.5 a to b)

Table 4.1: Psuedo first order rate constant at = 25°C ± 0.5°C keeping variation in salts: [BZC] = 1 X10^{-3}; [$KMnO_4$] = 8 X 10^{-3}; [H_2SO_4] = 9 X 10^{-3}; [Temp.] = 25°C ± 0.5°C

Conc. Of	Rate Const.(sec^{-1})					
Salt	NaCl	$CaCl_2$	$AlCl_3$	Na_2SO_4	Na_3PO_4	$MnSO_4$
1×10^{-2}	2.55×10^{-2}	2.24×10^{-2}	2.42×10^{-2}	3×10^{-2}	2.91×10^{-2}	5.46×10^{-2}
2×10^{-2}	2.48×10^{-2}	2.31×10^{-2}	2.41×10^{-2}	2.95×10^{-2}	2.71×10^{-2}	5.46×10^{-2}
3×10^{-2}	2.48×10^{-2}	2.27×10^{-2}	2.7×10^{-2}	2.89×10^{-2}	2.66×10^{-2}	7.88×10^{-2}
4×10^{-2}	2.36×10^{-2}	2.38×10^{-2}	2.56×10^{-2}	2.74×10^{-2}	2.6×10^{-2}	7.56×10^{-2}
5×10^{-2}	2.47×10^{-2}	2.58×10^{-2}	2.57×10^{-2}	2.89×10^{-2}	2.71×10^{-2}	7.98×10^{-2}
6×10^{-2}	2.43×10^{-2}	2.23×10^{-2}	2.63×10^{-2}	2.82×10^{-2}	2.86×10^{-2}	7.43×10^{-2}
7×10^{-2}	2.44×10^{-2}	2.23×10^{-2}	2.43×10^{-2}	2.78×10^{-2}	2.79×10^{-2}	5.23×10^{-2}
8×10^{-2}	2.31×10^{-2}	2.44×10^{-2}	2.52×10^{-2}	3.03×10^{-2}	2.94×10^{-2}	4.67×10^{-2}
9×10^{-2}	2.2×10^{-2}	2.32×10^{-2}	2.39×10^{-2}	3.77×10^{-2}	2.78×10^{-2}	5.59×10^{-2}

The probable mechanism can be given as;

$$MnO_4^- + H^+ \xrightleftharpoons[K_2]{K_1} HMnO_4$$

$$S + HMnO_4 \xrightleftharpoons[K_2]{K_1} Complex$$

$$Complex + H_2O \xrightarrow[slow]{K_3} P$$

Considering above mechanism, the rate expression can be derived as follows;

Rate of reaction depends on complex formation;

$$Rate = K_3\,[Complex]$$

$$K_1\,[MnO_4]\,[H^+] - K_{-1}\,[HMnO_4] - K_2\,[S][HMnO_4] = 0$$

$$K_1\,[MnO_4]\,[H^+] = (K_{-1} + K_2\,[S])\,[HMnO_4]$$

$$[HMnO_4] = \frac{K_1[MnO_4^-][H^+]}{K_{-1} + K_2[S]}$$

$$K_2[HMnO_4]\,[S] - K_{-2}\,[Complex] - K_3\,[Complex] = 0$$

$$K_2[HMnO_4]\,[S] = (K_{-2} + K_3)\,[Complex]$$

$$\therefore [Complex] = \frac{K_2[HMnO_4][S]}{K_{-2} + K_3}$$

$$= \frac{K_2[S]\,K_1\,[MnO_4^-][H^+]}{(K_{-2} + K_3)(K_{-1} + K_2[S])}$$

$$Rate = \frac{K_1K_2K_3\,[MnO_4^-][H^+][S]}{(K_{-2} + K_3)(K_{-1} + K_2[S])}$$

$$= \frac{K^{|}\,[MnO_4^-][H^+][S]}{K_{-1} + K_2[S]}$$

of $K_{-1} >> K_2\,[S]$

$$= \frac{K^{|}\,[MnO_4^-][H^+][S]}{K_{-1}}$$

of $K_{-1} >> K_2\,[S]$

$$Rate = \frac{K^{|}\,[MnO_4^-][H^+][S]}{K_2[S]}$$

$$= \frac{K_1}{K_2}[MnO_4^-][H^+]$$

Hence it is observed that the reaction is first order with respect to (H^+) and oxidant but shows variation with respect to substrate.

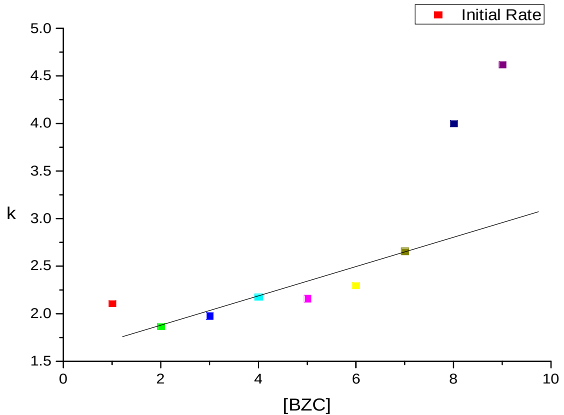


Fig.1 Variation of BZC

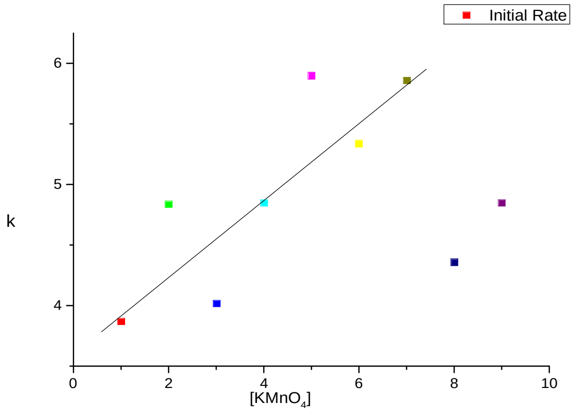


Fig.2 Variation of $KMnO_4$

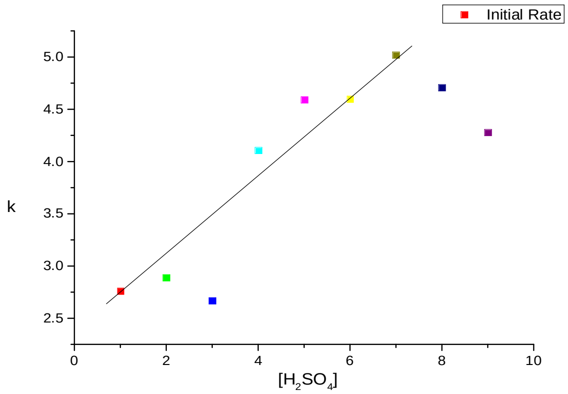


Fig.3 Variation of H_2SO_4

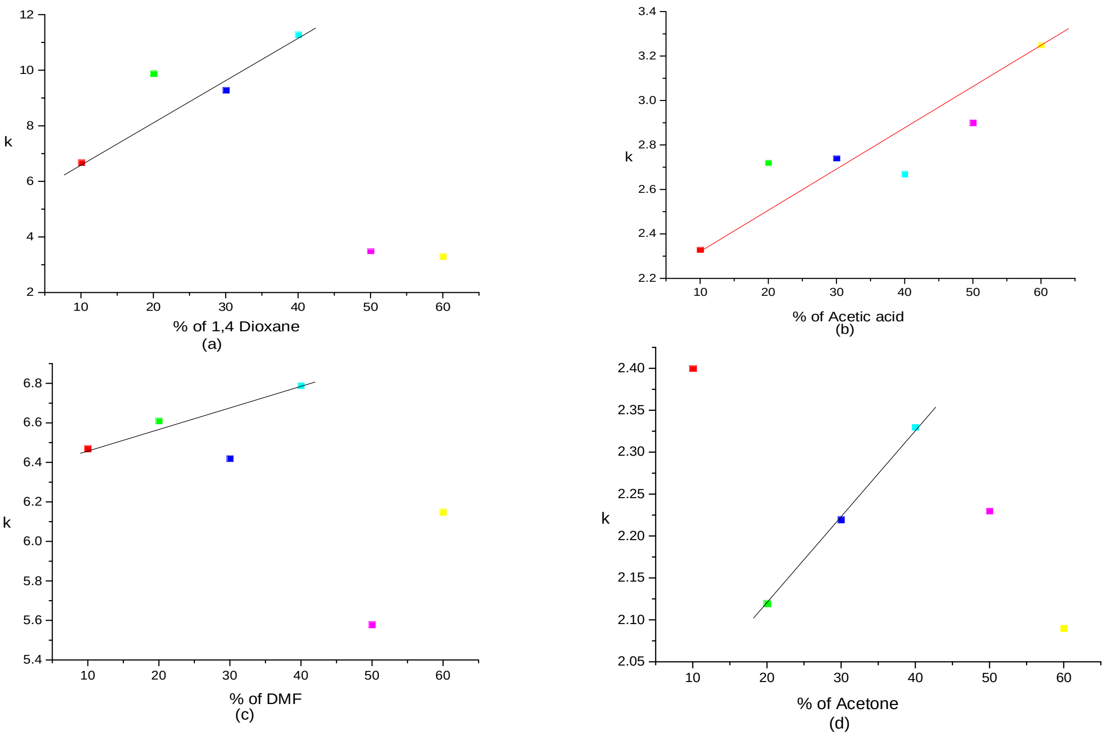
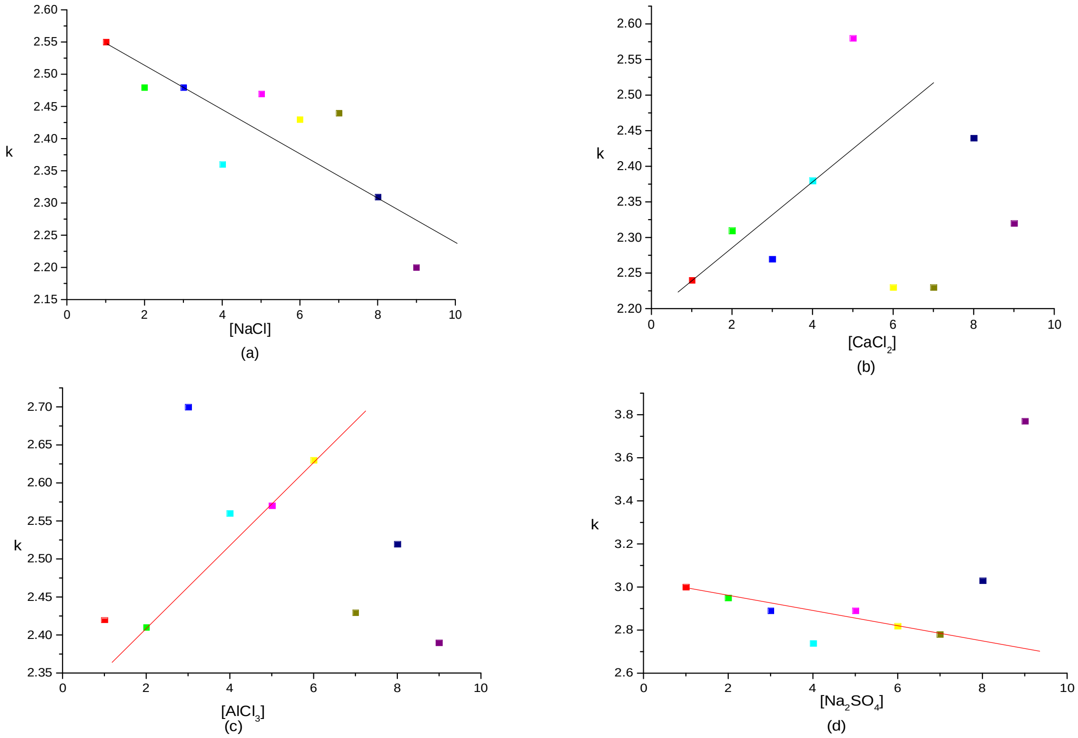


Fig 1 : Effect of solvents (a) 1,4 Dioxane (b) Acetic acid (c) DMF (d) Acetone



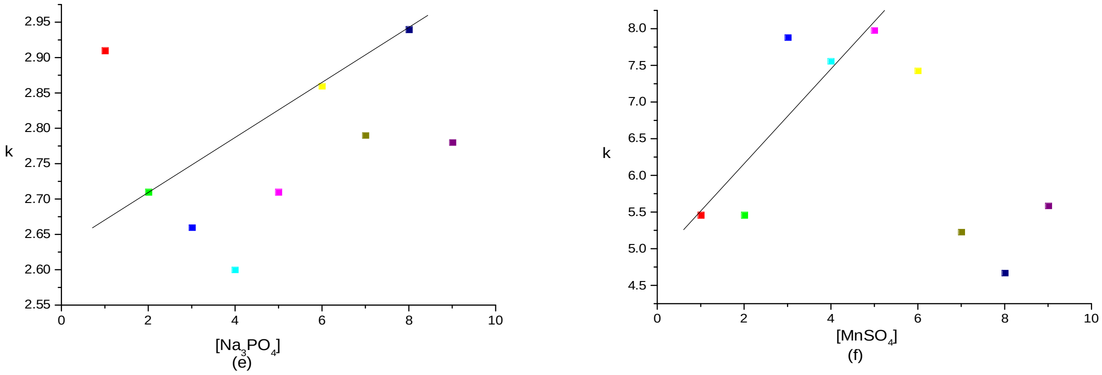


Fig 2: Effect of variation of salt (a) NaCl (b) $CaCl_2$ (c) $Alcl_3$ (d) Na_2SO_4 (e) Na_3PO_4 (f) $MnSO_4$

Conclusion

The Benzocaine has been undergone oxidative degradation under acidic condition by potassium permanganate. The reaction is first order with respect to substrate oxidant and acid.A detail mechanistic study of the oxidation of medicinal drug like BZC in acidic condition with study of oxidant can be done.

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