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Kinetic, Thermodynamic and Mechanistic Study of Benzylpiperazine Oxidation by Chloramine-T in Aqueous Medium

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***Abstract:** The Kinetic, thermodynamic and mechanistic study of benzylpiperazine oxidation by chloramine-T in Aqueous Medium has been studied at 303K. The oxidation products were identified and reaction stoichiometry was determined. A first order dependence on oxidant, fractional order on substrate and inverse fractional order on $[H^+]$ of rate was observed. The dielectric constant has a slight negative effect. Involvement of non ionic species in rate determining step was indicated by unchanged rate with ionic strength. Thermodynamic parameters were computed by performing the kinetic runs at different temperature and a mechanism consistent with observed parameters is proposed. Rate law is derived.*
***Keywords:** benzylpiperazine, stoichiometry, mechanism, Rate law, dielectric constant.*

I. INTRODUCTION

The heterocyle piperazine is a core structure in many pharmaceutical preparations. The derivative of piperazine, benzylpiperazine (BZP) is a recreational drug with euphoriant and stimulant properties. It was synthesized originally as a potential antihelmintic agent for use in farm animals. It exhibits a mixed mechanism of action, acting on the serotogenic and the dopaminergic receptor systems. It was found to increase activation of the surrounding serotonin receptors by increasing serotonin concentrations in the extracellular fluids surrounding the cell [1],[2]. It shows lower potency effect on the noradrenaline reuptake transporter and the dopamine reuptake transporter.

Aryl N-halosulfonamides are extensively used to perform a wide range of transformations as they react with variety of functional groups[3]. Due to the presence of strongly polarized N-linked halogen in +1 state they have ability to act as mild oxidants in both acid and alkaline solutions. Kinetics of oxidation of many organic substrates was studied by aryl N-halosulfonamides. Chloramine-T (CAT), a prominent member of this group is a well known analytical reagent. The kinetic and the mechanistic aspects of many of its reactions are well documented[4].

A survey of literature confirmed that, oxidation of BZP by mild oxidants has not been reported. In the present communication we are reporting kinetic and mechanistic aspects of BZP oxidation by CAT in $HClO_4$ medium at 303 K.

II. MATERIAL AND METHODS

1) *Experimental:* A solution of CAT (E. Merck) in water was standardized by the iodometric method and preserved in brown bottle to prevent any further photochemical deterioration. Aqueous solution of BZP (Sigma) of required strength was freshly prepared each time. The other reagents used were of analytical grade. Conductivity water was used for the kinetic runs. Ionic strength was maintained using concentrated solution of sodium per chlorate. Methanol was added to alter the dielectric constant. An excess of BZP over CAT was maintained to achive pseudo first-order conditions.
2) *Kinetic measurements:* A mixture of required volumes of solutions of BZP, $NaClO_4$ and acid was taken in a glass-stoppered Pyrex boiling tube. Requisite amount of water was added to keep the total volume constant for all runs and thermostated at 303K. Required amount of equilibrated solution of CAT was added to the mixture and shaken appropriately. The progress of reaction was studied iodometrically by the estimation of unreacted CAT in a measured aliquot (5 mL) of the reaction mixture with time up to about two half-lives. The pseudo first-order rate constants calculated from the plots of log [CAT] against time are reproducible within ±4%.
3) *Stoichiometry and product analysis:* The kinetic measurements performed by keeping excess of BZP over CAT in $HClO_4$ at 303K confirm the following stoichiometry that one mole of BZP consumed two moles of CAT.

$$C_{11}H_{16}N_2 + 2MBSO_2NClNa + 2H_2O \longrightarrow C_4H_{10}N_2 + C_7H_6O_2 + 2\,MBSO_2NH_2 + 2Cl^- + 2Na^+ \quad \textbf{(1)}$$

Where, MB = $CH_3C_6H_4$

The products of reaction were extracted with ether. From the ether layer the oxidation products of substrate benzoic acid and piperazine are taken in to queous sodium hydroxide and hydrochloric acid solutions respectively and identified by TLC and GC-MS analysis. The reduction product of CAT, p-toluenesulfonamide (PTS), was extracted with ethyl acetate and confirmed by TLC using the system of solvent petroleum ether-chloroform-1- butanol (2:2:1 v/v and the developing reagent iodine (Rf =0.839).

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III. RESULTS AND DISCUSSION

1) *Effect of concentration of reactants on the rate:* Kinetic runs were carried out in pseudo-first order conditions ([BZP] >> [CAT]) by varied [CAT], at constant [BZP], [$HClO_4$], and temperature. The plots of log [CAT] versus time are linear indicating a first-order dependence of reaction rate on $[CAT]_0$. The pseudo first-order rate constants (k') were calculated from the slopes (table 1). The unchanged k' values on varying oxidant concentration further confirm the first- order dependence of the rate on $[CAT]_0$. Reactions were studied under similar experimental conditions by varying the concentration of [BZP]. The k' values increased with increase in $[BZP]_0$ (table-1). The linear plot of log k' versus log $[BZP]_0$ (figure-1) with a slope of 0.62 indicate fractional-order dependence on $[BZP]_0$.
2) *Effect of $[H^+]$ on the rate:* Decrease in rate was observed with increase in $[H^+]$ using $HClO_4$ (table 1). Linear plot of log k' versus log $[H^+]$ (figure 1) with a negative slope of 0.45 indicate an inverse fractional-order dependence of rate on $[H^+]$.
3) *Effect of halide ions on the rate:* The unchanged rate with added Cl^- in the form of NaCl ($1x10^{-3}$-$10x10^{-3}$ mol dm^{-3}) indicate that their effect is not significant on the rate of reaction.
4) *Effect of ionic strength on the rate*: The ionic strength of the medium was varied by the addition of NaClO (0.1 –1.0 mol dm^{-3}). The unchanged rate of reaction confirmed the involvement of non ionic species in the rate limiting step.
5) *Effect of dielectric constant on the rate:* Methanol in different proportions was added (0 - 40 %, v/v) to vary dielectric constant of the medium. Kinetic results indicate that increase in dielectric permittivity (D) of the medium decreased the rate of reaction (table-2). The plot of log k' versus 1/D is linear with a negative slope (figure-2). Under the experimental conditions methanol was ionized to very slight extent (< 1%) as confirmed by the blank experiments.
6) *Effect of PTS concentration on the rate:* PTS ($1x10^{-3}$-$10x10^{-3}$ mol dm^{-3}), the reduced product of oxidant CAT when added shows no significant effect on the rate. This indicates its non involvement in pre-equilibrium step.
7) *Effect of temperature on the rate:* The kinetic measurements were done at different temperature (303–323 K) keeping other experimental conditions constant (table-3). The activation parameters of the reaction were computed from the linear Arrhenius plot of log k' versus 1/T (figure-3).
8) *Test for free radicals:* The reaction mixture when added to aqueous acrylamide fails to initiate polymerization. This indicates the absence of any free radical species in the course of reaction.

Table-1
Effect of oxidant, substrate and acid concentration on rate

10^4 [CAT] mol dm^{-3}	10^4 [BZP] mol dm^{-3}	10^4 [$HClO_4$] mol dm^{-3}	K^I $10^4 S^{-I}$
3	6	6	8.38
6	6	6	8.25
9	6	6	8.35
12	6	6	8.45
6	3	6	5.19
6	6	6	8.25
6	9	6	11.44
6	12	6	13.99
6	6	3	8.25
6	6	6	6.55
6	6	9	4.58
6	6	12	2.89

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IV. DEDUCTION OF RATE LAW AND MECHANISM

Both in acid and alkali solutions Chloramine-T acts as mild oxidant with a two electron change to give reduced products. It behaves as a strong electrolyte in aqueous solution. It exhibit following equilibria in aqueous acidic medium furnishing different ionic species as follows[5],[6].

$$MBSO_2NClNa \rightleftharpoons MBSO_2NCl^- + Na^+ \quad (2)$$

$$MBSO_2NCl^- + H^+ \rightleftharpoons MBSO_2NHCl \quad (3)$$

$$2\ MBSO_2NHCl \rightleftharpoons MBSO_2NH_2 + MBSO_2NCl_2 \quad (4)$$

$$MBSO_2NCl_2 + H_2O \rightleftharpoons MBSO_2NHCl + HOCl \quad (5)$$

$$MBSO_2NHCl + H_2O \rightleftharpoons MBSO_2NH_2 + HOCl \quad (6)$$

$$MBSO_2NHCl + H^+ \rightleftharpoons MBSO_2NH_2Cl^+ \quad (7)$$

Where MB = $CH_3C_6H_4$.

Hence the possible oxidizing species of CAT in aqueous acid mixture are $MBSO_2NHCl$, $MBSO_2NCl_2$ and HOCl. The possibility of $MBSO_2NCl_2$ as reactive species was ruled out as the rate is not second order with respect to $[CAT]_0$ as from (4). Further the rate does not show first order retardation by the added PTS. Hence HOCl is not primarily involved in oxidation. Thus $MBSO_2NHCl$ is considered as the active oxidising species. In acid medium (pH<2) $MBSO_2NHCl$ is protonated to give $MBSO_2NH_2Cl$[7]-[10].The protonation constant for (4) at 298K is 1.02×10^2. The rate is retarded on adding H^+ ions confirming the deprotonation of $MBSO_2NH_2Cl^+$ leading to the formation of unprotonated active oxidizing species $MBSO_2NHCl$.

Considering the experimental results of oxidation of BZP by CAT, following scheme-1 is proposed. In scheme 2 the detailed plausible mechanism of reaction is picturized.

Table-2
Effect of dielectric constant on rate

MeOH % v/v	D	$10^2/D$	$K^I 10^4\ S^{-I}$
0	76.7	1.30	8.25
10	72.4	1.39	7.69
20	67.4	1.47	6.82
30	62.7	1.60	6.34
40	58.1	1.72	5.92

[CAT] = 6 x 10^{-4}mol dm^{-3}, [BZP] = 6 x 10^{-3}mol dm-3, [H^+] = 6 x 10^{-3} mol dm^{-3}, μ = 0.5 mol/dm^{-3}.

Table-3
Effect of temperature and activation parameters on rate

Temperature (K)	$K^I\ 10^4(S^{-I})$	Thermodynamic parameter
298	6.9091	E_a= 18.1460kJ mol^{-I}
303	8.2567	$\Delta H^{\neq}$= 16.06306kJ mol^{-I}
308	11.1934	$\Delta S^{\neq}$ = -249.1988J K^{-I} mol^{-I}
313	12.3456	$\Delta G^{\neq}$ = 91.627744kJ mol^{-I}
318	13.1075	-

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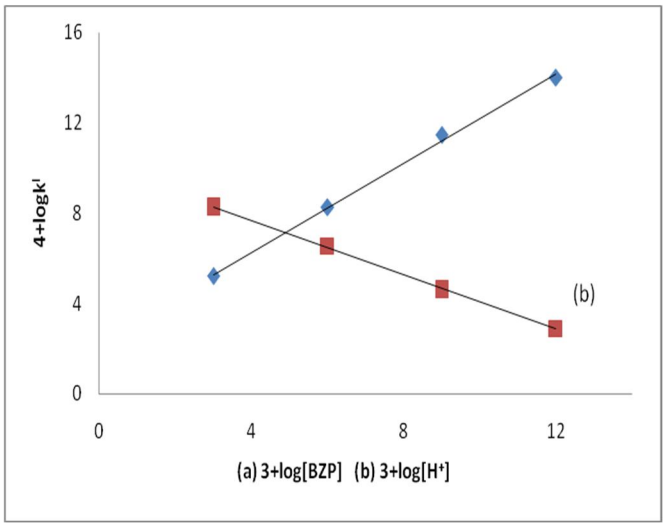

Figure-1 Effect of substrate and acid concentration on rate

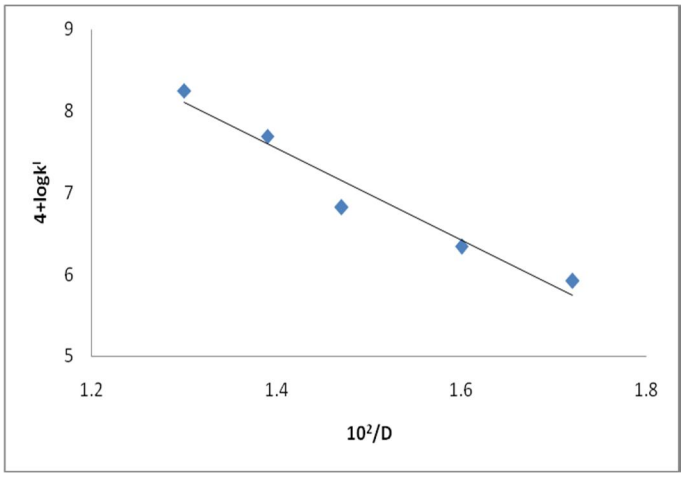

Figure-2 Effect of dielectric constant of the medium on rate

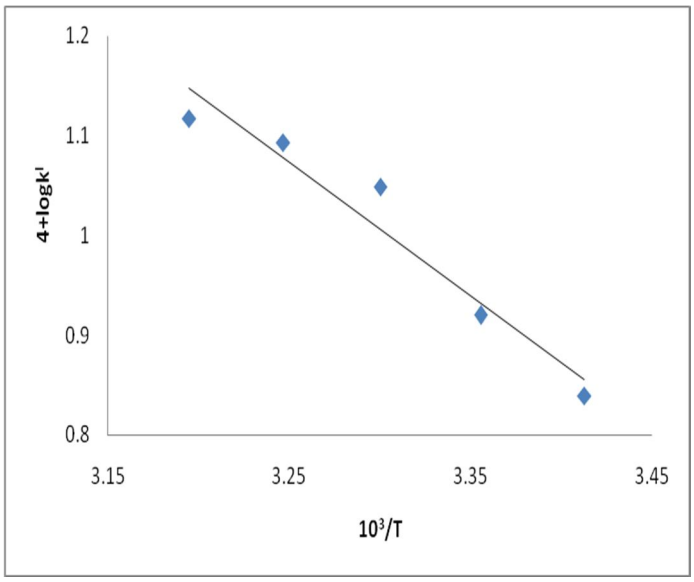

Figure-3 Effect of temperature on rate of reaction

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V. DEDUCTION OF RATE LAW AND MECHANIAM

$MBSO_2NHCl$ is considered as the active oxidising species and BZP represent the substrate. The intermediate complex species are represented by X and X^I . The reaction begins through the formation of $MBSO_2NHCl$ which attacks the substrate molecule to give an intermediate complex X which slowly dissociates in the rate determining step to give the complex cation X^I eliminating $MBSO_2NH_2$. Hydrolysis of X^I give X^{II} which reacts with another molecule of $MBSO_2NHCl$ to give final products.

$$MBSO_2NH_2Cl^+ \underset{}{\overset{k_1}{\rightleftharpoons}} MBSO_2NHCl + H^+ \qquad \text{(i) fast}$$

$$MBSO_2NHCl + LC \overset{k_2}{\rightleftharpoons} X \qquad \text{(ii) fast}$$

$$X \overset{k_3}{\rightleftharpoons} X^I \qquad \text{(iii) slow and r. d. s}$$

$$X^I + MBSO_2NHCl \overset{k_4}{\rightleftharpoons} \text{Products} \qquad \text{(iv)}$$

Scheme-1

The differential rate equation is $\frac{d[CAT]}{dt} = k_3\,[X]$ (8)

Let $[CAT]_t$ be the effective total concentration of CAT, then

$$[CAT]t = [MBSO_2NH_2Cl^+] + [MBSO_2NHCl] + [X] \qquad (9)$$

$$[CAT]t = ([MBSO_2NHCl][H^+])/k_1 + \frac{[X]}{k_2[BZP]} + [X] \qquad (10)$$

On solving for X,

$$[X] = \frac{k_1\ k_2\,[CAT]\,[BZP]}{[H^+]\,k_1(1 + k_2\ [BZP]} \qquad (11)$$

$$\frac{d[CAT]}{dt} = \frac{k_1 k_2 k_3\,[CAT]_t\,[BZP]}{[H^+] + k_1(1 + k_2)\,[BZP]} \qquad (12)$$

The deduced rate law agrees with the experimental results that a first, fractional and inverse fractional order dependence of reaction rate on $[CAT]_0$, $[BZP]_0$ and $[H^+]$ respectively.

Since rate = $k^I\,[CAT]_0$, from equation (13) we have,

$$k^I = \frac{k_1\,k_2\,k_3\,[BZP]}{[H^+] + k_1(1 + k_2)\,[BZP]} \qquad (13)$$

$$\frac{1}{k^I} = \frac{1}{k_2\,k_3\,[BZP]}\left\{\frac{[H^+]}{k_1} + 1\right\} + \frac{1}{k_3} \qquad (14)$$

From equations (13) and 14, plots of 1/k' *versus* 1/ [BZP] and 1/ k' *versus* $[H^+]$ were found to be linear. The values of k_1, k_2 and k_3 were calculated from the slopes and intercepts.

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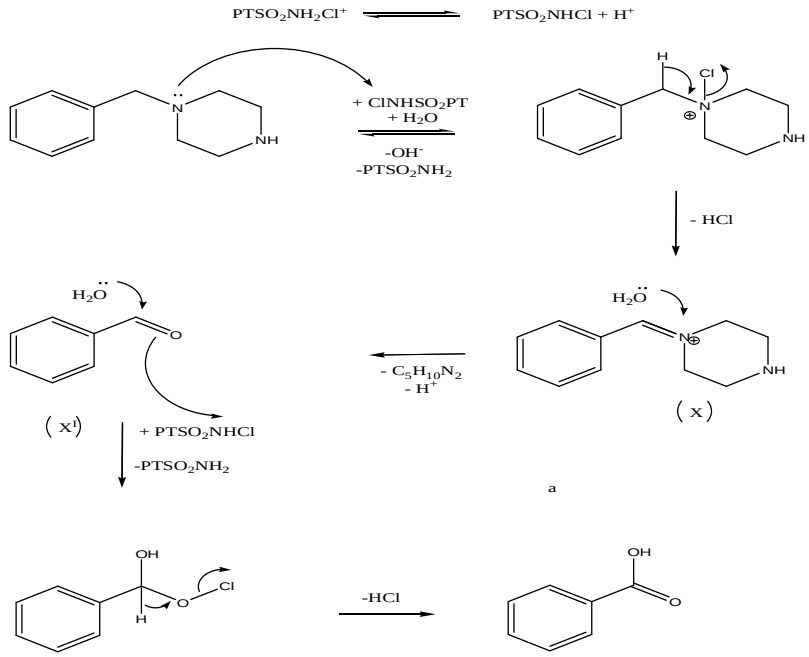
Dielectric constant of the medium was varied by adding methonol in different proportions (0 - 40 %, v/v). Plot of log k' versus 1/D has a negative slope indicating the presence of dipole-dipole interaction in the reaction[11]-[13]. The reduction product PTS has no influence on the rate indicating its non involvement in pre-equilibrium. The change in ionic strength of the medium fails to influence the rate indicating the involvement of non-ionic species in the rate limiting step. Halide ions also have no significant effect on the rate of reaction. Further the proposed mechanism is supported by computed thermodynamic parameters. Entropy of activation has large negative value. Free energy of activation and enthalpy of activation have moderate positive values. This indicate the formation of properly ordered compact transition state complex with less degrees of freedom.



Scheme-2

VI. CONCLUSION

The CAT-BZP redox reaction has been carried out in aques $HClO_4$ medium. The stoichiometry of reaction involvled is 2:1 (equation 1). The oxidation products are piperazine and benzoic acid. The effect of dielectric constant of medium and halide ions on rate were studied. From Arrhenius plots the activation parameters, Ea, $\Delta H^{\neq}$, $\Delta G^{\neq}$, and $\Delta S^{\neq}$, have been computed. A mechanism consistent has been proposed for the observed parameters and rate law is derived.

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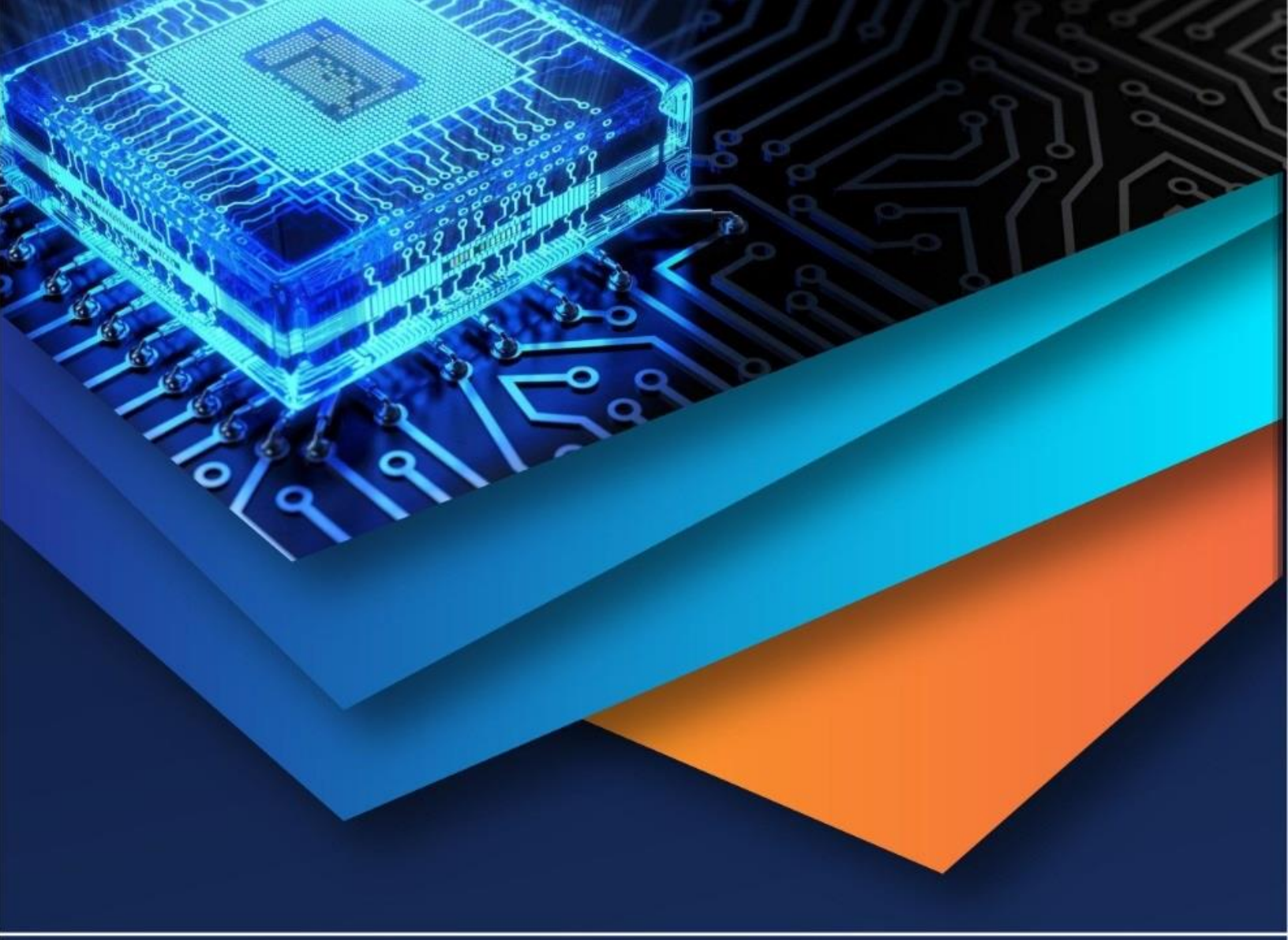

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