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RESEARCH PAPER

Synthesis, Kinetics, Reaction Mechanism and Biological Activity Studies of Novel 1, 3-Oxazine Compound

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A B S T R A C T:

A novel 1, 3-Oxazine compound ((E)-8-benzylidene-2-(4-methoxyphenyl)-3,4-diphenyl -3,4,5,6,7,8-hexahydro-2H-benzo[e][1,3]oxazine) was synthesized by reaction of N-(4-methoxybenzylidene)aniline(Schiff base) with 2,6-di((E)-benzylidene)cyclohexan-1-one(chalcone). The structure of 1, 3-Oxazine compound was characterized through spectral data (FT-IR, 1H- NMR and Ultraviolet-Visible spectrophotometer). The kinetics study of the novel synthesized 1, 3-Oxazine compound was studied to determine the order of the reaction and the mechanism pathway. It was found that the reaction is first order undergoes via (imino-Diels-Alder). The reaction rate, Arrhenius factor (A), thermodynamic functions (E_a (free energy of activation), $\Delta S^{\#}$(entropy of activation), and $\Delta G^{\#}$ (Gibbs energy of activation)) were also calculated and confirmed the formation of 1, 3-Oxazine cycle. Finally, the antibacterial activities against gram negative (*Escherichia coli*) with gram positive (*Staphylococcus aureus*) were evaluated optical density for finding minimum inhibition concentration (MIC).

KEY WORDS: *Schiff base, Chalcone, Oxazine, Kinetics, Rate Constant, Thermodynamic Functions, Biological Activity*.
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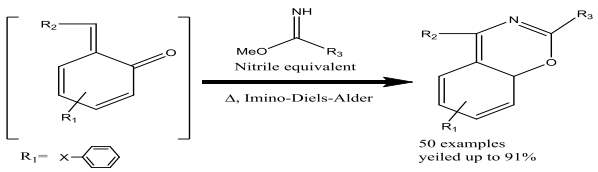
1. INTRODUCTION:

Oxazines are a type of heterocyclic compound that consist of one oxygen and one nitrogen atom within a double unsaturated six-membered ring. They are classified based on the location of the heteroatom and the double bond in relation to it. These compounds are commonly used as reagents in the Myers synthesis of aldehydes and as dyes such as Nile Red and Nile Blue, which are based on aromatic benzophenoxazines. Additionally, natural dioxazines such as Cinnamic and cinnamic acid can be derived from the biodegradation of tryptophan (Eicher et al., 2013, Stone et al., 2013). The synthesis of Oxazine often employs the use of Imino-Diels−Alder type reactions to form the cycle



Scheme 1. Reaction pathway for product of substituted 1,3-benzoxazines

The biological activities of Oxazine derivatives have been recognized in recent years as substantial synthetic intermediates in sedative, analgesic, anticonvulsant, antipyretic, antibacterial, antitubercular, antimalarial, antioxidant and anticancer properties. However, drug resistance can decrease a drug's effectiveness in treating disease. Oxazine compounds have been found to have in vitro anti-inflammatory activity using the bovine serum albumin with protease method, and

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their antioxidant activity was assessed using the diphenyl picryl hydrazide with nitric oxide method. Therefore, it is important to discover new classes of chemicals with effective mechanisms (Osipov et al., 2018, Chaitra and Rohini, 2018, Zinad et al., 2020, Doherty et al., 1995, Ananthula et al., 2014, Sabre, 2022, D'Andrea et al., 2005). The kinetics of the 2-methyl-5,6-dihydro-4H-1,3-oxazine (MeOZI) isomerization polymerization initiated by methyl tosylate (MeOTs) and methyl iodide (MeI) in nitrobenzene as a solvent have been described by Saegusa and colleagues. They used 1H-NMR spectroscopy to directly measure concentrations of monomer, initiator, and propagating species, which served as the basis for the kinetic analysis. The activation parameters of propagation and rate constants of initiation (k_i) and rate of propagation (k) were estimated. The reactivity of the MeOZI's was compared to other cyclic imino ethers with five and six members, and it was found that the polymerization of OZI continued via the oxazinium propagation species regardless of the initiator. The ring-opening isomerization polymerization of unsubstituted (OZI) using high-resolution NMR spectroscopy was also confirmed (Saegusa et al., 1974b, Saegusa et al., 1974a, Favaro et al., 1995).

Another study focuses on the synthesis of various compounds known as 5-(2H-tetrazol-5-yl)-4-thioxo-2-(substituted phenyl)-4,5-dihydro-1,3-oxazin-6-ones. The protocol used is a new, efficient, and simple method for creating these novel structures which have important 1,3-oxazine and tetrazole motifs. The reaction process and rate constants at different temperatures are examined, as well as the effects of acid and base on the reaction. The kinetics of the process are also analyzed, specifically the dispersive kinetics development and the blaze intensities in the nW to μW/cm2 range for the oxazine 720 dye in glycerol lorgnette and polyvinyl intoxicating polymer films(Qamar et al., 2019, Deng et al., 2014, Kenney et al., 1990). The study also looks at the synthesis of benzoxazines from phenols, primary amines, and formaldehyde, specifically the reaction of 2-phenylaminomethylphenol (Mannich-base) with formaldehyde in homogeneous dioxane/water solutions(Qamar et al., 2019, Deng et al., 2014, Kenney et al., 1990).

This study investigates the kinetics of a novel 1,3-Oxazine synthesized from the reaction of Chalcone with Schiff base, including the reaction rate, rate constant, and stability of the activating compound, as well as proposing a suitable mechanism for the reaction which is the Imino-Diels-Alder route.

The study also examines the biological activity of the synthesized 1, 3-Oxazine compound, specifically its antibacterial performance against gram-positive and negative bacteria using minimum inhibition concentration (MIC).

2. Experimental

The infrared spectra for the synthesis of 1, 3-Oxazine were obtained using a Fourier-transform IR spectrophotometer at the research center at the Faculty of Science and Health at Koya University. The UV-Visible spectra were determined using an Agilent Cary-100 instrument at the Chemistry Department at the same university. Nuclear Magnetic Resonance spectra were recorded using a BRUKER 400.133MHz spectrometer at Basrah University, with Dimethyl sulfoxide (DMSO) solvent as the medium. The instrument used to measure the optical density for biological activities was a BIOTEK-ELX800.

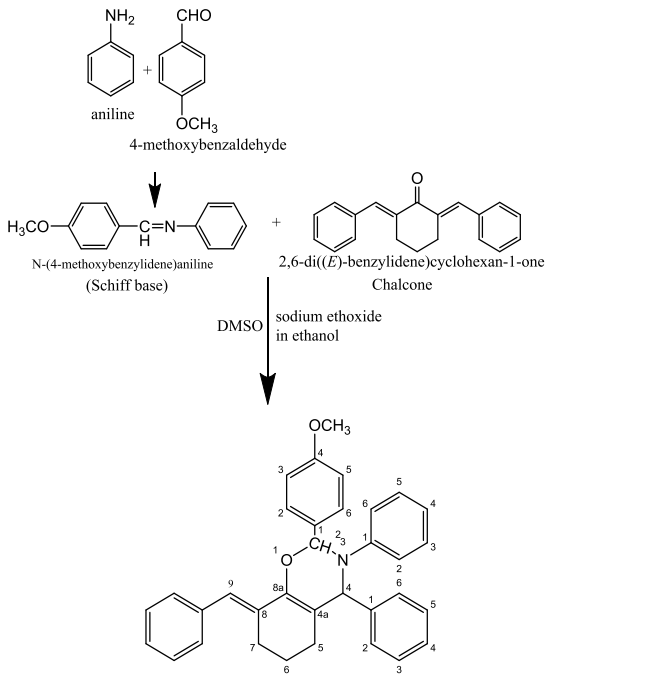
2.1. General Procedure

2.1.1. Preparation of N-(4-methoxybenzylidene)aniline (Schiff base)

The Schiff base were synthesized by mixing 1:1 mole ratio of aniline with 4-methoxybenzaldehyde and refluxed according to standard procedures (Batista et al., 2017).

2.1.2. preparation of 1, 3-Oxazine compound

1, 3-oxazine product ((E)-8-benzylidene-2-(4-methoxyphenyl)-3,4-diphenyl-3,4,5,6,7,8-hexahydro-2Hbenzo[e][1,3]Oxazine), yield (67%), (melting point (m.p. 82-83oC)) (red to black colour) were synthesized by dissolving (1mmole, 0.27g) of Chalcone (yellow colour) in Dimethyl sulfoxide (DMSO) as a solvent in a round bottom flask, then addition of a solution of (50% Sodium ethoxide in ethanol) and stirred for 10 minutes. The Schiff base were prepared compound N-(4-methoxybenzylidene)aniline (Schiff base) ((1mmole, 0.21g) (white colour) was then added and refluxed for 24 h, a new gelatinous precipitate was appeared, vacuumed until 12h then crushed and recrystallized from ethanol.



Scheme 2. Reaction pathway for products of Oxazine compound

An Agilent Cary100 UV-Visible spectrophotometer was utilized to measure changes in absorbance at a fixed wavelength. The device was equipped with a quartz cuvette and a Teflon quick fit stopper to hold the sample at a constant temperature. A temperature controller and built-in pump were used to maintain a consistent water circulation rate. Insulation on the pipe connections ensured that temperature fluctuations in the reaction cell were minimal. The study examined the kinetics of a reaction between Chalcone and Schiff base in DMSO and a basic medium of 10% sodium ethoxide in ethanol as a solvent (Kaka et al., 2019). The concentration of the Schiff base was 100 times greater than the concentration of Chalcone. The reaction was monitored at different temperatures (25, 35 and 45 degrees Celsius) and the absorbance was recorded at a wavelength of 350 nm. The color of the mixture changed from yellow to red to black as the reaction progressed and the rate constant was calculated using a linear regression program, as it is expressed in equation (1):

$$\ln \frac{A_o - A_\infty}{A_t - A_\infty} = k\ t \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (1)$$

Where:

A_o= Chalcone absorbance at time zero.

A_t= Chalcone absorbance at different time.

A_∞= Chalcone absorbance after reaction complete (when absorbance became constant) or at infinity concentration.

k = Rate constant of pseudo-first-order of the reaction.

Rate $=k^-[\text{Chalcone}]^n$; n= Chalcone Order as a pseudo-first-order; $k^- = k[\text{Schiff base}]$.

3. RESULTS AND DISCUSSION

The synthesis of 1, 3-Oxazine Compound was achieved by mixing 1 mmole of Chalcone with 1 mmole of Schiff base in DMSO as the solvent and 50% sodium ethylate as the basic medium. Absolute ethanol was also used as a solvent. The structure of the synthesized compound was confirmed through various spectroscopic techniques such as FT-IR, UV-Vis spectrophotometer, and 1H-NMR. The FT-IR spectrum of the 1, 3-Oxazine Compound displayed strong bands at 1244cm-1 and 1175cm-1, which were attributed to C-N stretching vibrations and C-O-C groups respectively. The C-H aryl stretching vibrations were observed near 3026cm-1 and the C-H alkyl stretching vibrations were observed near 2913cm-1. The C=C for the inside and outside the cyclohexanone ring were found to be 1603 and 1653 cm-1 respectively, as shown in Figure 1.

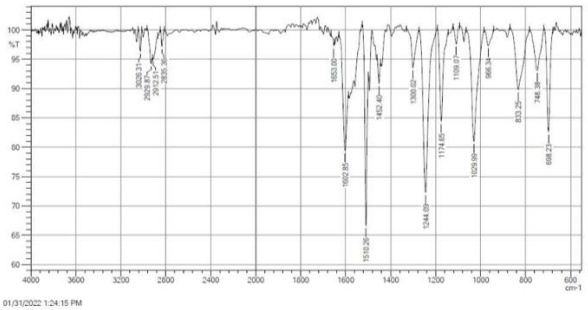


Figure 1. Infrared (IR) spectrum for the 1, 3-Oxazine compound

The ultraviolet absorption spectrum showed a maximum absorption λ_{max} in nm, as shown in the Table 1 and Figure 2

Table 1. Lambda max (λ_{max}) for all reactants and product in DMSO solvent

Compounds	Chalcone	Schiff base	1, 3-Oxazine	Sodium ethoxide in ethanol	DMSO in ethanol
Lambda max λ_{max} (nm)	350	280	263	202	0

The table above indicated the Lambda max (λ_{max}) for all reactant and product, shown that the reactant especially (Chalcone) have a value 350nm which is far from each Schiff base and 1, 3-Oxazine (product) (no interface). Therefore, kinetically studied and determined the rate and reaction order as shown in the figure below.

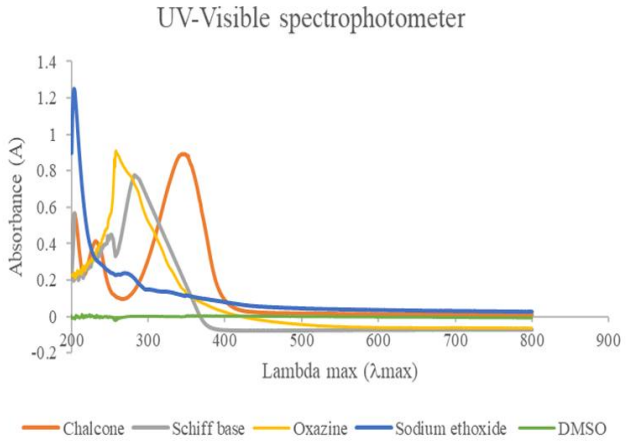


Figure 2. Ultraviolet (UV-Visible) spectra for Chalcone, Schiff base, sodium ethoxide and 1, 3-Oxazine compound in DMSO (each was singly measured)

The ^{1}H-NMR showed a quintet signal at δ=1.406 ppm of the C-H protons of the cyclohexanone at 6 position, while C-H in (5 and 7) position showed a triplet signal at δ (2.493-2.599) ppm, C-H of methoxide position near to 4 of benzene showed a singlet signal at δ3.851ppm, at position (4) of oxzine ring the (C-H) showed a singlet signal per proton at δ4.255ppm, at position (2) of oxzine ring the (C-H) showed a singlet signal for the proton at δ5.707ppm, at position (9) the (C-H) next to double bond outside the cyclohexanone showed a single signal per proton at δ6.305ppm and the (Ar-H) showed multiplet signal for the aromatic protons between δ7.129-8.012ppm as shown in figure 3.

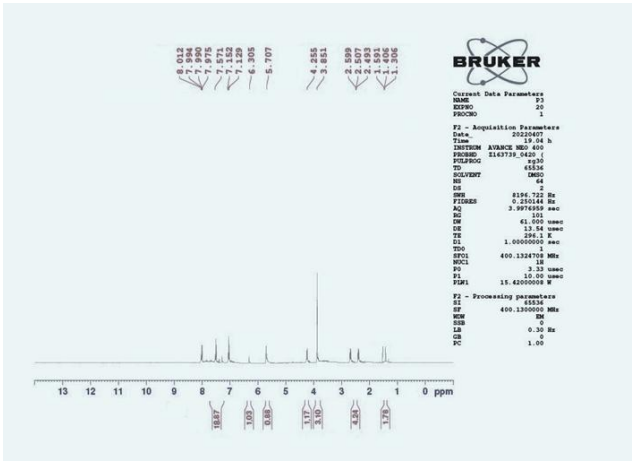


Figure 3. ^{1}H-NMR for 1, 3-Oxazine compound

3.1. Kinetic study of addition of Chalcone to Schiff base:

The purpose of this study is to investigate the dynamics of adding a Schiff base to Chalcone in order to comprehend the effect on reaction speeds and the stability of the activated complex. The data collected will assist in proposing a ring closure mechanism that occurs under moderate conditions. The research employs UV-Visible spectroscopy to monitor the decline in absorbance of the Chalcone reactant, which has a maximum wavelength of 350nm. The band of the Chalcone does not interfere with the bands of the Schiff base or the final product, the 1, 3-Oxazine compound. The decline in absorbance of the Chalcone relates to the remaining concentration of the reactants. Ethanol and DMSO were determined to be appropriate solvents for the kinetic measurements and the reaction was found to be slow. Efforts were made to identify an appropriate concentration range of reactants that comply with Beer-Lambert's law. A ratio of 1:100 [Chalcone: Schiff base] was determined to be appropriate and used in all measurements. Table 1 displays the λmax of the Chalcone, Schiff base, and 1, 3-Oxazine compound. A full scan of the reaction spectrum was initially performed to select a suitable wavelength for kinetic measurements, as shown in Figure 2.

3.2. Stoichiometry:

The adequate range of temperatures for the rate measurements of the reaction was found to be in the range between (298.15-318.15) K. Runs were carried out within this range. Kinetic measurements at early stages of the work showed that, the reaction is a total second order under study, first order with respect to each of Chalcone

and Schiff base, but in my studied show the pseudo first order for the chalcone. The product structure was confirmed by IR and ^{1}H-NMR as shown in the organic section. These observations indicate that the addition reaction clearly proceeds according to a simple stoichiometry of the reaction. Which was shown in scheme 2. The decreases in absorbance with time for the Chalcone during their reactions with the Schiff base.at fixed. different temperatures are shown in the following figure 4.

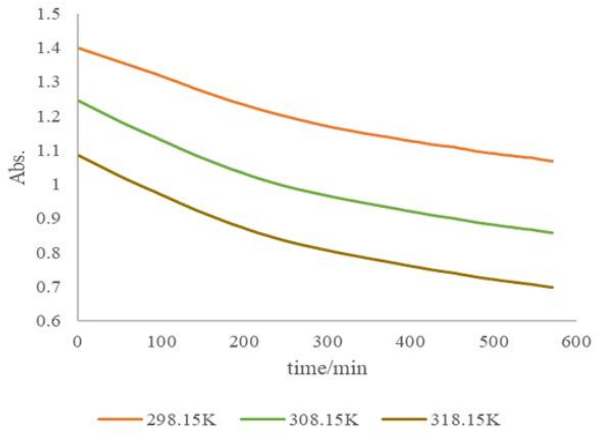


Figure 4. Decrease of absorbance with time for reaction. of Chalcone. with Schiff base in DMSO at different temperatures.

3.3. The rate equations:

As in the kinetic study of the reaction of Chalcone with Schiff base to produced 1, 3-Oxazine compound, a pseudo-first-order. reaction was considered using large excess of Schiff base (100. fold compared to Chalcone concentration.) and followed the decrease of absorbance of the Chalcone with time. Therefore, treated the obtained data using equation-1.

Plots of $\ln \frac{A_o - A_\infty}{A_t - A_\infty}$ vs. time which is always straight. lines with slopes that correspond to k, the equation (1) was applied for a mixture. of Chalcone concentration. of (0.001 mmole/l) and large amount of Schiff base (100 fold) (0.1mmole/l) for reaction under study and lead to straight lines with reasonable reaction rates even when different temperatures were used.

3.4. Rates of reaction at different. temperatures:

Numerous runs were carried out at various temperatures, and measurements were always kept up until the reaction was finished. Typical plots exhibit excellent fit to equation (1) and were always linear as shown in the following figure 5. Thus the assumption of pseudo-first-order of reaction was fully proven.

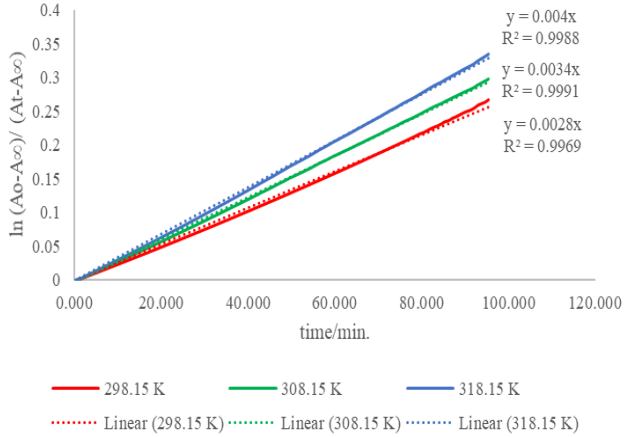


Figure 5. Pseudo-first-order plot for reaction. of Chalcone with. Schiff base in DMSO at different temperatures.

The observed. rate constants, were calculated. from the linear slope of equation (1), the standard deviation of the slope. of a plot also represents, the uncertainity which. is due to the scatter of. points about the regression line and is thus. a measure of the reproducibility. of the result rather than its. absolute accuracy.

Table 2. Observed rate constants. for the reaction of Chalcone with Schiff base obtained. from kinetic. plots at different temperatures.

Temperature K	10^5 k / s^{-1}	$t_{1/2}$ (sec.)	R^2	10^1 s.d. / s^{-1}
298.15	4.7	14745	0.9969	0.0028
308.15	5.7	12158	0.9991	0.0017
318.15	6.7	10343	0.9988	0.0024

The process of plotting lnk using data listed in tables 2 and the inverse of absolute temperature in the range of 298.15 to 318.15K was performed and resulted in straight lines. The least-square method was utilized to plot A-Factor equations, treating the mean rate-constants at each temperature as a single point with a unit weight, utilizing Microsoft excel 2019. The outcomes are recorded in table 3. The entropy of activation also provides insight into the shape of the activated complex and therefore, the mechanistic pathway. The $\Delta S^{\#}$ are calculated from the Arrhenius factor (A-Factor) at 308.15K according to equation (2).

$$A = \frac{e2k_BT}{h} e^{\Delta S^{\#}/R} \quad \text{.....(2)}$$

Where:

A Arrhenius .factor.

R Gas constant. Which is 8.314 J/K mol.

$\Delta S^{\#}$ Entropy of activation. J/K mol.

kB Boltzmann's constant .(1.381 x 10^{-23} J/K).

T Absolute .temperature in Kelvin (K).

h Planck's constant .(6.626 x 10^{-34} Js).

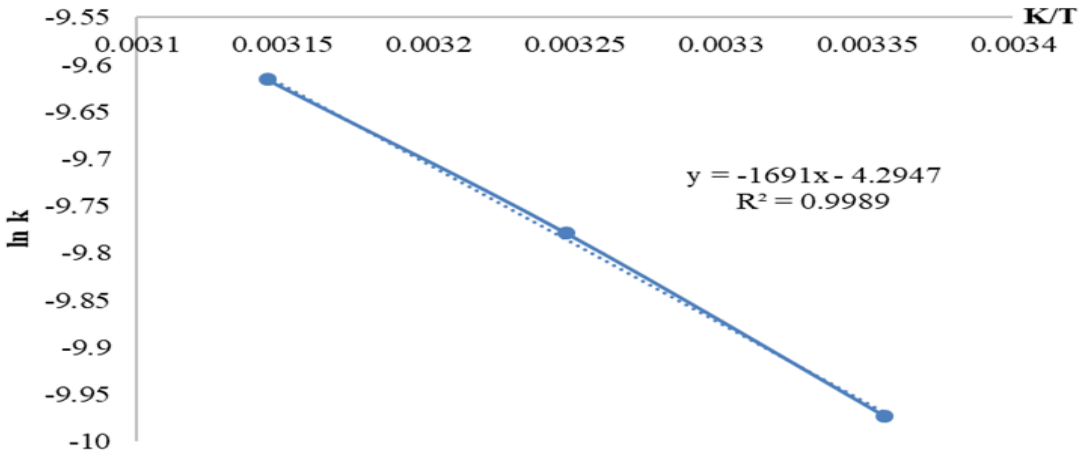


Figure 6. Arrhenius plots for the reaction Chalcone with. Schiff base in DMSO as a solvent.

Table 3. Energy of activation, Arrhenius parameters, entropies of activation, and Gibbs free energy of activation for produced 1, 3-Oxazine compound

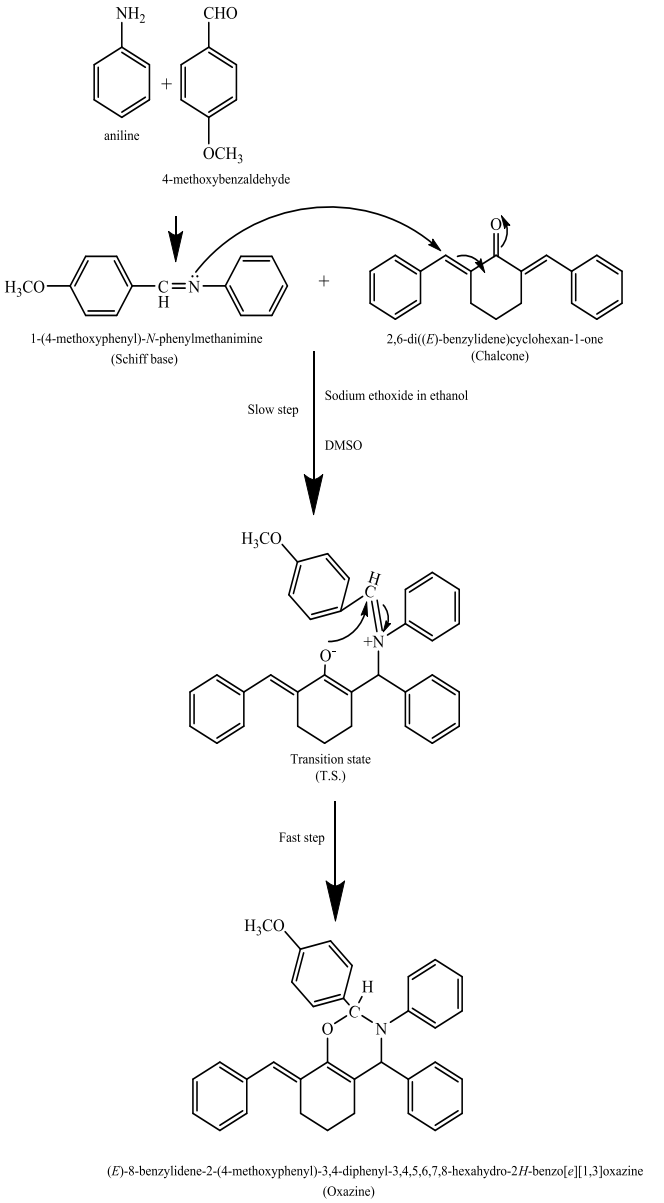
Compound	E_a / kJ.mol^{-1}	A / s^{-1}	$-\Delta S^{\#}$ / J.K^{-1}.mol^{-1}	$\Delta G^{\#}$ / kJ.mol^{-1}
Chalcone with Schiff base as transition state before produced 1, 3-Oxazine compound	14.060	13.641	297.5332	105.744

The Ea, or activation energy, for fast reactions is typically lower than that of reactions with a slower rate. This can be explained by the way in which the nucleophile attacks the partially positive reaction center. It is worth noting that the parent nucleophile only requires 14.060 kJ/mol to react quickly, as seen in equation 2, when the value of (A) approximately $10^{13.5}$ s^{-1} which was corresponding to $\Delta S^{\#}=0$. However, a decrease in this value leads to a negative activation entropy. The negative value of the $\Delta S^{\#}$ in the reaction of Chalcone with a Schiff base nucleophile, as seen in table 3, suggests that the transition state is restricted due to ring closure and lacks certain degrees of freedom compared to the reactants (Babbagh, 2022). The decrease in the Arrhenius-factor value is an indication of the stability of the transition state and helps explain the differences in the reaction rate and/or rate constants.

The Gibbs free energy change, $\Delta G^{\#}$ of a compound binding reaction can be written as:

$$\Delta G^{\#}=\Delta H^{\#}-T\Delta S^{\#} \quad \text{.....(3)}$$

The enthalpic contribution, represented by $\Delta H^{\#}$ or (Ea), and the entropic contribution, represented by $-T\Delta S^{\#}$, are used to measure the binding at the activated state in thermodynamics. The enthalpic component measures the change in heat associated with binding, while the entropic component measures the change in disorder of the overall system. Plotting the relationship between $\Delta H\#$ and $-T\Delta S^{\#}$ can reveal the effect of the electronegativity of the reaction center and indicate whether an external energy input is required for the reaction to occur (as a positive $\Delta G^{\#}$). Additionally, the values of the rate constant, Arrhenius parameter, Gibbs free energy of activation, and negative activation entropies are consistent with the proposed mechanistic route.



Scheme 3. The Mechanism proposed through Imino-Diels-Alder pathway

4. CONCLUSIONS

This study investigated the speed and specific process of the reaction between Chalcone and Schiff base to create the 1, 3-Oxazine compound. The reaction is a first-order with both reactants and involves a Imino-Diels-Alder reaction. The energy needed to activate the reaction was discovered to be low, which can be attributed to the nucleophile attacking the partially positive reaction center. It is noteworthy that the parent nucleophile only needs 14.060 kJ/mol to react quickly. The small values of the A-factor and the negative value of the $\Delta S^{\#}$ of the reaction between Chalcone and Schiff base suggest that the transition state is limited due to ring closure and has less degrees of freedom compared to the reactants. This supports the presence of electron density at the reaction center. Lastly, it was found that the 1, 3-Oxazine compound was more effective against *Staphylococcus aureus* at 25 ppm than against *Escherichia coli* at 50 ppm in terms of bactericidal activity.

5. Biological activity

Antibiotic resistance has been linked to antibiotic misuse in hospitals and communities, increased antibiotic use in the food industry, and an absence of specific medications to treat an increasing number of at-risk patients who have various co-morbidities Antimicrobial resistance is no longer limited to bacteria isolated in a hospital environment. The prevalence of multidrug-resistant bacteria in outpatients is rising, even in those with no established risk factors for antimicrobial agent resistance(Yum et al., 2002). It has been reported that Oxazine derivatives contain a variety of biological actions, including antibacterial and anticoagulant properties, anticancer and anti-inflammatory properties. (Li et al., 2008, Mathew et al., 2010). This study intends to investigate the antibacterial activity of 1, 3-Oxazine against *Staphylococcus aureus* as representative of the gram-positive bacterial group and *Escherichia coli* as representative of the gram-negative bacterial group.

5.1. Procedure

To determine the antibacterial activity of 1, 3-Oxazine against *Staphylococcus aureus* (*S. aureus*) and *Escherichia coli* (*E. coli*), the microdilution technique was carried out using 96-well microtiter plates with a flat bottom were used for this test.

Overnight cultures of *E. coli* and *S. aureus* in nutrient broth were adjusted approximately to $1x10^8$ CFU/ mL. 100 µL of Luria-Bertani (LB) media was dispensed into a microtiter plate well then 100 µL of 1, 3-Oxazine was added (100 ppm) to it. Two-fold serial dilution was prepared from the original well as follows; 100, 50, 25, 12.5, 6.25, 3.125, 1.5625, 0.78125 and 0.390625 ppm. The positive control contained the tested bacteria and DMSO. The negative control contained just DMSO. Finally, streptomycin (0.1 mg/ml) as antibiotic standard control. 5 µL of the overnight bacterial culture was added to all the wells except the negative control (well number 11). The microtiter plate was incubated for 24 hours at 37 ºC. The optical density (OD) was read by a plate reader (BIOTEK-ELX800) at 630 nm, and the minimum inhibitory concentration (MIC) was calculated, which is the lowest concentration of agents that kills 50% of the tested bacteria. This experiment was done in triplicate.

Table 4. Biological Activities for 1, 3-Oxazine

Conc.	1			2			3			4			5			6			7			8			9			10			11			12
	100 ppm			50 ppm			25 ppm			12.5 ppm			6.25 ppm			3.125 ppm			1.562 ppm			0.781 ppm			0.39 ppm			Positive Control			Negative Control			Streptomycin antibiotic
	A	BLK	Cal	A	BLK	Cal	A	BLK	Cal	A	BLK	Cal	A	BLK	Cal	A	BLK	Cal	A	BLK	Cal	A	BLK	Cal	A	BLK	Cal	A	BLK	Cal	A	BLK	Cal	Cal
Staphylococcus aureus	0.656	0.6495	0.0065	0.132	0.125	0.0004	0.094	0.0815	0.0125	0.258	0.059	0.199	0.291	0.051	0.24	0.289	0.0455	0.2435	0.289	0.041	0.248	0.303	0.0435	0.2595	0.327	0.0445	0.2825	0.340	0.0435	0.2965	0.039	0.0405	0.0015	0.0333
Escherichia coli	0.655	0.6495	0.0055	0.161	0.125	0.037	0.471	0.0815	0.3895	0.470	0.059	0.411	0.52	0.051	0.469	0.531	0.0455	0.4855	0.550	0.047	0.503	0.561	0.0435	0.5165	0.545	0.0445	0.5005	0.553	0.0435	0.5095	0.044	0.0405	0.0035	0.0381

A= Absorbance, BLK= blank, Cal = Calculated (Cal=A-BLK)

5.2. RESULTS

The effectiveness of a prepared 1, 3-Oxazine compound at 100 ppm was evaluated by analyzing its ability to inhibit the growth of *S. aureus* and *E. coli.* The minimal inhibitory concentration (MIC) was determined by testing different concentrations of 1, 3-Oxazine. The study revealed the impact of varying amounts of the 1, 3-Oxazine compound on the percentage of bacterial growth. The results indicated that 1, 3-Oxazine was more efficient in stopping the growth of *S. aureus* than *E. coli.* At a concentration of 25 ppm, all bacterial growth of *S. aureus* was halted, as shown in table 4. Additionally, 1, 3-Oxazine was found to be effective against *E. coli* at a concentration of 50 ppm, resulting in 100% inhibition of bacterial growth.

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