Asian Journal of Chemistry; Vol. 28, No. 4 (2016), 765-770

ASIAN JOURNAL OF CHEMISTRY

http://dx.doi.org/10.14233/ajchem.2016.19452

Kinetic Study on Chalcones and Schiff Base Proton Transfer Reactions

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Received: 2 July 2015; *Accepted*: 7 September 2015; *Published online*: 30 December 2015; AJC-17688

The rate of kinetics reaction of Schiff bases [N-(4-nitrobenzylidene-1-phenyl methanamine)] [N-(4-bromobenzylidene-1-phenyl methanamine)] and their derivatives with chalcone (2-benzylidine-1-tetralone) are investigated in this work. These compounds were prepared *via* Claisen-Schmidt condensation of drug ketones and the appropriate benzaldehyde derivative to form spiropyrrolidine. The kinetics was studied using spectrophotometer in dichloroethane as a solvent. The study was carried out in liquid phase using several techniques to follow the rates of the mechanistic; first step, the formation of the intermediate was followed by spectroscopic analysis. This study indicated a pseudo first order dependence with reaction rates of furan ring > H > *p*-NO_2 at any temperature range from 293 to 333 K. The second step involves measurement the rate of its cyclization to form the product. The reaction kinetics was monitored using spectrophotometer indicating a first order dependence with sequence of *p*-NO_2 > H > furan ring. A suitable mechanism for this type of reaction was proposed. The kinetic study provides information about the formation of the intermediate and cyclic process. Moreover, the calculated activation parameters and entropies of activation are used to support the proposed mechanism.

Keywords: Activation parameters, Spiropyrrolidine, Chalcone.

INTRODUCTION

Chalcones are one of the major classes of natural products, with widespread distribution in fruits, vegetables, spices, tea and soya based food stuff, which have been recently subjected to great interest for their interesting pharmacological activates [1]. Chalcone is a common natural pigment and considered as an important intermediate compound in the biosynthesis of flavone which is also known as anthoxanthin yellow pigment in the plant kingdom [2,3]. Chalcones are also present in normal human diet and represent one of the most important and interesting classes of biologically active compounds. Chalcones open chain (1,3-diaryl-2-propen-1-one) constitutes a class of naturally occurring and synthetic compounds. The first intermediate of flavonoid biosynthesis occurs sporadically in which they are located [4].

Numbers of naturally occurring chalcones are poly-hydroxylated in the aryl rings. The radical quenching properties of the phenolic groups present in many chalcones have been raised interest using the compounds or chalcone rich plant extracts as drug or food preservatives [5,6]. Chalcones and their derivatives hold a special place among pharmaceutically significant natural products and synthetic compounds [7,8].

Chalcones are very attractive starting material in combinatorial chemistry since years ago which are easy to prepare with large variability at the two aromatic rings and the enone provides a bifunctional site for 1,3-dinucleophiles affording several heterocyclic ring system[9,10]. Chalcones have been generally prepared through the crossed aldol condensation or Claisen-Schmidt condensation *via* the reaction between ketones that have two α hydrogen with appropriate aldehyde in the presence of bases. It has been reported that both naturally and synthetic chalcones possess a wide spectrum of biological activity which includes antimalarial, antibacterial, antioxidative, antifungal, antiflammatory [11,12]. However, arylidene cyclanones are frequently used as an α,β-unsaturated carbonyl compounds. Their most important synthesis is based on the reaction of the appropriate cyclic ketone with aldehydes, *via* the well known aldol reaction [13].

Kinetic study is great importance in understanding the nature of chalcone with Schiff base reaction in a flow kinetic for a bigger and important group of compound. The simplest type is naturally the first order case. Many kinetic systems involve highly reactive intermediates such as atoms or radicals within the reaction environment [14]. Moreover, the effect of temperature on reaction rate has been observed to increases

as the temperature is raised. The reaction molecules must bring to a level of collision at certain minimum threshold of activation energy in order to involve in reaction. In fact, the well-known increase in the rate of reaction, as the temperature rises, is due to the growing proportion of molecules with enough energy to react [15]. The entropy of activation ($\Delta S^{\neq}$) is the difference between the standard entropy of the activation complex and the standard entropy of the reactants in their ground states [16-20]. Furthermore, the solubility data were correlated against temperature and were found to increase with temperature. A thermodynamic parameters such as dissolution enthalpy (ΔH), Gibbs free energy (ΔG) and entropy (ΔS) of mixing have also been reported [21].

Chemical kinetics includes investigation of how different experimental conditions on the rate of a chemical reaction and yield information about the reactions mechanism and transition states are investigated in this work. It also provides the prediction construction of mathematical equations that can describe the characteristics of a chemical reactions [22,23].

In this study, a chalcone and their interaction with the Schiff bases were investigated *via* keeping the flow kinetic interactions between both reactant and the central challenge of their interaction were studied spectroscopicaly. The rate constant interaction and the account tidy interaction and study the effect of different temperature is presented. The interaction and activation energy *via* finding the coefficient is guided to calculate and study the effect of temperature on the various interactions. The activation energy and entropy were calculated depending on Arriunos constant.

EXPERIMENTAL

Chalcones solutions: Chalcone solution (10^{-3} M) was freshly prepared by dissolving the corresponding weight of the individual chalcone in a certain volume of dichloroethene and then raised to a 10 mL volume.

1 mL of this solution was used with 2 mL of other reactants in the reaction cell, so that its final concentration becomes (3.3×10^{-4} M), as required [24]. Analysis was performed using Shimadzu UV-visible spectrophotometer type T90. The temperature of the reaction cell was maintained constant temperature up to ± 0.1 °C.

Schiff base solutions: Schiff base solutions (10^{-2} M) were freshly prepared by dissolving the corresponding weight of the Schiff base in a certain volume of dichloroethene and then raised to a 10 mL volume. 1 mL of this solution was used with 2 mL of other reactants in the reaction cell, so that its final concentration becomes (3.3×10^{-3} M), as reported [25].

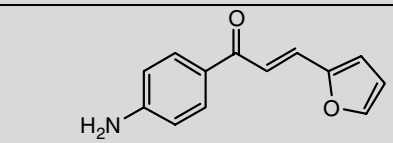
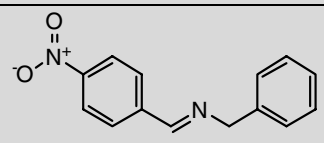
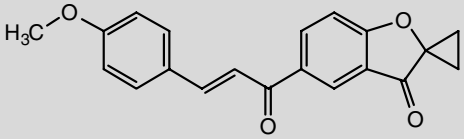
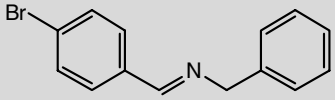
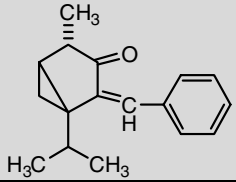
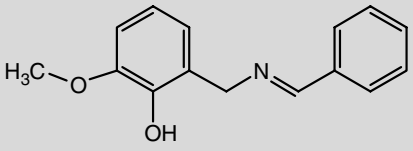
Kinetic study: The reaction rates were determined using spectrophotometric technique for the reaction between chalcones and Schiff bases in dichloroethane as solvent. The wavelength scan was λ_{max} (200-600 nm) depending on the substituted reactant used. The kinetic studies were carried out in 1 cm × 1 cm × 5 cm quartz cuvett. The cell was placed in the thermostated compartment at the desired temperature in the compartment Shimadzu UV-visible spectrophotometer. Prior to each kinetic run, the reaction components (chalcone, Schiff base and potassium hydroxide solutions) were placed separately in a thermostated box at the same temperature of the reaction cell, in order to bring all of them to the same reaction temperature.

The concentration of Schiff base used was always exactly 10 times as much as the chalcone concentration inside the reaction cell. Prior to starting each run, a mixture of 1 mL of 0.01 M potassium hydroxide and (1×10^{-3} M) chalcone was prepared in the reaction cell and kept thermostated at the required temperature. A solution of 1mL of (1×10^{-2}) M Schiff base was then added with instant vigorous shaking and placed inside the spectrophotometer cell immediately to start the kinetic run. The time was recorded automatically. Absorbance was recorded at fixed wavelength each 1-2 min as required. Repeated runs were always carried out (2-3) times to ensure of the consistency of measurements.

RESULTS AND DISCUSSION

Rate constant for formation of intermediate: The present work provides detailed information about the anionic cycloaddition of Schiff bases to chalcones as given in Table-1 and Fig. 1. The reaction background [26] and the present study

TABLE-1
MECHANISTIC ROUTE OF THE REACTION BETWEEN CHALCONES AND SCHIFF BASES UNDER STUDY SHOWING THEIR SUBSTITUTION ON PHENYL RING (X AND Y)

Chalcones		X	Schiff bases		Y
A1		Furan ring	B1		*p*-NO_2
A2		*p*-OCH_3	B2		*p*-Br
A3		*p*-H	B3		*p*-OCH

of these synthesis mechanism is presented. The structure of the transition state is proposed according to the most common rearrangements as suggested by Claisen and Wittig rearrangements with some modifications. The present study on natural product syntheses using a sigmatropic rearrangement is proposed to explain the selectivity of transition-state structures.

Kinetic order reaction of chalcone: The rates of these reactions were found to be sensitive to the temperature in the range between (20-60 °C). In our conventional experiments the temperature of the reaction mixture were held constant throughout the course of the reaction of each run.

The early investigation during the reaction course shows that only one mole of chalcone or its substituents reacted with one mole of the Schiff base or its substituents to give the product *via* the intermediate formation. No other products or side reaction were observed and the pyrolydine structure was confirmed [27,28].

Previous studies have shown that rate of reaction of (N-benzylidene-4-picolyamine) and its derivatives with chalcone (2-benzylidine-1-tetralone) in DMF by means of spectrophotometer were appeared in literature. The first study indicated the reaction rate is dependence on each of reactants. The effect of substituents on the reaction rate showed that electronic factors, inductive and resonance effects play a role on the stability of the intermediates. The kinetic studies for these reactions revealed that these reactions are nucleophilic addition type which characterized by the formation of intermediates in which transformed to the desired products. The suggested suitable rate laws and the calculation equations depend on of the proposed mechanisms interaction [15]. This proposal shows that the interaction depends on the concentrations of chalcone only which is considered a first order. In the cyclization process of the intermediate shows a linear relation when plotting of (eqn. 1), $\ln (A_t-A_\infty)$ *vs.* time within first order reaction as shown in Fig. 2. In contrast the linear curve was not obtained within second order reaction.

$$\ln (A_t-A_\infty) = Kt \quad (1)$$

This result obtained gaves strong evidence on the formation of the mentioned intermediate that converted to the product throughout unimolecular is first order cyclization reaction as presented in Fig. 2.

A typical runs of reaction toward completion is clearly demonstrated showing how the absorbance band of intermediate is completely disappeared with the time during the course of the reaction at any temperature, indicating that no equilibrium occurred at all between the intermediate and either of reactants or product as shown in Fig. 3.

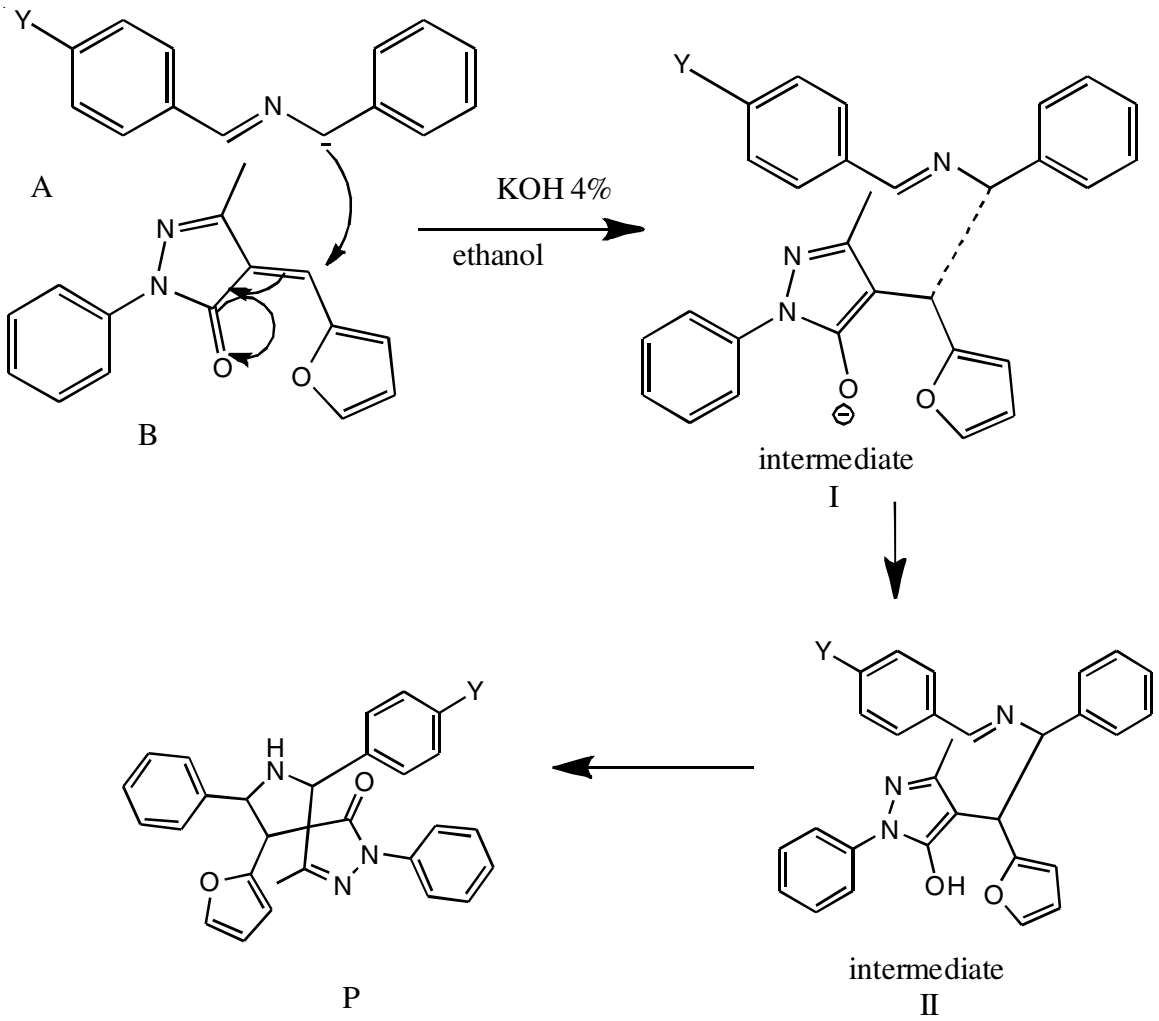


Fig. 1. Reaction between chalcone and Schiff bases *via* intermediate

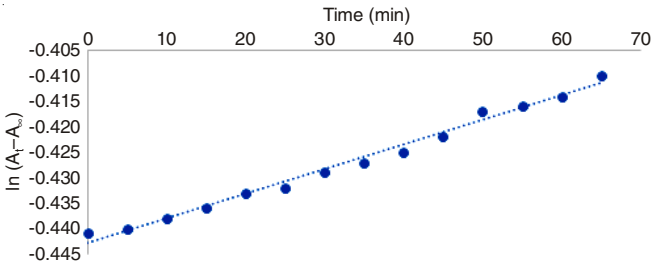


Fig. 2. First order plot for the reaction of chalcone A1 with the Schiff base B1 in dichloroethane at 20 °C using equimolar reactants

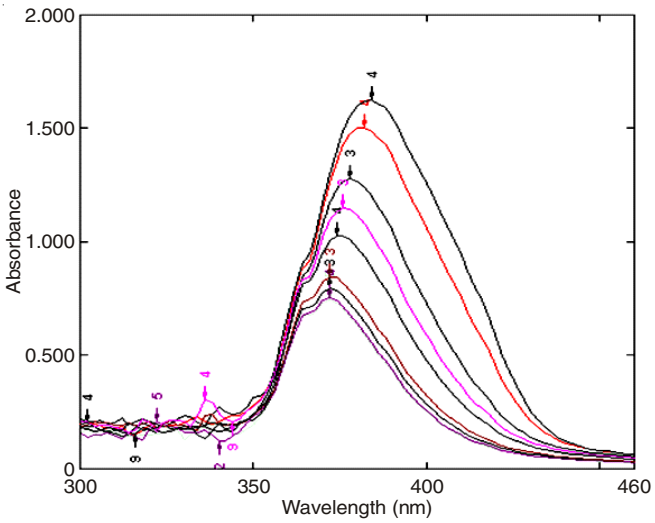
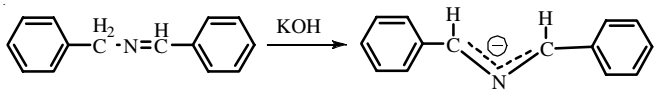


Fig. 3. Formation of the intermediate for the reaction between chalcone A1 and Schiff base B1 (λ = 368) at 20 °C

It was also noticed that the rate of formation of intermediates is much faster than their decay in a way that it cannot be followed kinetically using normal spectroscopic techniques. Therefore, using the UV spectra is adequate to measure the formation steps [15]. It was noticed that the Schiff base peak decreases as soon as potassium hydroxide was added. This was attributed to the formation of the anion as shown in equation [16].



Reaction at different temperatures: The reactions were carried out at different temperatures. Several runs were performed at each temperature and the measurements were always followed toward the completion of reactions. A typical plots shows a linear relations as shown in Fig. 4a-c up to at least $2t_{1/2}$ (75 %). Typical runs of reaction toward completion demonstrated clearly how the absorbance of the product increased with time during the course of the reaction at different temperatures indicating that no equilibrium occurred between the product and reactants within the studied time period. The kinetic measurements carried out at five different temperature (20, 30, 40, 50 and 60) °C and the measurements were always followed toward the completion of reactions. The assumption of pseudo-first order reaction was fully proved.

The observed rate constants, k were calculated from the slopes of eqn. 1 and are given in Table-2.

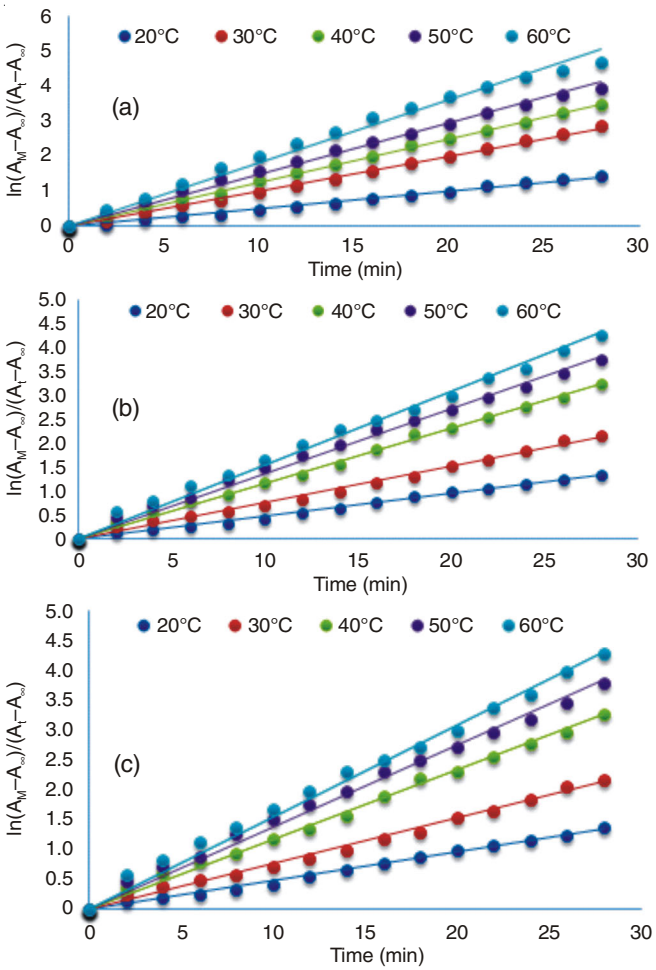


Fig. 4. First order plot for the cyclization of the intermediate from the reaction between chalcone A1 with the Schiff base, (a) B1, (b) B2, (c) B3 in dichloroethene at different temperatures

TABLE-2
OBSERVED RATE CONSTANTS FOR THE REACTION OF CHALCONES WITH SCHIFF BASE, OBTAINED FROM KINETIC PLOTS AT DIFFERENT TEMPERATURES

Temp. (°C)	10^3 k min^{-1}		
	B1	B2	B3
A1 with B1, B2, B3			
20	6.13	5.01	3.68
30	9.45	10.01	5.35
40	8.15	11.68	10.01
50	10.65	15.01	13.35
60	11.65	20.01	15.18
A2 with B1, B2, B3			
20	5.55	4.70	4.96
30	10.55	11.36	12.46
40	14.70	14.70	13.90
50	15.38	16.36	17.60
60	20.38	19.20	24.30
A3 with B1, B2, B3			
20	7.08	8.61	5.80
30	12.08	11.95	12.46
40	13.91	15.28	15.63
50	15.58	18.28	17.46
60	20.05	21.06	19.30

Variation of rate constant with temperatures: The rate of reaction between chalcone and Schiff base depends on the

variation in temperature. It is the most important key for the mechanistic description. It has been suggested by Arrhenius (eqn. 2) [17,18] that the molecule must acquire certain energy called the activation energy (E_a) before its react [19]:

$$k = Ae^{-E_a/RT} \quad \text{or} \quad \ln k = \ln A - \frac{E_a}{R}\frac{1}{T} \qquad (2)$$

This energy can simply be obtained by performing the logarithmic plot of the above equation. The linearity of the plot provides strong evidence for the consistence of the results. In fact, the reaction under this study is observed to be a consecutive reaction. It can be noticed that this reaction involves step require for the bond linkage between the chalcone and Schiff base. By measuring its rates of reactions at different temperatures enable us to measure their activation energy as shown in Figs. 5-7.

The plot of ln k using data listed in Table-3, *versus* reciprocal of absolute temperature (between 293-333 K) were carried out and were showed a straight lines. The least square method was used for plotting Arrhenius equations. Treating the mean rate constants at each temperature as a single point with unit weight has been considered. The results are tabulated in Table-3. The entropies of activation for the cyclization process also give good evidence about the shape of the intermediate during its cyclization to form the product and hence about the mechanistic pathway. The entropies of activation were estimated from the frequency factors, (A-factor), at mean reaction temperature of 303 K, according to the following equation [20].

$$\Delta S^{\neq} = R\left(\ln A - \ln\frac{ekT}{h}\right) \qquad (3)$$

where: k: Boltzman constant; h: Plank constant; T: reaction temperature.

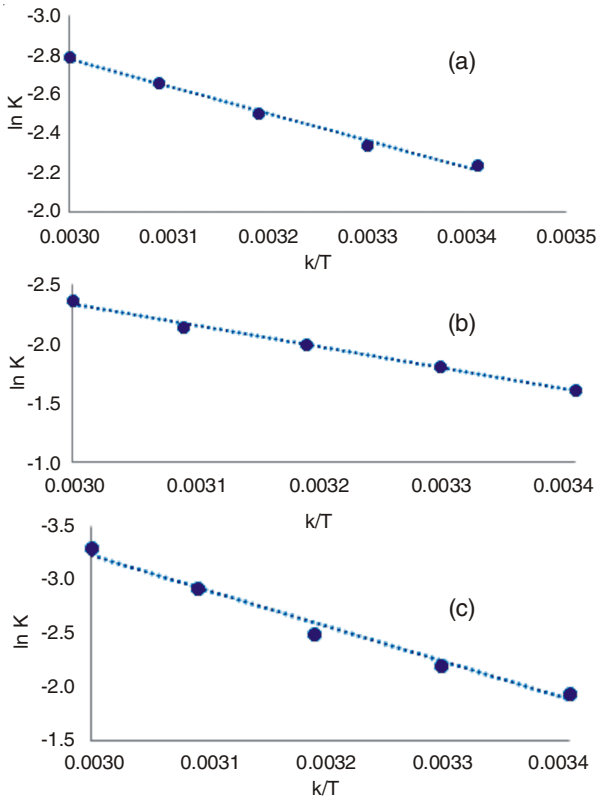


Fig. 5. Arrhenius plot for the cyclization of the intermediate for the reaction between chalcone A1 with the Schiff base (a) B1, (b) B2, (c) B3 in dichloroethane

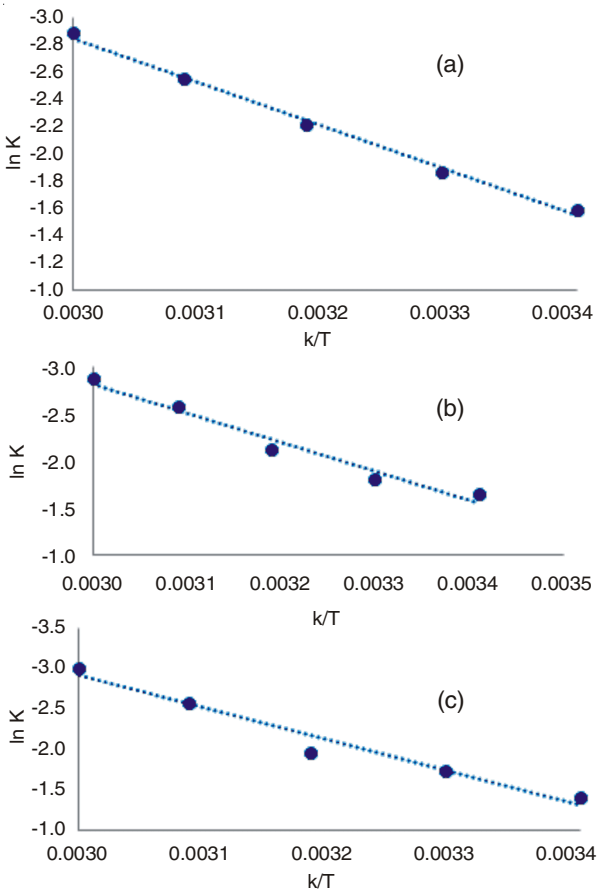


Fig. 6. Arrhenius plot for the cyclization of the intermediate for the reaction between chalcone A2 with the Schiff base (a) B1, (b) B2, (c) B3 in dichloroethane

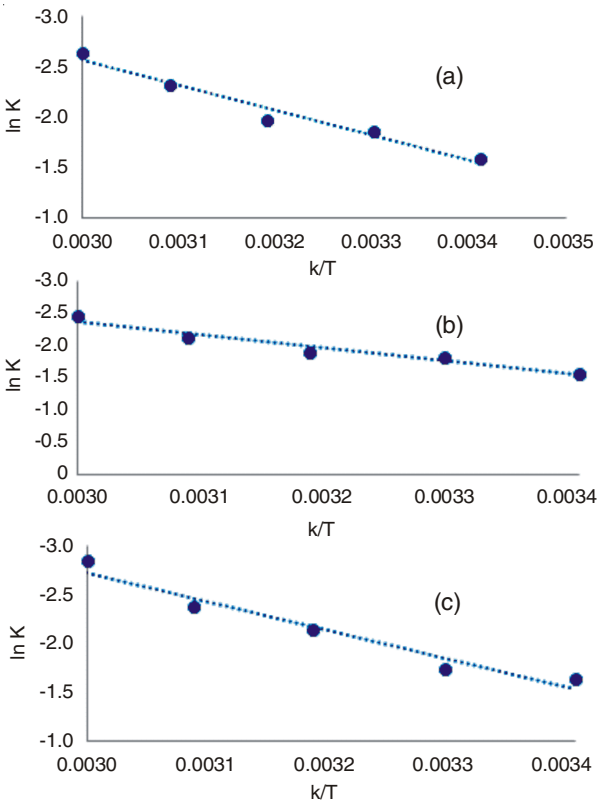


Fig. 7. Arrhenius plot for the cyclization of the intermediate for the reaction between chalcone A3 with the Schiff base (a) B1, (b) B2, (c) B3 in dichloroethane

TABLE-3
ARRHENIUS PARAMETERS AND ENTROPIES OF ACTIVATION FOR THE REACTION OF (A1, A2, A3) WITH SCHIFF BASE (B1, B2 AND B3)

Reaction between (chalcones + Schiff bases)	E (kJ mol^{-1})	A-factor (min^{-1})	DS^{1} (JK^{-1} mol^{-1} at 303 K)
A1 + B1	27.588	6.020×10^{3}	-501.551
A1 + B2	36.092	9.170×10^{3}	-77.287
A1 + B3	65.876	3.725×10^{5}	-31.976
A2 + B1	63.516	5.200×10^{3}	-44.281
A2 + B2	62.220	5.500×10^{3}	-46.775
A2 + B3	77.580	4.970×10^{4}	-413.31
A3 + B1	49.868	7.510×10^{3}	-625.429
A3 + B2	40.366	3.070×10^{4}	-256.288
A3 + B3	58.632	6.140×10^{5}	-52.096

Activation energies: In present work, the condensation process for all reactants was of low activation energies which vary within 27-77 kJ mol^{-1}. The variation of these values may be attributed to the electron donating or withdrawing capabilities of the attacked groups and to steric factor.

Our observations were focused on the cyclization process of the intermediate in order form the product. The intramolecular cyclization of the intermediate was found to go through a first order unimolecular process.

A unimolecular reaction is in principle the simplest kind of elementary reactions, since it involves the isomerization (including intermolecular cyclization) or decomposition of a single isolated reactant molecule through an activated complex which involves no other molecule. It is well known that these types of reactions are first order processes in the high concentration (or pressure) region of reactant. For all of the reported unimolecular cyclization processes, it was observed that they are of low Arrhenius parameters with negative activation entropy. This was taken as an evidence that the reaction proceeds through a cyclic activated complex rather than a linear biradical or zwitterion centers [22,23]. In present work, the cyclization process for all reactants were of small activation energies which vary within 27-77 kJ mol^{-1} and also with –ve activation of entropies presumably the interaction forces of the substituents and their steric crowding play an important role in the variation of E_a and $\Delta S^{\neq}$.

Entropies of activation: Other important factors that control the reactions rate are the A-factor and its corresponding entropy of activation $\Delta S^{\neq}$. These parameters estimate the rigidity of the cyclic transition state that is formed during the intramolecular cyclization process.

The lower value of A-factor or $\Delta S^{\neq}$, the more rigid they formed cyclic transition state, which lead to a faster process [15], as it was mentioned before.

These two factors are related to each other by eqn. 3, which is derived from the activation complex theory.

Using the above equation, a value of $A \approx 10^{13.5}$ s^{-1} corresponds to $\Delta S^{\neq} = 0$. The decrease in this value results in a negative entropy of activation. It is noted that all of A-factors obtained for all the reactions under study were with lower A values than the above mentioned and correspondingly all the $\Delta S^{\neq}$ obtained were negative values.

The negative values of the $\Delta S^{\neq}$ of the cyclization process under study (Table-3), indicate the formation of a restricted intermediate which suffers from lack of certain degrees of freedom as compared to the reactants. The decrease in the values of A-factor provides an important indication about the stability of the intermediate and hence gives good support for explaining the reason of the differences in the values of rate constants, since the decrease in the values of both A-factor and $\Delta S^{\neq}$ leads to the same target.

Conclusion

The rate of kinetic reaction study of Schiff bases [N-(4-nitrobenzylidene-1-phenyl methanamine)] [N-(4-bromo-benzylidene-1-phenyl methanamine)] and its derivatives with chalcone (2-benzylidine-1-tetralone) shows a first order reaction with cyclization intermediate. The reaction rate and thermodynamic parameters were calculated at difference temperature and presented in this study.

ACKNOWLEDGEMENTS

The authors gratefully acknowledge to Baghdad University and Universiti Kebangsaan Malaysia for their support for research grant.

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