Kinetic investigation of tetrahydrobenzo[b]pyran synthesis in the presence of fructose as a catalyst via a three-component reaction: an experimental study

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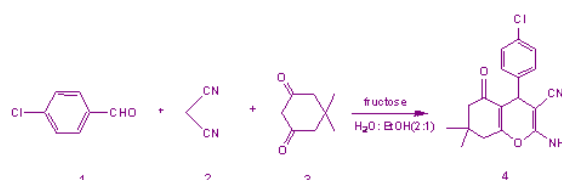
The synthesis reaction of tetrahydrobenzo[b]pyran from the reaction between 4-chlorobenzaldehyde, malononitrile with dimedone in the presence of fructose as a catalyst were subjected to a kinetic and mechanistic study by a UV spectrophotometric technique. The effects of various parameters such as the concentration, temperature, solvent composition and various catalysts on the reaction rate were examined. Experimental data fully matched the second order fits. The resultant rate constants obeyed the Arrhenius and Eyring equations. The relevant activation parameters(Ea, $\Delta H^{\ddagger}$, $\Delta S^{\ddagger}$ and $\Delta G^{\ddagger}$) were determined from these. In a solvent with a lower dielectric constant the rate of reaction decreased. In accordance with the experimental observations and steady state approximation, the first step of the proposed mechanism was recognized as a rate-determining step.

Keywords: Kinetics, Catalyst, Mechanism, Tetrahydrobenzo[b]pyran

INTRODUCTION

Benzopyrans and their derivatives, as a useful class of heterocyclic compounds, show biological and pharmacological properties, such as diuretic, anticancer, spasmolytic, anticoagulant and antianaphylactin activities [1]. They can also be employed as cognitive enhancers for the treatment of some neurodegenerative diseases, including Parkinson, Alzheimer, Huntington, AIDS associated dementia, Down's syndrome and also for the treatment of schizophrenia and myoclonus [2]. Furthermore, these compounds can be applied as potential biodegradable agrochemicals, pigments and photoactive materials [3-6]. In recent years, many studies on the synthesis of tetrahydrobenzo[b]pyrans have been reported[7-11]. Multi component reactions (MCRs) occur in one-pot and so these reactions are easier to perform than multistep syntheses reactions [12]. The considerable benefits due to MCR sconta in low expenses, avoiding of time-consuming purification processes and complex synthetic pathways, shorter times of reaction, high yields and saving the energy [13]. Three-component reactions have appeared as a beneficial approach among the multi-component reactions since the combination of three compounds to obtain related products in a single step is quite economical [14-17]. Therefore, an effective and suitable synthesis of tetrahydrobenzo[b]pyrans can usually be performed via a three-component reaction of an aromatic aldehyde, an acting methylene compound and dimedone in the presence of an appropriate catalyst [18]. In addition to synthesis, very valuable information about these compounds is the mechanism and rate of the reactions, the effect of various parameters can be obtained from the kinetic studies [19]. In previous works we have investigated the kinetics of the synthesis of new organics such as phosphorus ylides, phosphonate esters and others, both experimental and theoretical studies [20-24]. In this work we examine the experimental kinetics and mechanism of the reaction between 4-chlorobenzaldehyde 1, malononitrile 2, and dimedone 3 in the presence of fructose as a catalyst to attain tetrahydrobenzo[b]pyran 4 (Scheme1). Fructose is a popular, commensurate, stable, cheap and clean catalyst, dissolvable in water synthesized by an environmentally desirable procedure.

Scheme1. Synthesis reaction of tetrahydrobenzo [b]pyran, 4-chlorobenzaldehyde, malononitrile, and dimedone in the presence of fructose as a catalyst.
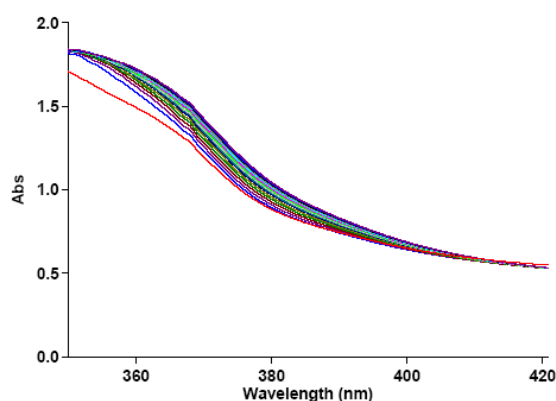
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EXPERIMENTAL SECTION

4-chlorobenzaldehyde **1**, malononitrile **2**, dimedone **3**, fructose and ethanol were obtained from Merck (Darmstadt, Germany) and Fluka (Buchs, Switzerland), these were used without any purification. All of the experiments were accomplished by a carry UV-Vis spectrophotometer as follow:

General procedure

At first, 10^{-2} M solution of each compound (**1, 2, 3** and catalyst) was prepared in a mixture of 2:1 water: ethanol as a solvent. Then, the spectrum of each compound was recorded in the wavelength range 200-800 nm. In the second experiment, 0.2 mL of the solution of the catalyst and each reactant **2** and **3** were added into the cell, respectively (as there is no reaction between them).Then, 0.2 mL of reactant **1** was added to the mixture and the progress of the reaction was monitored at the ambient temperature (Fig.1).
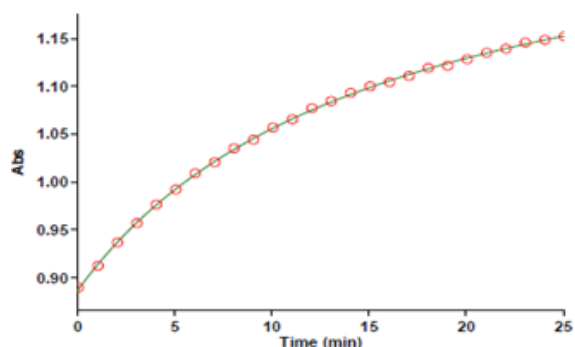

Fig. 1. The UV/Vis spectra of the reaction between 4-chlorobenzaldehyde **1** (10^{-2}M), malononitrile **2**(10^{-2}M) and dimedone **3** (10^{-2}M) in the presence of the fructose catalyst (10^{-2}M) and in a mixture of water: ethanol (2:1), the upward arrow showing the progress of the reaction

Thereupon, the suitable wavelength at which reactants **1, 2, 3** and the catalyst have relatively no absorbance was found to be 380 nm. The full kinetics and mechanism of the reaction can be investigated at this wavelength. Herein, in all the experiments, the UV-Vis spectrum of the product was measured over the concentration range (10^{-3} M < M product < 10^{-2} M) to corroborate a linear relation between the absorbance and concentrations values. In the third experiment under the same conditions just as the previous experiment, the absorbance curve was recorded versus the time at 40°C and 380 nm (Fig.2). Zero, first or second curve fittings can be drawn using the software associated with the UV-Vis instrument; also, the relevant rate constant can be calculated

automatically [25]. As can be seen in Fig. 2, the experimental absorbance data (dotted line) accurately fits the second order curve (solid line). Thus, the overall order of the reaction according to the rate law expressed in equation (1), can be written as: $\alpha+\beta+\gamma = 2$

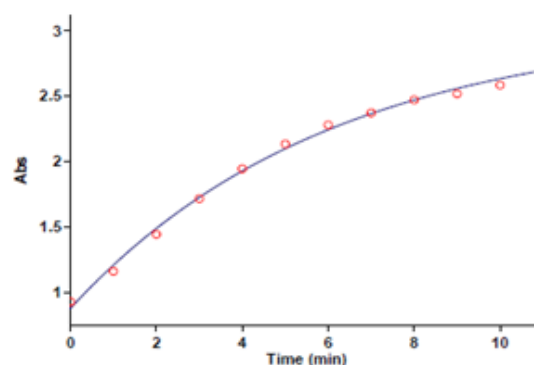$$Rate= k_{ovr} [1]^{\alpha} [2]^{\beta} [3]^{\gamma} [cat], (1)$$

Fig. 2. Second order fit curve (solid line) accompanied by the original experimental curve (dotted line) for the reaction between compounds **1** (10^{-2}M), **2** (10^{-2}M) and **3** (10^{-2}M) in the presence of fructose (10^{-2}M) in a mixture of water: ethanol (2:1) at 380nm
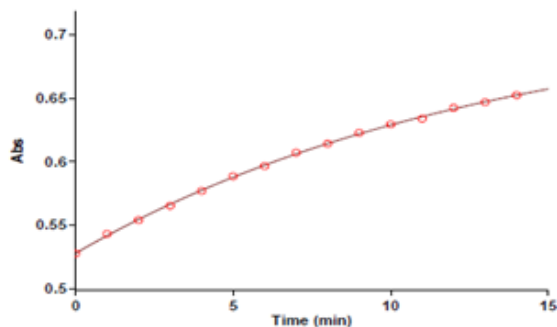
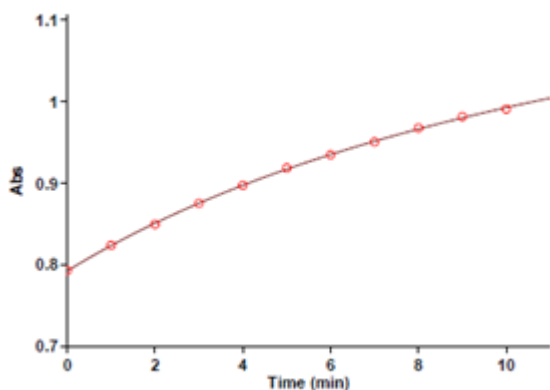## RESULTS AND DISCUSSIONS

The Effect of Concentration

In order to determine the partial order with respect to each component three experiments were carried out in which the concentration of one of the components **1**, **2** or **3** was selected much less (5×10^{-3}) than the others (10^{-2}), separately. In other words, pseudo-order conditions were set for these reactions. The absorbance curves are shown in Figures (3-5).

Fig. 3. The first pseudo order fit curve (solid line) along with the original experimental curve (dotted line) in relation to 4-chlorobenzaldehyde **1**, for the reaction between **1**(5×10^{-3} M), **2** (10^{-3} M) and **3** (10^{-3} M) in the presence of fructose and a mixture of water: ethanol (2:1) at 380nm

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Fig. 4. First pseudo order fit curve (solid line) along with the original experimental curve (dotted line) in relation to malononitrile **1**, for the reaction between **1**(10^{-3} M), **2** (5×10^{-3} M) and **3** (10^{-3} M) in the presence of fructose and a mixture of water: ethanol (2:1) at 380nm

Fig. 5. Second pseudo order fit curve (solid line) accompanied by the original experimental curve (dotted line) for the reaction between compounds **1** (10^{-2}M), **2**

(10^{-2}M) and **3** (5×10^{-3}M) in the presence of fructose (10^{-2}M) in a mixture of water: ethanol (2:1) at 380nm

It is obvious that under pseudo-order conditions, the partial order of the reaction with respect to compounds **1** and **2** is one (Figs. 3, 4). In the other hands, $\alpha = \beta = 1$. Also by matching the experimental data with a second order fit (Fig. 5) given the similarity of the calculated rate constants. From this plot of the rate constants calculated from the graph of Fig. 2, we thus say by changing the concentration of compound **3**, rate constants have not changed substantially. So we can rewrite equation 1 as follow:

$$\text{Rate} = k_{ovr}[1][2][\text{cat}] \, , \, k_{obs} = k_{ovr}[\text{cat}] \, , \, (2)$$

$$\text{Rate} = k_{obs}[1][2] \, , \, (3)$$

The Effect of Solvent and Temperature

Several experiments were performed for various temperatures and solvents under the same concentration of each component (10^{-2}M). The relevant rate constants obtained from the software are given in Table 1. The dependency of the rate constants ($\ln k$ and $\ln k/T$) on the reciprocal temperature showed adaptability with the Arrhenius and Eyring equations. Furthermore, the linearized form of the Eyring equations was investigated to compare these methods [13] (Figs. 6, 7). The activation parameters are given in Table2.

Table 1. Values of observed rate constants for the reaction between **1**, **2** and **3** in the presence of the fructose catalyst at 380nm and various temperatures.
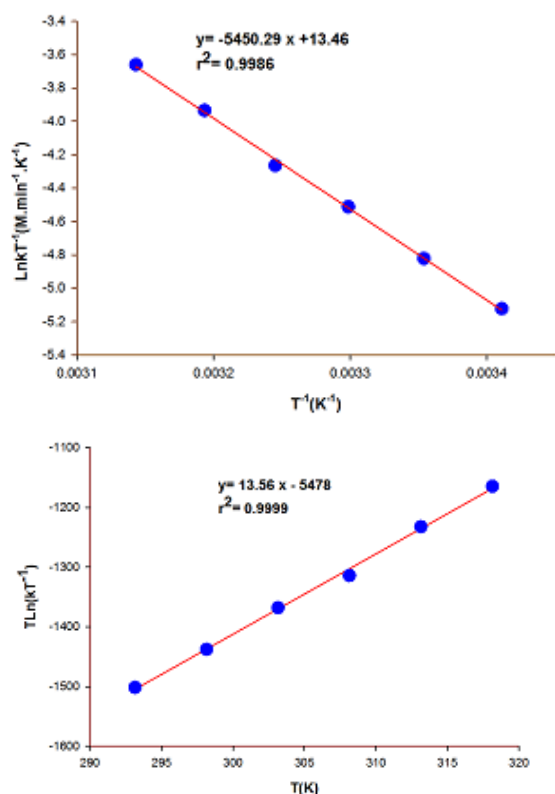
		k_{obs}(M.min^{-1})						
λ(nm)	Solvent	[a] 45.0 °C	[a] 40.0 °C	[a] 35.0 °C	[a] 30.0 °C	[a] 25.0 °C	[a] 20.0 °C	[b] 40.0°C
380	Water: ethanol (2:1)	8.18	6.12	4.33	3.33	2.40	1.75	6.18
380	ethanol	4.36	3.14	1.09	0. 42	0.110	0.078	3.13

a: **1** (10^{-2} M), **2** (10^{-2} M),**3** (10^{-2} M), catalyst (10^{-2}M)
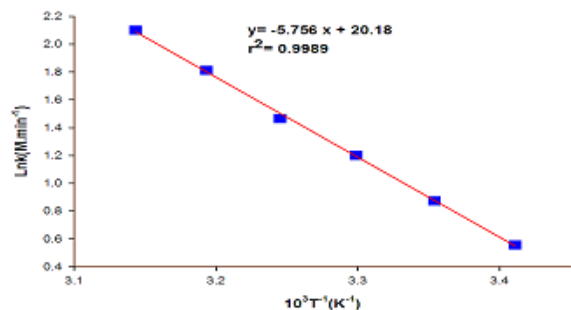b: **1** (10^{-2} M), **2** (10^{-2} M),**3** (5×10^{-3}M), catalyst (10^{-2}M)

Table 2. Activation parameters for the reaction between 1, 2 and 3 in the presence of the fructose catalyst at 380nm.

solvent	$\Delta H^{\ddagger}$(kJ.mol^{-1})	$\Delta S^{\ddagger}$(J.mol^{-1}.K^{-1})	$\Delta G^{\ddagger}$(kJ.mol^{-1})	Ea(kJ.mol^{-1})
Water: ethanol(2:1)	[a] 45.31 [b] 45.54	[a] -85.64 [b] -84.80	[a] 70.84 [b] 70.82	47.86

a: according to the Eyring equation,
b: according to the linearizied form of the Eyring equation

Fig. 6. Eyring plots for the reaction between 1, 2, 3 and fructose in a mixture of water: ethanol (2:1) at 380nm.

Fig. 7. An Arrhenius plot for the reaction between **1, 2, 3** and fructose in a mixture of water: ethanol (2:1) at 380nm.

According to the data in Table1, it can be seen that the reaction rate increases with increasing temperature. Moreover, in a solvent with a lower dielectric constant (ethanol) in comparison with a higher dielectric constant (mixture 2:1 water: ethanol) the reaction rate decreased. That can be attributed to the change in stability of the reactants and activated complexes in these environments. Furthermore, the positive value of $\Delta H^{\ddagger}$(Table2) indicates that the reaction is needed to obtain a high value of the activation energy endothermic and a large negative value of $\Delta S^{\ddagger}$ determines a transition state that is more strongly ordered than the reactants.
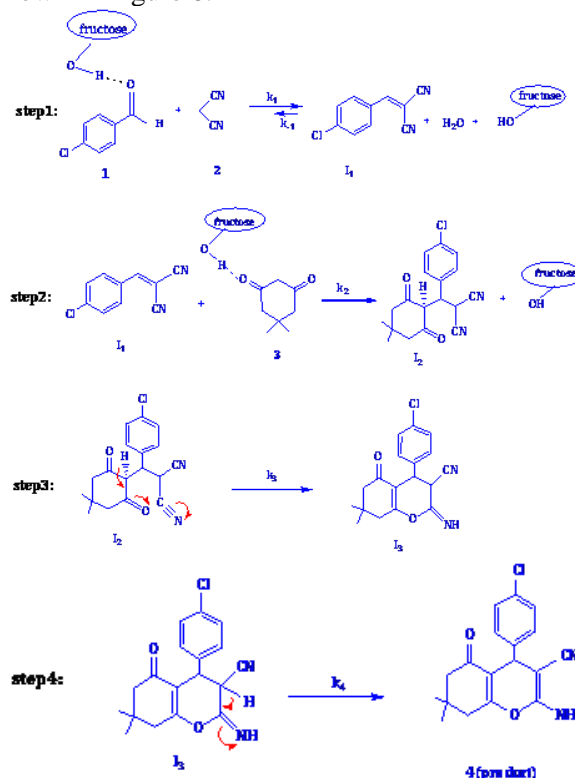
Effect of the catalyst

The reaction between **1, 2 and 3** was repeated in the presence of agar, sucrose and 1,4-diazabicyclo[2.2.2]octane(DABCO) as a catalyst in a mixture of water:ethanol (2:1). The reaction rate was increased in the presence of agar, sucrose and DABCO in comparison with the fructose (Table 3). Agar and DABCO have a poor interaction with a polar solvent compared to fructose, such that, it has more freedom to carry out its catalytic role. Also, due to sucrose it can establish hydrogen bonding with an oxygen atom in the 4-chlorobenzaldehyde more than fructose and was more active for the nucleophilic attack of the malononitrile compound.

Table 3. Effect of Various catalysts on the reaction between **1**, **2** and **3** at 45ºC and 380nm.

solvent	catalyst	k_{obs}(M.min^{-1})
Water: ethanol(2:1)	Fructose	8.18
	Agar	10.01
	Sucrose	8.84
	DABCO	9.36

Mechanism

By using the above results, the proposed reaction mechanism as a possible comment is shown in Figure 8:

Scheme 2. The proposed mechanism for the reaction between **1**, **2** and **3** in the presence of fructose in a mixture of water: ethanol (2:1).

To determine which step of the proposed mechanism is the rate-determining step, the rate law was written for the final step of the reaction as:

$$\text{Rate} = k_4 [I_3], \quad (4)$$

By using the steady state approximation to obtain the concentration of all intermediates (I_1, I_2 and I_3), the rate equation becomes:

$$\text{Rate} = \frac{k_1 k_2 [1][2][3][cat]}{k_{-1}[H_2O] + k_2[3]}, \quad (5)$$

This equation is independent of the rate constants for the third and fourth steps. Thus, these steps have no chance to be rate determining steps; if $k_{-1}[H_2O] \ll k_2[3]$; then, we can conclude:

$$\text{Rate} = k_1 [1][2][cat], \quad (6)$$

Hence, from the comparison between both equations (6) and (2) and the experimental data

$$\text{rate} = k_{obs}[1][2], \quad (7)$$

According to this equation, the order of the reaction with respect to compounds (**1, 2and 3**) is 1, 1 and zero, respectively and the overall order of the reaction is two, which was previously confirmed by the experimental data.

The presence of k_1 in the rate law (equation (6)) indicates that the first step is a rate-determining step and step 2 should be a fast step. In this case, the transition state (Scheme 2, step 1) carries a dispersed charge; hereupon, the solvent with a higher dielectric constant can be more effective on this dispersed charge in comparison with reactants **1** and **2**, that do not have any charge. Thus, the solvent stabilizes the species at the transition state more than the reactants. Therefore, E_a would be lower and accelerate the reaction rate.

CONCLUSION

The reaction rate was accelerated by the increase in temperature and was in compatibility with the Eyring and Arrhenius equations. It also followed the second-order kinetics and partial order with respect to compounds **1**, **2**, and **3** was 1, 1 and 0, respectively. The first step of the proposed mechanism was identified as a rate-determining step and this was affirmed by the steady-state approximation. Furthermore, in a solvent with a higher dielectric constant, the rate of the reaction increased. This pertains to different stabilizing effects of the solvent on the reactants and activated complex.

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КИНЕТИЧНО ИЗСЛЕДВАНЕ НА СИНТЕЗАТА НА ТЕТРАХИДРОБЕНЗО[b]ПИРАН В ПРИСЪСТВИЕ НА ФРУКТОЗА КАТО КАТАЛИЗАТОР ЧРЕЗ ТРИКОМПОНЕНТНА РЕАКЦИЯ: ЕКСПЕРИМЕНТАЛНО ИЗСЛЕДВАНЕ

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(Резюме)

Синтезата на тетрахидробензо[b]пиран при реакцията между 4-хлоробензалдехид, малононитрил и димедон в присъствие на фруктоза като катализатор. Извършено е кинетично и механистично изследване чрез ултравиолетова спектроскопия. Изследван е ефектът на различни параметри, като концентрации, температура, състав на разтворителя и различни катализатори върху скоростта на реакцията. Експерименталните данни напълно съответстват на реакции от втори порядък. Резултантните скоростни константи се подчиняват на уравненията на Arrhenius и Eyring. Съществените параметри за активацията (Ea, $\Delta H^{\ddagger}$, $\Delta S^{\ddagger}$ и $\Delta G^{\ddagger}$) са определени от тези уравнения. Скоростите на реакциите се понижават в разтворители с по-ниска диелектрична константа. В съответствие с експерименталните наблюдения и стационарно приближение е прието, че първият етап на предложения механизъм е скоросто-определящ за общата реакция.