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## Medium Effects on Ring-Opening Reaction of Some *para*-Substituted Azlactones in Ethanol-Water Mixtures

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### ABSTRACT

Medium effects on the kinetics of the morpholine-catalyzed solvolysis of azlactone and its derivatives *e.g.*, *p*-chloro and *p*-methoxy have been investigated within the temperature range (40-65 °C) in ethanol-water mixtures of varying ethanol compositions from 30 to 80 % by volume of the organic solvent component. The order of decreasing reactivity of *p*-substituted azlactones reaction in the ethanol-water mixtures is in the order *p*-Cl > *p*-H > *p*-OMe. The variation of activation parameters ( $\Delta G^\ddagger$ ,  $\Delta H^\ddagger$  and  $\Delta S^\ddagger$ ) with the mole fraction of the ethanol was analyzed and discussed. The rates of the amine catalyzed reaction were found to increase with an increase of the dielectric constant. The isokinetic plots were linear in all media and revealed the existence of compensation effect due to strong solute-solvent interactions. Moreover, the correlation of  $\log k_{\text{obs}}$  with the reciprocal of temperature was linear and a good linear relationship was obtained from plots of  $\log k_{\text{obs}}$  versus the  $\sigma$ -Hammett parameter with a positive slope ( $\rho$ ). The Hammett substituent's  $\sigma$  for the various substituents in the benzylidene moiety gave good straight lines with values varying between 1.843 to 2.140.

### KEYWORDS

Ring-opening, Azlactones, Kinetics, Solvent effect.

### INTRODUCTION

Azlactones are important intermediates for the synthesis of several biologically active compounds and also is a part of great importance for its drug characteristics [1-7]. They can be used as a sensor for Fe<sup>3+</sup> sensing [1] and pH measurements [2]. However, only a few studies on the kinetics of azlactone ring-opening have been reported [8-13]. The phenomenon of solvation is an important part concerning this study. The dissolution of a substance requires two factors to be overcome, the interaction energy of the solute molecules (for crystals the lattice energy) and the interaction energy between the solvent molecules themselves. This is compensated by the gain in Gibbs energy of solvation ( $\Delta G_{\text{sol}}^\circ$ ). This thermodynamic function is the result of a superimposition of principle components of energy of different nature concerning the solute and the solvent [14]. The situation with respect to aqueous mixtures is usually more complicated, since there are inter- and intra-component

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interactions to consider in the solvent mixtures. A recent study [15] has been done and revealed a detailed picture about the structure of the solvation sheath, by measuring the solvent relaxation times of anthracene fluorescent probe. One may conclude that (i) the solvent molecules in the solvation sheath are labile, so they could be exchanged with the solvent molecules in the bulk, (ii) the stability of clusters in the solvation sheath depends on the energy released due to such exchange and depends on the nature of the replaced solvent molecules.

The present work reports a study of the medium effects on the morpholine-catalyzed reaction of *para*-substituted (*Z*)-4-benzylidene-2-phenyloxazolin-5-one in ethanol-water mixtures.

## EXPERIMENTAL

*para*-(*Z*)-4-Benzylidene-2-phenyloxazolin-5-one (**I<sub>a</sub>**) and its substituted *p*-chloro (**I<sub>b</sub>**) and *p*-methoxy (**I<sub>c</sub>**) derivatives were prepared and purified by literature methods [16]. Morpholine and the solvent ethanol were supplied by BDH. The aqueous binary mixtures (H<sub>2</sub>O + C<sub>2</sub>H<sub>5</sub>OH) have been prepared with different ethanol composition using distilled water.

**Kinetic measurements:** The morpholine-catalyzed reaction of azlactones were followed spectrophotometrically in the temperature range of 40-65 °C, using equal initial concentrations for both substrate and morpholine of  $4 \times 10^{-4}$  M. The reaction was followed at  $\lambda_{\max} = 364, 368, 392$  nm for unsubstituted azlactone, *p*-Cl and *p*-OMe (**I<sub>a</sub>**, **I<sub>b</sub>** and **I<sub>c</sub>**) azalactone, respectively. The hypochromic shift of the optical density with time was recorded on a computerized Unicam Heλiosα spectrophotometer.

The reaction carried out within the temperature range (40-65 °C). The temperature was set automatically to  $t \pm 0.05$  °C using Raypa thermostat temperature control. The reaction was carried under second order conditions. The variation of absorbance with concentration for azlactones obey Bears lambard law and gave straight lines with positive slope equal to  $\epsilon$ , where  $\epsilon = 29692, 31571, 32985$  for (**I<sub>a</sub>**, **I<sub>b</sub>** and **I<sub>c</sub>**) azalactone, respectively.

## RESULTS AND DISCUSSION

The morpholine-catalyzed reactions of azlactones have been measured in ethanol-water medium of different ethanol compositions (30-80 % v/v) within the temperature range (40-65 °C). The data obtained obey the second order rate constant, where good linear plots were obtained by plotting  $1/(a-x)$  versus time  $t$ . The obtained values are listed in Table-1. The reaction rates are consistent with the following rate equation for two parallel reactions [10].

$$r = (k[\text{H}_2\text{O}]^2 + k_{\text{Am}}[\text{Am}])(\text{azlactone})$$

$$k_{\text{obs}} = k_w + k_{\text{Am}}[\text{Am}]$$

where  $k_w = k_{\text{H}_2\text{O}}[\text{H}_2\text{O}]^2$

$k_w$ ,  $k_{\text{Am}}$  are the uncatalyzed and amine-catalyzed solvolysis rate constant, respectively,  $[\text{H}_2\text{O}]$ ,  $[\text{Am}]$  and  $[\text{azlactone}]$  are the concentration of water, morpholine and the desired azlactone used, respectively.

However, the perusal of data given in Table-1 indicates that the rates of ring-opening of azlactones in presence of

TABLE-1  
SECOND-ORDER RATE CONSTANT  $k_2$  ( $\text{M}^{-1} \text{s}^{-1}$ ) FOR AMINE-CATALYZED REACTION OF AZLACTONES **I<sub>a-c</sub>** IN ETHANOL-WATER MIXTURES AT DIFFERENT TEMPERATURES

% v/v	Temperature (°C)					
	40	45	50	55	60	65
<i>p</i> -H						
30	3.97	7.70	14.10	24.16	42.50	–
40	2.60	4.64	6.75	10.93	16.66	–
50	2.47	3.89	5.69	9.07	13.05	–
60	2.18	3.44	5.35	8.48	11.76	–
70	1.95	3.13	4.99	7.57	10.55	–
<i>p</i> -Cl						
40	6.97	12.80	22.68	39.85	68.13	–
50	5.51	10.53	18.93	32.61	55.64	–
60	5.12	9.72	18.15	28.97	51.09	–
70	4.70	7.95	17.24	27.62	48.85	–
80	3.35	5.05	7.60	11.29	16.65	–
<i>p</i> -OMe						
30	–	2.15	3.53	5.47	8.68	12.86
35	–	1.81	2.94	4.41	7.99	11.99
40	–	1.53	2.38	3.62	5.66	8.64
45	–	1.20	2.07	3.06	5.21	7.86
50	–	0.91	1.58	2.69	4.12	6.39

morpholine in several water-ethanol mixtures decreased with changing the organic solvent mixture. The dramatically rate decreases with increasing the mole fraction of the cosolvent, may be attributed to hydrophobic interactions [10]. Also, comparing the data in Table-1 with those obtained previously [12] shows that the rate of ring opening for *p*-H and *p*-OMe in presence of morpholine is greater in the present work than the previous one where the solvent used was acetonitrile-water mixtures, this may be due to the structure of the solvent. Where when small amounts of ethanol are added to water, usually it cause some enhancement of water structure. The successive additions of ethanol eventually lead to disruption of the solvent structure. The intermolecular interaction at higher concentration of ethanol is significantly high. Consequently, one could predict that clusters in the solvation sheath of the activated state are somewhat different in aqueous-, ethanol and acetonitrile solutions. The disruption of the clusters in the solvation sheath on going from the ground state and rebuilding of a different cluster when the reactants reach to the activated state energy should be released which reflects its effect on the values of the change in free energy of activation as shown in Table-2.

The change in free energy of activation for the reaction in aqueous ethanol is less than the corresponding values in aqueous acetonitrile that is why the reaction in the later solvent is slower than in the former one.

This interpretation was supported by previous work [15], where a reaction was started by reactants differ in their solvation sheath. Two channels of association reaction were studied, one was started by dissolving the reaction reactants in water and the other by dissolving the reactants in water-ethanol mixtures, prior to their mixing. The rate in the two cases was different giving different activation energies.

It is clear that the magnitude of the second order rate constant of the ring opening of azlactones (**I<sub>a</sub>**, **I<sub>b</sub>** and **I<sub>c</sub>**) is a measure of the reactivity towards alkali. The order of decreasing reactivity of *p*-substituted azlactones in the solvolysis reaction in

TABLE-2  
ACTIVATION PARAMETERS FOR MORPHOLINE-CATALYZED REACTION OF AZLACTONES IN ETHANOL-WATER MIXTURES AT 25 °C

X <sub>2</sub> (Ethanol)	$\Delta H^\ddagger$ (kJ mol <sup>-1</sup> )	$-\Delta S^\ddagger$ (J mol <sup>-1</sup> deg <sup>-1</sup> )	$\Delta G^\ddagger$ (kJ mol <sup>-1</sup> )	
<i>p</i> -H	0.12	99.7 ± 1.5	-84.6 ± 4.5	74.4 ± 2.8
	0.17	76.9 ± 2.5	-8.7 ± 7.7	74.4 ± 4.8
	0.24	70.0 ± 1.4	14.1 ± 4.2	74.2 ± 2.6
	0.32	71.7 ± 1.9	9.8 ± 5.8	74.6 ± 3.6
	0.42	71.5 ± 2.2	11.2 ± 6.8	74.9 ± 4.2
<i>p</i> -Cl	0.17	96.3 ± 0.3	-78.5 ± 0.9	72.9 ± 0.6
	0.24	97.4 ± 1.3	-80.2 ± 4.1	73.5 ± 2.6
	0.32	96.4 ± 2.4	-76.2 ± 7.5	73.6 ± 4.7
	0.42	100.4 ± 4.0	-88.0 ± 12.3	74.2 ± 7.7
	0.55	67.2 ± 0.3	20.8 ± 0.8	73.4 ± 0.5
<i>p</i> -OMe	0.12	77.7 ± 1.0	-5.2 ± 3.1	76.1 ± 2.0
	0.14	83.0 ± 2.3	-20.3 ± 9.1	77.0 ± 5.7
	0.17	75.1 ± 0.8	6.0 ± 2.4	76.9 ± 1.5
	0.20	81.3 ± 2.2	-11.9 ± 6.6	77.8 ± 4.1
	0.24	84.6 ± 2.3	-20.0 ± 6.9	78.7 ± 4.3

the ethanol-water mixtures is in the order *p*-Cl > *p*-H > *p*-OMe, may be attributed to the differences in the chemical structure, as shown in Fig. 1. Thus the variation in the rate may be attributed to:

- The electron-withdrawing substituent *p*-Cl decreases the electron density at the carbon of the reaction centre, *i.e.* it increases the electrophilicity of the reaction centre, so the rate is higher than the unsubstituted azlactone [11].
- The electron-donating substituent *p*-OMe reduces the ease of nucleophilic attack on the reaction centre, so rate is lower than the unsubstituted azlactone.
- $\Delta G^\ddagger$  values for *para*-substituted azlactones decrease in the order (*p*-OMe > *p*-H > *p*-Cl). This observation can be discussed as the steric strain generate in the transition state of *p*-OMe, the energy increase and hence,  $\Delta G^\ddagger$  increase.

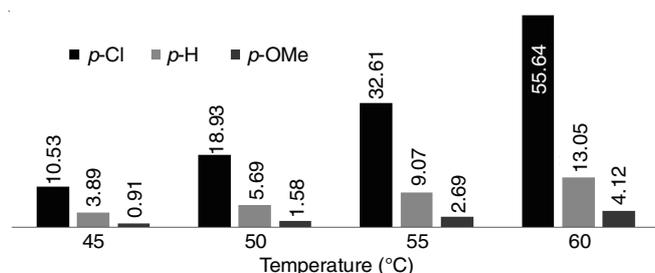


Fig. 1. Variation of rate constant of azlactones with temperatures

Thermodynamic parameters  $\Delta S^\ddagger$ ,  $\Delta H^\ddagger$  and  $\Delta G^\ddagger$  were obtained using least squares procedures with their standard deviation as shown in Table-2. Values of  $\Delta S^\ddagger$  and  $\Delta H^\ddagger$  were plotted *versus* the mole fraction of EtOH. Non-linear plot, were obtained, this non linearity indicates the presence of specific solvation effects and the profile of the curves obtained predicts that a compensation effect may be exist. Plot of  $\Delta H^\ddagger$  *versus*  $\Delta S^\ddagger$  for the reactions under investigating at 25 °C as shown in Fig. 2, gave a straight line where the slope  $\beta = 283$  K. This value lies below the experimental temperatures which indicates that the rate of the reaction is entropic controlled, where the solute-solvent interactions play an important role. The plot of  $T\Delta S^\ddagger$  against  $\Delta H^\ddagger$  was a straight line with approximately unit slope (Fig. 3), which indicates that there will be no variation in  $\Delta G^\ddagger$  in all media.

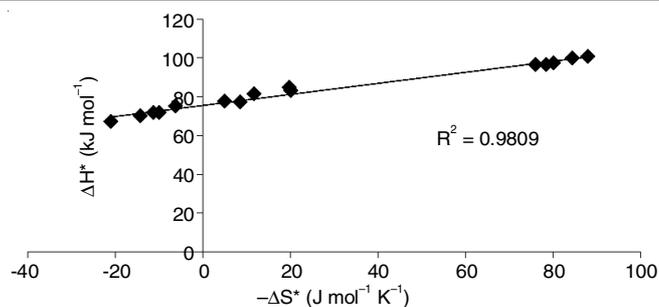


Fig. 2. Variation of  $\Delta H^\ddagger$  *versus*  $\Delta S^\ddagger$  for ring-opening of azlactones at different solvent composition at 25 °C

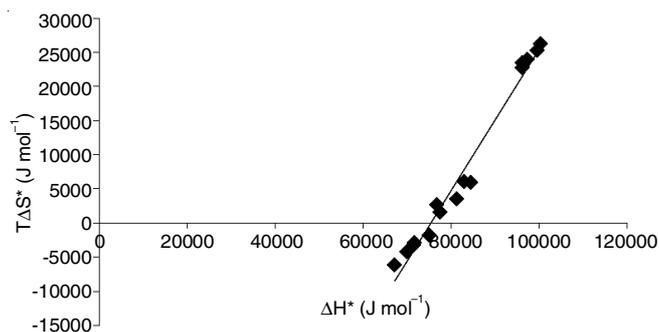


Fig. 3. Plot  $T\Delta S^\ddagger$  *versus*  $\Delta H^\ddagger$

Plots of  $\log k_{\text{obs}}$  values in solvent mixtures at different temperatures *versus* the Hammett substituent's  $\sigma$  [17] for the various substituent in the benzyldene moiety gave good straight lines with values varying between (1.843 to 2.140) the Hammett ( $\rho$ ) slope as shown in Table-3. The linear plots were statistically analyzed using least-squares method. The positive  $\rho$  values obtained are due to the presence of substituents on the [substrate]. The estimated positive  $\rho$  values are in accordance with the proposed multistep mechanism for the present reaction. These confirm an anionic character for the transition states. The observed positive value indicates stronger electronic interactions between the polar attracting substituent and the developed negative center in the transition state, which is in agreement with the prediction of the substituent effects on  $S_N2$  transition states [11]. The positive values of  $\rho$  for the reactions show that the reaction is accelerated by electron withdrawing substituent. Thus, a positive value of  $\rho$  indicates that the reaction center has higher electron density in the transition state than in the ground state.

TABLE-3  
VALUES OF  $\log k_2/k_0$ ,  $\rho$ ,  $S_r$  AND  $R^2$  FOR RING-OPENING OF AZLACTONE I<sub>a-c</sub> IN PRESENCE OF MORPHOLINE AT DIFFERENT TEMPERATURES IN 40 % ETHANOL-WATER MIXTURES

	40 % v/v	45 °C	50 °C	55 °C	60 °C
$\log (k_2/k_0)$ <i>p</i> -Cl		0.441	0.527	0.562	0.612
$\log (k_2/k_0)$ <i>p</i> -OMe		-0.483	-0.453	-0.480	-0.469
$\rho$		1.843	1.943	2.068	2.140
$S_r$		0.023	0.064	0.069	0.090
$R^2$		0.998	0.987	0.987	0.979

Plot of  $\log k$  *versus* the reciprocal of the dielectric constant  $D^{-1}$ , (values of  $D$  were interpolated from the data of Akerlof [18]) which is linear in all media. The rate of the amine catalyzed

reaction were found to increase with an increase of the dielectric constant. This can be explained in terms of the fact that the activated complex are much more polar than the reactants so that their formation encouraged by the higher dielectric constant component (water) of the mixed solvent [19].

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