Solvent Effect on the Amine-Catalyzed Ring-Opening of Azlactone in Acetonitrile-Water Mixtures

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The kinetics of teriethylamine-catalyzed solvolysis of azlactone (oxazolinone) in acetonitrile-water mixtures (10-50 %) in the temperature range (30-60 °C) have been studied. Non-linear plots of log k_{obs} with the reciprocal of relative permittivity were obtained. The thermodynamic parameters ΔH*, ΔS* and ΔG* have been determined; ΔG* increases gradually as the mole fraction of the cosolvent increase, due to a complex quasi-mirror image compensation of ΔH* and ΔS*. The negative values of the entropy of activation and the non-linear relation of log k_{obs} with the reciprocal of relative permittivity suggested selective solvation by the higher polar water molecules. The isokinetic temperature obtained indicated, that the reaction was enthalpic controlled. The presence of methoxy group in the *para* position retarded the reaction by about three times of hydrogen. The rate was also decreased with increasing the organic cosolvent. The reactivity was analyzed using Kamlet-Taft solvatochromic parameters and were applied successfully in mixed aqueous -acetonitrile mixtures.

Key Words: Oxazolinone, Solvent effect, Ring-opening, Solvatochromic parameters.

INTRODUCTION

Azlactone of the 4-hydroxybenzylideneimidazolinone is considered as the chromophore of the green fluorescent protein[1]. The photophysical and photochemical properties of the azlactone derivative, 4-(2-furylmethylene)-2-phyenyl-5-oxazolone have been examined in different solvents[2]. Azlactone anions are used as the key intermediate in the classical Erlenmer syntheses of amino acid which possess aromatic stabilization[3].

The proton sensitive azlactone derivative, 4-[(*p*-N,N-dimethylamine)benzylidene-]-2-phenyloxazol 5-one exhibits high quantum yield, excellent photo stability and high molar absorpitivity in sol-gel[4]. Kinetic investigations of the nucleophilic ring-opening of azlactone[5-8] and its derivatives in aqueous organic solvent and subsequent correlation of the reaction rates with solvent parameters provide important information regarding the mechanism of such reactions. Solvent variations may affect the kinetics and the energy of electron transfer processes, particularly in mixed solvent media, in a complex manner as the physico-chemical properties of mixed solvent media are often quite different from those of pure solvents or of their ideal mixtures[9]. A number of solvent polarity scales[10], as relative permittivity, solvent ionizing power, *etc*., have been established to quantify the influence of the solvent on reactivity of both initial and transition states. In spite of the observation that single empirical parameter can be used as a good approximation of solvent polarity, multiple solvent effects on kinetic processes are revealed only by using linear combination of solvent parameters. Although there are several empirical methods to correlate the general effects of the solvent, using pure solvent and water-organic cosolvent mixtures[11], the most ambitious and also most successful quantitative treatments of solvent effects using a multiparameter equation is that of Kamlet and Taft[12-14], also known as the linear solvation-energy relationship (LSER). The objective of the present work, concerns with the study of the solvent effect on the nucleophlic ring-opening of azlactones in acetonitrile-water mixtures of various composition (10, 20, 30, 40, 50 % v/v) where, water-acetonitrile solvent mixtures are a recurring reaction medium in physical chemistry, plays a central role in atmospheric chemistry and has an effective choice for recover charged ion-pair. Acetonitrile, is completely water-soluble throughout the mole fraction range, it appears to form heterogeneous mixtures with water and the physico-chemical properties of which suggest that they consist of structurally different regions[15].

EXPERIMENTAL

Azlactone and its derivatives were prepared as reported[16], the solvent used, acetonitrile (ACN) was of reagent grade (WinLab). Triethylamine (TEA) was of reagent grade (Loba). All reagents were spectroscopic grade. The solvent-water binary mixture was prepared using doubly distilled water.

Kinetic measurements: The studies of solvolysis reactions of oxazolinone in presence of triethylamine in acetonitrile-water mixtures (10-50 % v/v) were followed spectrophotometrically in the temperature range 30-60 ºC. Using initial concentration for the substrate and morpholine after mixing were 4×10^{-5} and 4×10^{-4} mol dm^{-3}, respectively. The hypo- chromic shift of the optical density with time was recorded on a computerized Unicam Heλiosα spectrophotometer. The temperature was set automatically to $\pm$ 0.05 ºC using Raypa thermostat temperature control. The reactions were carried under pseudo-first order condition. The progress of the reaction was followed spectrophotometrically at λ_{max} = 360 for the unsubstituted azlactone and at λ_{max} 384 for *para*-methoxy, respectively.

RESULTS AND DISCUSSION

Variation of rate constant with chemical structures and solvent composition: Good pseudo-first order kinetics were obtained by plotting log (A_t-A_∞) against t where A_t, A_∞ are the absorbance at time t and at the infinity of the reaction, respectively. The observed pseudo-first order rate constants k_{obs} as shown in Table-1, were remarkably sensitive to the composition of the mixed solvent used it decreased with increasing the mole fraction of acetonitrile in the mixture.

TABLE-1
PSEUDO-FIRST ORDER RATE CONSTANT $k_{obs} \times (10^4 \text{ s}^{-1})$
FOR THE RING-OPENING OF *PARA*-SUBSTITUTED
OXAZOLINONE IN ACETONITRILE-WATER MIXTURES
AT DIFFERENT TEMPERATURES

t (ºC)	v/v (%)				
	10	20	30	40	50
p-H					
30	240.6	72.5	16.2	4.5	1.1
35	294.3	107.0	22.1	7.2	1.8
40	301.6	126.0	26.0	10.3	3.3
45	346.0	151.0	41.8	13.5	3.8
50	374.3	178.3	65.4	19.7	6.9
p-OMe					
30	89.6	19.2	8.2	1.5	–
35	95.2	24.7	9.1	3.1	–
40	106.1	31.3	12.1	4.5	–
45	118.6	36.6	14.2	6.3	1.8
50	134.3	49.2	18.0	–	2.8
55	–	–	–	–	3.2
60	–	–	–	–	4.5

However, the perusal of data given in Table-1 indicates that the rates of ring-opening of oxazolinone in presence of triethylamine as a nucleophile in water-acetonitrile mixtures are decreased by changing the solvent mixture from 10-50 % organic solvent. Also the rate of ring opening of *p*-H is greater by about three fold than *p*-OMe at all percentage compositions of the solvent used. The dramatically rate decreases with increasing the mole fraction of the cosolvent, may be attributed to hydrophobic interactions. The decrease in the fraction of the free water molecules due to the fact that addition of solvent causes the water tetrahedral structure to be gradually broken by interposition of organic solvent molecules and the hydrogen

bonding between water molecules replaced by hydrogen bonding between water and solvent molecules. Addition of acetonitrile to water lowers the dielectric constant of the medium. Thus, from an electrostatic point, a rate decrease might be expected because of destabilization of the polar transition state when the bulk dielectric constant is lowered by successive addition of acetonitrile.

Comparing the data in Table-1 and those obtained previously[7] using morpholine as nucleophile shows that, the rate constant in the present work is greater than the previously obtained which is in the same order as the basic strength of the amines[17].

Variation of the rate constant with dielectric constant of medium: As shown in Fig. 1, the variation of log k_{obs} *versus* the reciprocal of relative permittivity ε^{-1} obtained from Moreau[18], non-linear relation was obtained for each substituent, indicating the importance of hydrogen bonding and other non-electrostatic medium effects in controlling the reactivity of the substrate and also this non-linearity may be due to differential solvation between the initial and transition states[19].
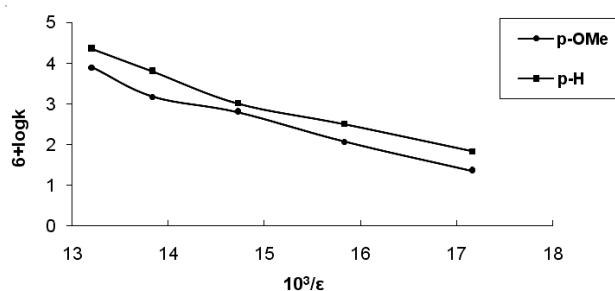

Fig. 1. Variation of log k_{obs} *versus* the reciprocal of relative permittivity ε^{-1} for water-acetonitrile mixtures at 25 ºC

Variation of transition state parameters with solvent composition: The activation free energy ΔG^*, the activation enthalpy ΔH^* and the activation entropy ΔS^* were calculated by least square procedure program and the values with their standard deviation are given in Table-2. The variation of the activation parameters with the mole fraction of acetonitrile was depicted in Fig. 2. The variation of ΔH^* and ΔS^* with

TABLE-2
THERMODYNAMIC PARAMETER OF ACTIVATION
FOR TERIETHYLAMINE-CATALYSED RING-OPENING
OF *PARA*-SUBSTITUTED OXAZOLINONE IN ACETONITRILE-
WATER MIXTURES AT 25 ºC

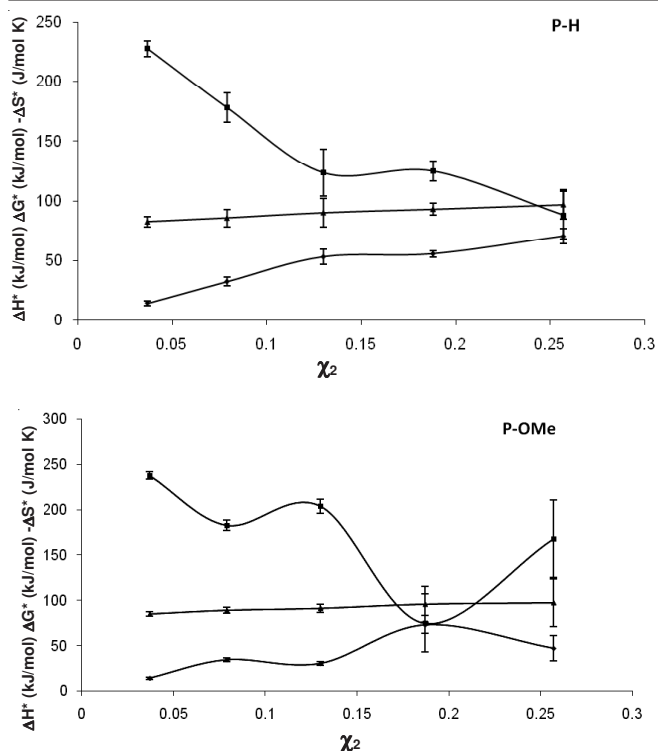| Mole fraction X_2	ΔH^* (J mol^{-1} K^{-1})		- ΔS^* (kJ mol^{-1})		ΔG^* (J mol^{-1} K^{-1})	
p-H						
0.370	14.5	±2.1	227.8	±6.7	82.5	±4.1
0.790	32.5	±3.8	178.1	±12.0	85.6	±7.3
0.130	53.2	±6.1	123.5	±19.5	90.0	±11.9
0.188	55.7	±2.6	124.9	±8.4	93.0	±5.1
0.257	70.6	±6.3	88.0	±20.1	96.8	±12.3
p-OMe						
0.370	14.2	±1.3	237.5	±3.99	85.1	±2.4
0.790	34.7	±1.8	182.6	±5.79	89.1	±3.5
0.130	30.6	±2.4	203.8	±7.80	91.3	±4.7
0.188	73.5	±9.6	75.0	±31.1	95.9	±18.9
0.257	47.4	±7.1	167.7	±21.7	97.4	±13.5

Fig. 2. Variation of the activation parameters of the teriethylamine-catalyzed ring-opening of *para*-substituted oxazolinone with mole fraction (χ_2) of ACN at 25 °C

solvent is non-linear relationship, an indication of specific solvation effects.

Thermodynamic parameters of activation: The computed values of the thermodynamic activation parameters (ΔH^*, ΔS^* and ΔG^*) together with their standard errors are collected in Table-2. Fig. 2 shows that both ΔH^* and ΔS^* curves pass through a maximum or minimum, which are similar to those obtain previously in the same solvent mixtures[7]. This behavior can be visualized in light of change of water structure in the presence of organic solvent for different solvent composition. ΔG^* gradually decreases as a function of increasing [H_2O] due to a complex, quasi-mirror image compensation of ΔH^* and ΔS^*. The non-linear variation of ΔS^* with mole fraction of the organic solvent is a criteria of specific solvation. Furthermore, the highly negative values of ΔS^* for the entire range of solvent composition support the formation of a highly charged transition state. The strong electrostriction developed in the activated state restricts the freedom of motion of solvent molecules in the neighbourhood of the activated species and causes loss of entropy.

The isokinetic temperature β values 398, 359 K for *p*-H and *p*-methoxy, respectively calculated from the slope of ΔH^* *versus* ΔS^*, β value is more than the experimental temperature range (303-333) K which indicates that the reaction is enthalpic controlled. On the other hand, ΔG^* increases smoothly with increasing mole fraction of acetonitrile, a behaviour which gives a good indication of the pronounced solvation of reactants in water-acetonitrile medium. ΔG^* values for *p*-methoxy were always higher than ΔG^* in the case of *p*-H and consequently the rate of *p*-H is higher than *p*-methoxy. This observation can be discussed as the steric strain generate in the transition state, the energy increase and the ΔG^* increase.

Solvent -reactivity correlation: The effect of co-solvent on reactivity may lead to an understanding of some specific solvation effect[20]. This type of dual dependence of reactivity on the composition of the solvent was illustrated by the solvatochromic comparison method of Kamlet and Taft, also known as the linear free energy relationship (LFER). This method provides an improved quantification, correlation and rationalization of the multi interacting solvent effects on reactivity based on Kamlet-Taft. Thus, rate data were correlated with solvatochromic parameters in the form of the linear free energy relationship (LFER):

$$\log k = A_o + s\pi^* + a\alpha + b\beta$$

where π* is the solvent polarity/polarizability, α is the solvent hydrogen-bond-donating (acidity), β is the solvent hydrogen-bond-accepting (basicity).

The values of the solvatochromic parameters π*, α and β in water-acetonitrile mixture have been taken from literature[21].

The rates of nucleophilic ring-opening of oxazolinone and its derivative *p*-methoxy in all acetonitrile-water mixtures in the presence of triethylamine show excellent correlation with the solvent parameters in the above LFER. The obtained correlations using SPSS program are given below:

For *p*-H: log k = -37.291 + 17.228π* + 1.858α + 24.659β
(N = 5, R = 1, R^2 = 1, Sd = 0.01997)

For *p*-OMe: log k = 3.049 + 15.401π* - 4.286α - 30.412β
(N = 5, R = 0.999, R^2 = 0.997, Sd = 0.1051)

From the values of the regression coefficients, the contribution of each parameter on a percentage basis to the reactivity was calculated and listed in Table-3.

TABLE-3
PERCENTAGE CONTRIBUTIONS OF VARIOUS
SOLVENT PARAMETERS TO THE REACTIVITY FOR *p*-H
AND *p*-OMe AZLACTONE

Substrate	α	β	π*
p-H	4.24	56.41	39.35
p-OMe	-8.6	-60.49	30.91

The observation of this systematic multiple regression analysis leads to the following conclusions: The excellent correlation indicates the existence of special local electrostatic solute-solvent interaction. The solvent basicity β plays a dominant role in *p*-H and *p*-methoxy. For *p*-H the positive sign of α, β and π* suggests that the specific interaction between the transition state and the solvent through α, β and π* properties is more than reactants and the solvent, while the negative value of α and β for *p*-methoxy suggests that the specific interaction between reactants and solvent is more than transition state. The contribution of solvent α, to the total solvent effect is not prevalent. As the summation of the above factors the rate of *p*-H is greater than the rate of *p*-methoxy.

Proposed reaction mechanism: In the light of the above considerations, the mechanism of the amine catalyzed ring opening of azlactone should satisfactory account for the role and the effects of the solvent on the reaction rate. It was noticed that successive addition of the organic solvent alters the rate of reaction without influencing its mechanism and so the mechanism is the same for the different solvent compositions.

This finding was confirmed previously for the amine catalyzed azlactone in some other solvent systems[5-8] and gives good support for the previous mechanism[7].

Conclusion

This work described the solvent effect on the amine catalyzed ring opening of unsubistituted azlactonectone and *p*-methoxy azlactone in mixed acetonitile-water mixtures. The rate of unsubistituted azlactone is greater than *p*-methoxy by about three fold and the rate data were analyzed using Kamlet-Taft equation. The correlation indicates the existence of special local electrostatic solute-solvent interaction. The basicity plays a dominant role. The isokinetic temperature obtained indicates that the reaction is enthalpic controlled.

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