

# Kinetic Study on the Morpholinolysis of Esters Analogues to Flutamide in MeOH-H<sub>2</sub>O Mixtures: Effect of Medium on Reactivity & Mechanism

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## Abstract

The kinetics of the reaction of esters analogous to flutamide namely substituted phenyl acetate, butyrate and isobutyrate with morpholine in different percentages of MeOH-H<sub>2</sub>O solvent mixture are measured spectrophotometrically at 25°C. The second order rate constants increased with increasing water content. The correlation between rate constants, single, dual and multiparameters of MeOH-H<sub>2</sub>O mixed solvents namely solvatochromic parameters  $\alpha$ ,  $\beta$ ,  $\pi^*$ , as well as correlation with solvent properties such as  $\chi_{H_2O}$ ,  $\chi_{MeOH}$ ,  $[H_2O]$ ,  $\log[H_2O]$ , and  $1/\epsilon$  are examined. Single-parameter correlations of  $\log k_A$  versus  $\pi^*$ , and  $\alpha$ -parameters give good and acceptable results respectively. However,  $\beta$ -parameter shows different behaviours. Addition of a second and a third parameter improved the correlation. The coefficient values of these parameters show that the titled reactions depend mainly on the non-specific solvation and minor specific solvation of the mixed solvent. The media effect can be described by means of the solvatochromic parameters of the mixed solvent.

**Keywords:** Solvation; hydrogen bond donor ability; linear solvation energy relationship (LSER); solvatochromic parameters; n-butyrate, isobutyrate, Morpholine, 90% Methanol-water.

## 1. Introduction

Kinetic solvent effects on chemical reactions in different media are usually correlated in terms of 'solvent polarity' which sums up all the specific and non-specific interactions of the media with initial and transition states (Mousa, M.A., Diefallah E. H., Dessouk, H. A., Atwa S. T., 1989 & Mandal. U, Kundu, K. K., 1986). Consequently, solvent effects are closely related to the nature and extent of solute-solvent interactions locally developed in the immediate vicinity of solutes. Solute-solvent interactions are much more complex in mixture of solvents than in pure solvents due to the possibility of preferential solvation by any of the solvents present in the mixtures (Rose S. M., Ra' fols, C., Ortega, J., Bosch, E., 1995 & Buhvestov, U., Rived, F., Ra' fols, C., Bosch, E and Rose' S. M., 1998 & Herodes, K., Leito, I., Koppel, I., Rose, S. M., 1999. Garcí'a, B., Aparicio, S., Alcalde, R., Ruiz, R., Da'vila, M. J., Leal, J.M., 2004). The complexity of solvent effects on reaction rates is evident from the fact that there is no perfect single theory to deal with such a complexity and there are several empirical equations that are claimed to explain only certain specific solvent effects, such as polarity (Skiwierczynski, R. D., Connors, K. A., 1994).

Methanol water mixtures have very special properties, which are different from that of the other alcohol-water mixtures. It may be due to the larger dielectric constant of the methanol-water mixtures. When methanol is mixed with water, other physical properties such as density, viscosity, surface tension, are changed due to molecular interactions (Carr C, Riddick J.A., 1951 & Mikhail S. Z., Kimel W.R., 1961). The presence of methanol decreases the number of hydrogen bonds between the water molecules (Farhadian and Shariaty-Niassar., 2009) due to which the hydrophobic repulsion decreases.

Several studies have been reported on the application of Kamlet-Taft parameters (Kamlet, M. J., Abboud, J. L., Abraham, M. H., Taft, R. W., 1983 & Pyleta, O., Wevecna, T., Ludwing, M., 1990 & Banerjee, K. K., Mathur, D., Sharma, O. K., 1993).

This work discusses the reactivity of the esters **1-9** with Morpholine (Youssef. M. N., El-Shazly.A.S., Hamed. A. E, 2015) in 90%-10% MeOH-H<sub>2</sub>O mixed solvents as well as investigates the effect of their solvatochromic parameters on reaction rate. Our interest is extended to see the effects of concentration and relative permittivity on the rate constants in methanol-water mixed solvent media.

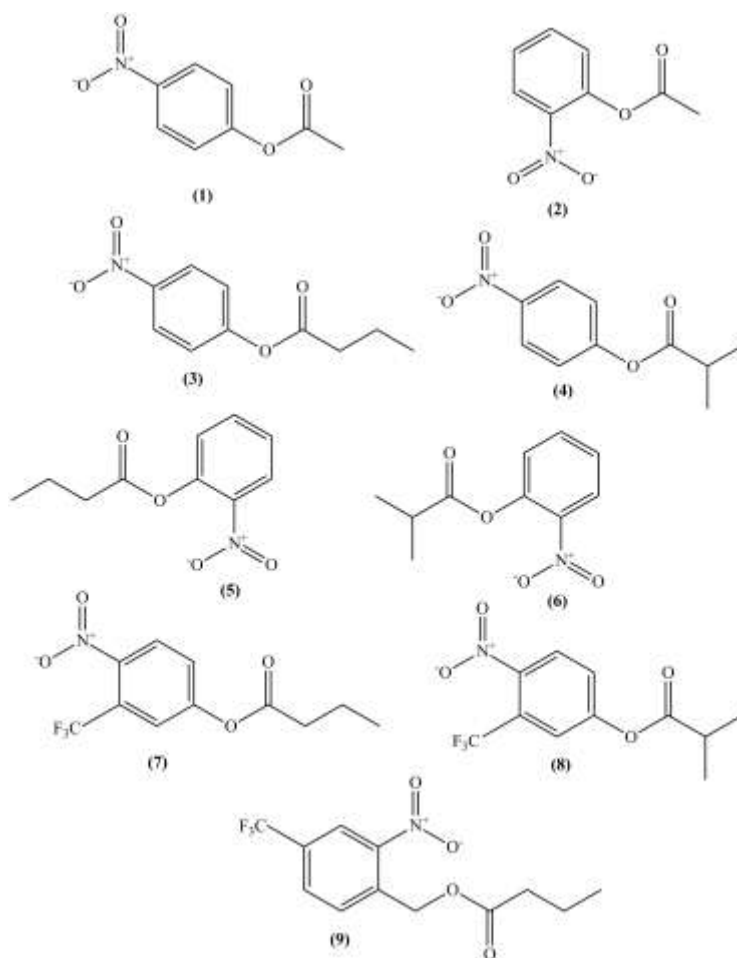


Figure 1.

Ester 8 is analogous to flutamide (4-nitro-3-trifluoromethyl-isobutylamide), (**Fig. 2**), while the other esters are different from flutamide in the position of substituent in the aromatic ring and the structure of the ester group – OR.

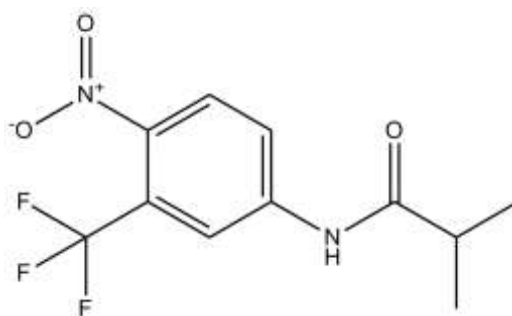


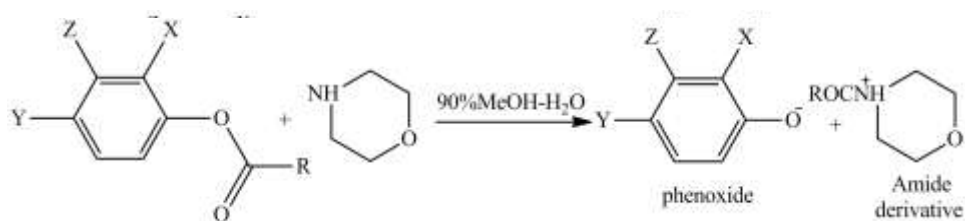
Figure 2

## 2. Material and Methods

Methanol was obtained from Sigma Aldrich >99.99% and were used without further purification. Morpholine was obtained from Sigma Aldrich and used without distillation. The UV spectra were carried out on a V-730, UV-VIS spectrophotometer.

### 3. Results & Discussion

The morpholinolysis of substituted phenyl acetate, n-butyrate and isobutyrate **1-9** with morpholine (Mo) in various H<sub>2</sub>O-MeOH mixed solvents (10%-90%) proceeds exclusively through acyl-oxygen scission as indicated from the identification of substituted phenoxide, equation (1). Also, the reaction obeyed clean second order rate constant (Youssef. M. N., El-Shazly.A.S., Hamed. A. E, 2015).

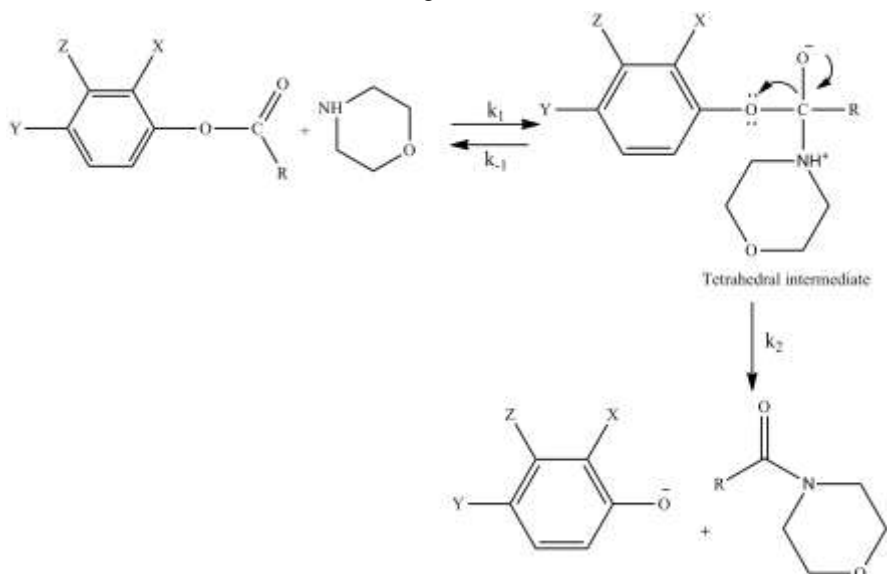


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|--|--|
| 1. X=Z=H, Y=NO <sub>2</sub> , R= CH <sub>3</sub> | 7. X=H, Y=NO <sub>2</sub> , Z= CF <sub>3</sub> , R= n-propyl   |
| 2. X=NO <sub>2</sub> , Y=Z=H, R= CH <sub>3</sub> | 8. X=H, Y=NO <sub>2</sub> , Z= CF <sub>3</sub> , R= isopropyl  |
| 3. X=Z=H, Y=NO <sub>2</sub> , R= n-propyl        | 9. X= NO <sub>2</sub> , Y= CF <sub>3</sub> , Z= H, R= n-propyl |
| 4. X=Z=H, Y=NO <sub>2</sub> , R= isopropyl       | 10. X=Z=H, Y=NO <sub>2</sub>                                   |
| 5. X=NO <sub>2</sub> , Y=Z=H, R= n-propyl        | 11. X=NO <sub>2</sub> , Y=Z=H                                  |
| 6. X=NO <sub>2</sub> , Y=Z=H, R= isopropyl       | 12. X=H, Y=NO <sub>2</sub> , Z= CF <sub>3</sub>                |
|  | 13. X=NO <sub>2</sub> , Y= CF <sub>3</sub> , Z=H               |

It has been reported that the reactions of esters **1 to 9** (Figure 1) proceed through a stepwise mechanism, Scheme (1). It shows TS1 as the TS structure for the reaction of esters **1,3,5,7** and TS2 as for the reactions of esters **2,4,6,8**. (Figure 3) (Youssef. M. N., El-Shazly.A.S., Hamed. A. E, 2015).



Figure 3.



Scheme 1

Table 1. Second order rate constants and solvatochromic parameters for the reaction of 1-9<sup>a</sup> with morpholine in water-methanol mixed solvent.

%MeOH	$10^2 k_2 \text{ l mol}^{-1} \text{ s}^{-1}$												
	1	2	3	4	5	6	7	8	9	$\alpha$	$\beta$	$\pi^{\#}$	[H <sub>2</sub> O]
100	3.00	2.00	0.61	0.38	0.56	0.06	9.08	2.44	25.00	0.93	0.620	0.60	0.00
90	8.10	7.20	1.84	1.70	0.80	0.110	26.00	6.40	27.00	1.009	0.652	0.73	5.55
80	10.50	7.60	3.50	1.75	1.60	0.260	29.00	7.80	55.00	0.995	0.692	0.82	11.11
70	14.97	8.72	5.40	3.00	2.90	0.480	40.00	10.80	63.00	0.981	0.727	0.91	16.66
60	22.60	18.00	7.60	5.50	4.00	0.910	50.40	16.00	73.00	0.980	0.700	0.98	22.22
50	43.00	28.90	14.18	8.90	5.10	1.440	65.00	23.88	96.00	1.011	0.640	1.04	27.77
40	74.00	48.60	16.00	12.12	7.30	2.200	76.00	27.00	113.00	1.037	0.562	1.09	33.33
30	80.60	65.00	27.50	14.70	14.00	3.600	107.00	42.40	126.00	1.067	0.520	1.12	38.88
20	116.0	80.60	39.00	24.50	16.00	4.200	124.00	51.00	200.00	1.107	0.465	1.16	44.49
10	130.5	98.50	46.00	31.00	22.00	5.500	172.30	70.00	230.00	1.142	0.466	1.20	50.00
a	7.650	7.955	8.40	8.460	7.490	9.134	5.427	6.5	4.486	-----	-----	-----	-----
100-70%	5.718	5.260	8.550	7.346	6.812	8.640	5.387	5.600	4.270	-----	-----	-----	-----
b	-3.27	-3.45	-2.85	-3.23	-3.03	-3.50	-1.97	-2.59	-1.88	-----	-----	-----	-----
10-70%													
c	2.725	2.750	3.04	3.010	2.700	3.458	1.884	2.277	1.614	-----	-----	-----	-----
d	0.054	0.053	0.053	0.056	0.05647	0.068	0.0342	0.043	0.034	-----	-----	-----	-----
n	1.41	1.89	1.51	1.42	1.50	1.85	1.14	1.35	0.9	-----	-----	-----	-----

Where **a**: slope of  $\log k_A$  vs  $\alpha$ , **b**: slope of  $\log k_A$  vs  $\beta$ , **c**: slope of  $\log k_A$  vs  $\pi^*$ , **d**: slope of  $\log k_A$  vs [H<sub>2</sub>O], **n**: slope of  $\log k_A$  vs  $\log[\text{H}_2\text{O}]$ , [ester]= $10^{-4} \text{ mol.l}^{-1}$ .

The plots of rate constants (**Table 1**) of the esters **1** (acetate and 4-NO<sub>2</sub>) against **2** (acetate and 2-NO<sub>2</sub>) and **3,5** (n-butyrate, 4-NO<sub>2</sub>) against **4,6** (isobutyrate, 4-NO<sub>2</sub>) respectively, as well as **7** (n-butyrate, 3-CF<sub>3</sub>, 4-NO<sub>2</sub>) versus **8** (isobutyrate, 3-CF<sub>3</sub>, 4-NO<sub>2</sub>) give straight lines in 100%-10% MeOH-H<sub>2</sub>O mixed solvents. This correlation points out that all esters 1-9 have common mechanism in various MeOH-H<sub>2</sub>O mixed solvents and form the same intermediate namely tetrahedral intermediate.

The kinetic expression is derived with reference to the mechanism in Scheme (1) and on the basis of the steady state assumption, where the Mo symbolizes morpholine. The overall kinetic expression is given by equation 2

$$k_{\text{obs}} = k_1 k_2 [\text{Mo}] / (k_{-1} + k_2) \quad (2)$$

Where  $k_{\text{obs}}$  is the pseudo first-order rate constant. Considering the formation of tetrahedral intermediate through TS1 and departure of aryloxy anion is fast and thus  $k_2 \gg k_{-1}$ , the overall kinetic expression is reduced to equation 3

$$k_{\text{obs}} = k_1 k_2 [\text{Mo}] / k_2 = k_1 [\text{Mo}] \quad (3)$$

The formulation of  $k_A$  yields

$$k_2 = k_{\text{obs}} / [\text{Mo}] = k_1 \quad (4)$$

Where  $k_A$  is the apparent second-order rate constant obtained by dividing the pseudo first-order constant  $k_{\text{obs}} \text{ s}^{-1}$  by the amine concentration or equal to the slope of the linear correlation of  $k_{\text{obs}}$  versus  $[\text{Mo}]$ .

An alternative consideration is that  $k_{-1} \gg k_2$  i.e. the departure of aryloxy anion through TS2 is the rate limiting step. Thus equation 2 is reduced to equation 5.

$$k_{\text{obs}} = k_1 k_2 [\text{Mo}] / k_{-1} = K_1 k_2 [\text{Mo}] \quad (5)$$

Where  $K_1$  is the equilibrium constant of the first and fast reversible step. The formulation of  $k_A$  yields equation 6.

$$k_{\text{obs}} / [\text{Mo}] = k_A = K_1 k_2 \quad (6)$$

The first-order dependence on Mo concentration is compatible with rate limiting nucleophilic attack and also with a tetrahedral intermediate decomposition.

Table (1) reveals that:

- (i) The rate constants of reaction increase with progressive addition of water to MeOH. It must be mentioned here that the increase in stability of the activated complex is responsible for the increase in the rate constants. The stability in the present investigation arises from the solvation of the transition state TS1 that leads to the tetrahedral intermediate or the TS2 develops from decomposition of the tetrahedral intermediate to the product. This stabilization depends on solvent properties, namely, preferential solvation, related to the ability of solvent to stabilize charge separation, the polarity/polarizability  $\pi^*$ , which is a measure of the ability of solvent to stabilize a charge or a dipole by its own dielectric effect, hydrogen bond donor (HBD)  $\alpha$ , and hydrogen bond acceptor (HBA)  $\beta$  parameters, describes the ability of solvent to accept a proton in a solute to a solvent hydrogen bond. These values in various MeOH-H<sub>2</sub>O mixtures were obtained from literature (G. Anastopoulos & T. Latsinoglou., (2005).
- (ii) A systematic increase in rate constant is observed by each increase in H<sub>2</sub>O% by 10%. This points out that as the polarity of the solvent increased, the stabilization of the activated complex involves in the rate determining step increased. i.e. a polar activated complex is formed.

### 3.1 Effect of Varying Mole Fraction of MeOH on Reaction Rate

The  $k_A$  values obtained in MeOH-water mixtures increase with increasing percentage of H<sub>2</sub>O. These variations could be attributable to (a) an excess or deficiency of molecules of one of the solvents, (b) The composition of the immediate surroundings of the activated complex either TS1 or TS2 may differ from the composition of the bulk mixture. (Marcus, Y., Migron, Y., 1991), (c) the different preferential solvation between the initial and transition states. (Terrier, F., Ferrer, H. 1991). It is interesting to note that there is actually a linear relationship between the  $k_A$  values and the mole fraction of MeOH ( $\chi_{\text{MeOH}}$ ) in the binary mixed solvents.

The rate constants of esters 1-9 decrease with increasing proportion of each alcohol in the mixed solvents. This is because in the water-rich composition, the MeOH molecules occupy the cavities between the water molecules

without disrupting the water structure (Marques, I., Fonrodona, G., Baro, A., Guiteras, J., Beltran, J. L., 2002) but in the alcohol-rich composition, clusters of molecules of either water or alcohol are surrounded by regions containing both kinds of molecules. (Barbosa, J., Fonrodona, G., Marques, I., Sanz-Nebot, V., 1997) and therefore, a change in polarity of the medium has a major effect on the substitution process. Therefore, any variation in polarity of the medium exerts a strong influence on the substitution process.

### 3.2 Effect of Varying $H_2O$ on Reaction Rate

The plots of  $k_A$  against  $H_2O\%$  (v/v) for the reactions of esters 1-9 with Mo show that the  $k_A$  values increase with increasing percentages of  $H_2O$  in the mixed solvents. Table (1) shows that the rate constant values of all esters 1-9 show small changes when the percentage of water increase by 10%. This variation in the percentage of the  $H_2O$ -cosolvent is due to solute-solvent and solvent-solvent interaction effects. In fact, solvent-solvent interactions can be influenced by intermolecular forces between the solution components. This effect possibly changes the structure of the mixture when the percentage of the organic solvents increases to higher values (Barbosa, J., Fonrodona, G., Marques, I., Sanz-Nebot, V., 1997). This explanation is in accordance with previous results for other aqueous-organic solvent mixtures and in agreement with the present results. (Demirelli, H., 2005).

The plot of  $\log k_2$  versus  $\chi_{H_2O}$  for the reactions of esters 1-9 with Mo gives good straight line with positive slope ( $r = 0.94-0.99$ ) indicating that water is the preferential solvent. i.e. preferential solvation of the activated complex TS1 and TS2 as well as the polarity of the tetrahedral intermediate is increasing by increase the ratio of water. This is because in water-rich medium the water structure remains more or less intact to the MeOH molecules without disrupting water structure (Marques, I., Fonrodona, G., Baro, A., Guiteras, J., Beltran, J. L. 2002)

The decrease in reaction rate for each 10% increase of MeOH ratio may be due to (a) the tetrahedral structure of water has been slightly broken, causing small free water molecules which preferentially solvates the tetrahedral intermediate and (b) the Mo molecule affinity will decrease since the water and/or MeOH molecules can associate with it. These two factors compensate the effect on reaction rate in which the first factor overcomes the second one and a net increase in rate is observed.

The same trend has already been reported for various organic reactions in different  $H_2O$ -cosolvent mixtures. It has been reasonably assumed that preferential solvation of the charged intermediate or transition state developed from neutral reactants by water is mainly responsible for such a monotonic dependence of  $k_A$  on the solvent composition. (Ismail, A. M., Zaghoul, A. A. 1998 & Amel M. Ismail, Ramyah F. Radman and Nada A. Al-Jallal, 2010)

The trend of reaction rates with solvent composition can also be observed in the light of  $\log k_A$  versus  $\log [H_2O]$  correlation. The slope gives the number of water molecules ( $n$ ) contaminated in the transition state. Some reactions has shown that ( $n$ ) value decreases or increases when  $[H_2O]$  increases depending on the type of reaction (Easteal, A.J., Aust. J. Chem. 1979 & Humeres, E. R., Nunes, J., Machado, V.G., Gasques, M.D.D., Machado, C. 2001 & Henederson, J. Wijnen, J. W., Zavarise, S. J., Engberts, J. B. F.N. (1996). & El Seoud, O. A., Siviero, F. (2006). The ( $n$ ) value reflects the number of water molecules in the transition state (Suppan, P., Ghonium, N., 1997 & Marcus Y., Monatsh. 2001 & Abboud, J., Douhal, A., Arin, J., Diez, M. T., Homan, H., 1989). In the present reaction in MeOH- $H_2O$  mixed solvent, the number of molecules surrounding the activated complex are small in magnitude ( $n = 0.9-1.89$ ) indicating little solvation and in turn little stabilization of the activated complex. This reject that the free water molecules are responsible for the increase rate constant with progressive addition of water. Another treatment for the effect of various  $H_2O$  concentrations on the reaction rate is tried for a range of  $n$  from 1 to 9 from the plot of  $k_A$  against  $[H_2O]^n$ . Curves were obtained in each case except for the plots when  $n = 2$  and  $n = 3$  with very good correlation coefficient ( $r$ ). The  $n$  values are quite equal from the plots of  $k_A$  versus  $\log [H_2O]$ .

### 3.3 Effect of Dielectric Constants on the Reaction Rates

In general, the effect of solvent on rate constant depends upon electrostatic and non electrostatic factors. Activated complex is stabilized by the nature of co-solvent, specific solvent-water interactions and specific interactions of co-solvent with solute. If the dielectric constant and the solvating ability of the solvent are decreased, high energy of activation will be required to form the developed activated complex and consequently the rate of the reaction will be lowered.

It is found that the logarithm of  $k_A$  varies linearly as a function of the reciprocal of dielectric constant ( $1/\epsilon$ ) of the medium for reactions of esters 2, 4, 6 and 8 with Mo in the whole range of water concentrations. This linearity

indicates an electrostatic treatment of reaction rates and postulates a continuous dielectric medium, this behaviour is in agreement with the postulate of the theory upon which the relation between  $\log k_A$  and  $1/\epsilon$  is linear. (E.S. Amis, 1966). In contrast, the plot of  $\log k_A$  for the reactions of esters 1, 3, 5 and 7 with Mo at various composition of H<sub>2</sub>O-MeOH reveals a non-linear relationship for each ester over the whole range of solvent composition. This deviation from linearity is explained by (i) It may attributed to the electrostatic forces developed in the activated state, (ii) A large differential effect of solvent structure is acting on the initial and transition state, (iii) A change in solvent structure with varying solvent composition (Laidler K. J., Skroener P. A., 1956) and finally a charge development in the transition state involves a more polar activated complex than the reactants.

### 3.4 Test the Correlation between Rate $k_A$ and the Total Number of Moles ( $n_1 + n_2$ ) of Various MeOH-H<sub>2</sub>O Mixed Solvents at 25°C.

S. A. El-Shazly et al. (El-Shazly.S et al. 1991), proposed a general equation for the variation of specific rate constant,  $k$ , with total number of moles ( $n_1 + n_2$ ) for any reaction in mixed water-organic solvent. The correlation takes the mathematical form shown in equation 6 below:

$$\ln k = \ln k \frac{T}{n} - \frac{\Delta\mu^*(n_1+n_2)}{RT} \quad (6)$$

In this equation,  $\Delta\mu^*$  is the chemical potential of transition state. The plot of the logarithm of the rate constant against ( $n_1 + n_2$ ) gives a good straight line with a slope equal to  $-\frac{\Delta\mu^*}{RT}$ . This relationship obeyed a good approximation ( $r = 0.96-0.99$ ). The estimated values of the change in the chemical potential,  $\Delta\mu^*$  are found to be -30.10, -29.48, -, -29.50, -30.79, -31.30, -31.78, kJ/mol for the esters **1, 2, 3, 4, 5, 6** at 25°C respectively. This indicates that these compounds pass through the same pathway mechanism. The estimated values of the change in the chemical potential,  $\Delta\mu^*$  are found to be -18.60, -23.7 & -18.88 kJ/mol for the esters **7, 8, 9**. The higher values of chemical potential for compounds (**7 to 9**) than those of compounds (**1 to 6**), may arise from the presence of CF<sub>3</sub> which assists the formation of hydrogen bond in the transition state leading to stabilize the transition state more stable than the reactant. Accordingly, the rate increases as shown in the present data consistent to the theory of absolute reaction rates.

### 3.5 Multiparameter Analysis

To decide which factor(s) has a large contribution on the reaction rate, an examination of the (LSER) can explain which microscopic parameter of the solvent influenced the reaction. We attempt to examine quantitatively the correlation between rate constants of the titled reactions and single, dual and multiparameters of MeOH-H<sub>2</sub>O mixed solvents namely  $\alpha$ ,  $\beta$ ,  $\pi^*$ .

Table 1 reveals the coefficient and correlation coefficients for the reaction of the esters **1-9** with Mo from the plots of rate constants  $k_A$  against these solvent parameters.

Usually  $\alpha$ ,  $\beta$ ,  $\pi^*$ , solvatochromic parameters of the media are not individually the main factor in determining solvent effect on the reaction rate. The Taft-Kamlet Abboud equation ( Kamlet, M. J., Abboud, J. M., Abraham, M. H., Taft, R. W. 1983) takes the general formula of equation 7 as:

$$\text{SDP} = \text{Constant} + a\alpha + b\beta + c\pi^* \quad (7)$$

Where the solvent dependent phenomena (SDP) such as rate constant, equilibrium constant, spectroscopic shift, are modeled as a linear combination of  $a\alpha$ ,  $b\beta$  &  $c\pi^*$ , The contributions of the mixed solvent properties to solvation can be extracted from the regression coefficients (a), (b) and (c) respectively. These coefficients permit a comparison of the response of different substrates and activated complex to the same solvent property.

Correlation of  $\log k_A$  values with different solvent parameters, viz,  $\alpha$ ,  $\beta$ , and  $\pi^\ddagger$  gives different behaviour. A better correlation is observed with  $\pi^\ddagger$  and poor correlation with  $\alpha$  while  $\beta$  parameter shows good correlation coefficients in two regions. Table (1) shows that  $\alpha$ -parameters increase as the rate constants are increased. Also, the correlation coefficient 'a' for  $\alpha$ -parameters is ranged between 0.7-0.811 with positive slope indicating that the solvent moderately stabilizes the activated complex by specific solvation more than the reactant. Similarly, the 'c' coefficient of  $\pi^*$ -parameters give value with positive slope ( $r = 0.95-0.99$ ). This points out that the activated complex involved in the rate determining step is stabilized through non-specific solvation.

However,  $\beta$ -parameters of the MeOH-H<sub>2</sub>O mixed solvent show two behaviours: the first region from 100%MeOH to 70%MeOH shows an increase in rate constant while the second region starting from 60% to 10%MeOH shows a decrease in rate constant. This is compatible with the  $\beta$ -values, cited in Table (1). This leads to suggest that the reactions of esters 1-9 with Mo is suggested to be affected by specific solvation.

Addition of a second parameter to this single equation slightly improved the strength of the correlation. Table (2)

shows that the influence of  $\pi^*$  solvatochromic parameter on the rate of the titled reaction is more than those of  $\alpha$ -parameters. This indicates that the reaction rate is influenced by great non-specific solvation and small specific solvation.

Table 2. Showing a and c coefficients for the reaction of esters 1-9 with Mo in 100%-10% MeOH-H<sub>2</sub>O at 25°C

$\log k_A = \text{constant} + a\alpha + c\pi^*$			
Ester	a	c	r
1	1.60	2.30	0.98
2	2.27	2.15	0.99
3	1.25	2.71	0.99
4	1.74	2.54	0.99
5	1.08	2.46	0.99
6	0.13	3.42	0.99
7	1.50	1.48	0.99
8	1.65	1.84	0.99
9	0.85	1.38	0.99

The introduction of a third parameter yields good correlation as shown in Table (3). The three parameters  $\alpha$ ,  $\beta$  and  $\pi^*$  indicate that the rate of the titled reaction is ranged between small to negligible effect by  $\alpha$  and  $\beta$  solvent parameters while the parameter  $\pi^*$  predominates. This means that the titled reaction of esters 1-9 with Mo depends mainly on the non-specific solvation of the mixed solvent.

Table 3. Showing a, b and c coefficients for the reaction of esters 1-9 with Mo in 100%-10% MeOH-H<sub>2</sub>O at 25°C.

$\log k_A = \text{constant} + a\alpha + b\beta + c\pi^*$				
Ester	a	b	c	r
1	0.45	-0.75	2.41	0.99
2	1.36	-0.59	2.21	0.99
3	1.61	0.23	2.68	0.99
4	2.16	0.27	2.51	0.98
5	-0.49	-0.89	2.55	0.99
6	-1.29	-0.92	3.52	0.99
7	2.55	0.68	1.41	0.99
8	1.76	0.077	1.83	0.99
9	0.27	-0.38	1.42	0.96

The positive sign of  $\pi^*$  coefficients suggests that the transition state is more solvated than reactants due to a charge separation in the transition state. The rate of reaction is minor influenced by  $\alpha$  and  $\beta$  parameters which indicates that the specific solvation plays a part in the effect on rate.

To show the efficiency of the tri correlation, for example, the calculated values of the reaction rate constants in MeOH-H<sub>2</sub>O mixed solvents have been plotted versus the experimental values. The correlation shows a good agreement between the experimental and the calculated values of  $\log k_A$ . Thus, results indicate that the media effect on this reaction can be described by means of the solvatochromic parameters of the mixed solvent.

#### 4. Conclusion

The second order rate constants for the reaction of esters analogous to flutamide namely substituted phenyl acetate, butyrate and isobutyrate with morpholine in different percentages of MeOH-H<sub>2</sub>O solvent mixture at 25°C were correlated with solvent parameters using Kamel-Taft solvatochromic equation:  $\log k_a = a\alpha + b\beta + c\pi^* + \text{Constant}$ . The signs of the coefficients were in agreement with the postulated reaction mechanism. The rate of the reaction increased by adding water. The influence of H<sub>2</sub>O on the reaction rate was discussed on the bases of correlation coefficient for the correlation of  $k_a$  versus  $V_{H_2O}$ ,  $[H_2O]$  and  $\log k_a$  against  $\chi_{H_2O}$  as well  $\log[H_2O]$ , these showed that free water molecules are not responsible for the increase in rate with progressive addition of water. The correlation between  $\log k_a$  and  $1/\epsilon$  is linear for esters (1,3,5,7) & non-linear for esters (2,4,6,8). The coefficient values of solvatochromic parameters as well as the linearity of correlations indicate that the titled reactions depend mainly on the non-specific solvation and minor specific solvation of the mixed solvent.

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