

Kinetics of the Reaction of 2-Chloro-quinoxaline with Hydroxide Ion in ACN–H₂O and DMSO–H₂O Binary Solvent Mixtures

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Received: 4 October 2010 / Accepted: 27 December 2010 / Published online: 13 July 2011
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Abstract The kinetics of alkaline hydrolysis of 2-chloroquinoxaline (QCl) with hydroxide ion was investigated spectrophotometrically at different percentages of aqueous–organic solvent mixtures with acetonitrile (10–60% v/v) and with dimethylsulphoxide (10–80%) over the temperature range from 25 to 45 °C. The reaction was performed under pseudo first order conditions with respect to 2-chloroquinoxaline (QCl). An increase in the percentage of organic solvent (v/v) has different effects on the reaction rate constants, presumably due to hydrogen bond donor and acceptor differences of the media and other solvatochromic parameters. The data were discussed in terms of the Kamelt-Taft parameter and $E_T(30)$. A nonlinear relation between the logarithm of the rate constant and reciprocal of the dielectric constant suggests the presence of selective solvation by the polar water molecules. Activation parameters ΔH^\ddagger , ΔS^\ddagger and ΔG^\ddagger were determined and discussed.

Keywords 2-Chloroquinoxaline · Hydrolysis · Spectrophotometry · Kinetics · Activation parameters

1 Introduction

2-Chloroquinoxaline (QCl) is a reagent used in the synthesis of chloroquinoxaline sulfamide, which is active against human cancers [1–3]. Quinoxaline derivatives play a vital role in some biological fields. Many antimalarial [4], antifungal [5], antibacterial [6], antidiabetic, and antiviral drugs contain a quinoxaline nucleus [7, 8].

Aromatic nucleophilic substitution reactions are affected by solvent polarity and specific hydrogen bond, electron pair donor, electron–pair acceptor and solvophobic interactions [9]. Meisenheimer complexes are possible intermediates in *ipso* nucleophilic substitution reactions. Another pathway for this type of reaction is nucleophilic substitution via a ring opening/ring closure S_N mechanism (ANRORC) [10]. Either mechanism for these

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substitutions can prevail depending on the solvent-leaving group as well as the type of nucleophile [10, 11]. Recently, the alkaline hydrolysis of 2-chloroquinoxaline was reported to follow a $S_N(AE)^{iD_{SO}}$ mechanism [12–16].

Solvents effects are closely related to the nature and extent of solute–solvent interactions [13, 14, 17–19]. Some models considered the solvent as a continuum dielectric, whereas others treat the solvent as having both bulk interactions and those arising from the particular molecular properties.

One key approach to understand solvent effects is solvatochromism. The solvatochromic parameter approach, pioneered by Taft and Kamlet and co-workers [20–23], attempts to separate the bulk and specific effects of solvents on a variety of observable solute properties in terms of their solvatochromic parameters.

The aim work of this work is to study the effect of solvent on the alkaline hydrolysis of the title compound as the substrate in two different organic solvents acetonitrile (ACN) and dimethylsulfoxide (DMSO) in mixtures with water as co-solvent, at various mixed solvent compositions, in order to check the utility of varying these composition to explain the reaction mechanism. The data are discussed in terms of Kamelt-Taft parameter and $E_T(30)$.

2 Experimental

2-chloroquinoxaline was commercially available, 98% (Aldrich product), melting point 47–50 °C. The solvents acetonitrile (ACN) from SCHARLAU, AC032S extra pure 99.5% (0.1% water), and dimethylsulphoxide (DMSO), reagent grade (BDH), were further purified as reported previously [24]. Fresh solvent mixtures were prepared by mixing known volumes of one of the organic solvents with doubly distilled water before beginning each kinetic run. Carbonate-free sodium hydroxide was prepared as reported previously [24].

3 Reaction Products

General procedure: 2-chloroquinoxaline (0.5 g) was treated with sodium hydroxide (DMSO–H₂O, v/v 1:100) and refluxed at 40 °C for 1 hour. Upon cooling and acidification, 2-hydroxy quinoxaline was obtained and separated by fractional crystallization. Its melting point was determined to be 271–272 °C.

3.1 Caution

2-Chloroquinoxaline is toxic if swallowed, irritating to the eyes and respiratory system, and irritating to skin. Protective clothing, suitable gloves, suitable respiratory equipment and eye/face protection should be worn to avoid hazards from contact with 2-chloroquinoxaline.

4 Kinetic Measurements

The kinetics of alkaline hydrolysis of 2-chloroquinoxaline, compound **1**, with OH[−] in large excess were measured spectrophotometrically using a JASCO (V-30) UV-VIS spectrophotometer in conjunction with a thermostatted cell compartment controlled to ± 0.1 °C. The reaction was followed at $\lambda_{max} = 356$ nm at temperatures ranging from 25 °C to 45 °C,

with spectroscopic changes with time followed through the hypochromic shift. The kinetic runs were carried out at different percentage of co-solvent over the range 10–60% (v/v) with respect to ACN, and ranging from 10–80% (v/v) DMSO, where concentrations of $5 \times 10^{-5} \text{ mol}\cdot\text{dm}^{-3}$ for **1** and $0.1 \text{ mol}\cdot\text{dm}^{-3}$ for NaOH were used.

The reaction was started after preparing a stock solution of the substrate ($1 \times 10^{-3} \text{ mol}\cdot\text{dm}^{-3}$) in a suitable amount of ACN or DMSO (the substrate was found to be very insoluble in pure water). A 0.5 mL sample of this stock solution was transferred into a 10 mL measuring flask to attain the final concentration of $5 \times 10^{-5} \text{ mol}\cdot\text{dm}^{-3}$. The rest of the solvent for a given mixture was added to get the desired mole fraction solvent composition x_{AN} or x_{DMSO} at 25 °C. The solution was thermally equilibrated at the desired temperature, followed by addition of NaOH to give the desired concentration. The above solution was then transferred quickly into a 1 cm stoppered quartz cuvette to start the measurements. The reaction was followed under pseudo first order conditions using NaOH in large excess. The k_{obs} values were calculated from the slopes of plots of $\ln(A_{\infty} - A_t)$ versus time t , where A_{∞} , A_t are the absorbance values at the end and at time t of the reaction. All rate constants were obtained from linear plots with correlation coefficient ≈ 0.9981 .

5 Result and Discussion

The reaction of **1** with OH^- in all solvents under similar conditions gave 2-hydroxy quinoxaline, Scheme 1.

5.1 Variation of the Rate Constant k_{obs} with the Preferential Solvation Parameter $E_T(30)$, with $1/\epsilon$ and with the Solvent Mole Fractions of ACN–H₂O and DMSO–H₂O

Values of k_{obs} over the temperature range from 25 °C to 45 °C for the reaction of QCl with OH^- in ACN–H₂O and DMSO–H₂O mixtures are reported in Tables 1 and 2, respectively. Activation parameters at different mole fraction of the organic solvent were computed from linear least-squares Arrhenius plots, and these results also collected in Tables 1 and 2.

Tables 1 and 2 reveal that k_{obs} increases with the addition of DMSO, while it decreases with addition of ACN. It is assumed that the decreases in k_{obs} with increasing percentage of ACN is due to the tendency of ACN to form a separate liquid layer at higher concentrations of water [10] which is consistent with the decrease in polarity of the medium. Accordingly, further addition ACN solvates OH^- and thereby decreases its nucleophilicity, leading to the observed decrease in the rate of reaction. The ACN–H₂O mixtures have been examined in molecular dynamic simulations, and Kovacs and Laaksonen [25, 26] concluded that

Scheme 1 Reaction of 2-chloro-quinoxaline with hydroxide ion

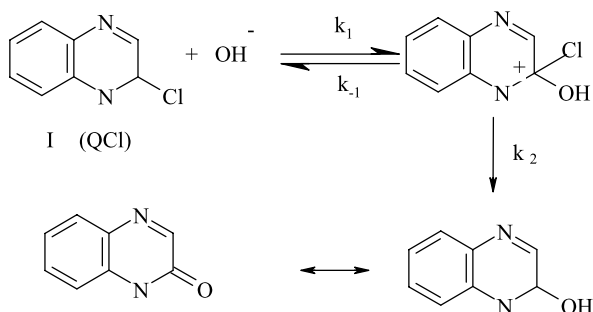


Table 1 First order rate constant, k_{obs} at different temperatures and activation parameters at 25 °C for the reaction of 2-chloroquinoxaline with OH^- (0.1 mol·dm $^{-3}$) in ACN–H $_2$ O mixtures

V-%	x (ACN)	$10^5 k_{\text{obs}}$, s $^{-1}$				Activated parameters at 25 °C			$-\Delta S^\ddagger$ J·mol $^{-1}$ ·K $^{-1}$	ΔG^\ddagger kJ·mol $^{-1}$
		25 °C	30 °C	35 °C	45 °C	E_a kJ·mol $^{-1}$	ΔH^\ddagger kJ·mol $^{-1}$	$-\Delta S^\ddagger$ J·mol $^{-1}$ ·K $^{-1}$		
10	0.037	1.55	2.59	3.58	9.83	69.71 ± 3.5	67.23 ± 3.5	92.34 ± 11.5	94.76 ± 7.0	
20	0.079	1.03	1.87	2.75	8.22	80.75 ± 3.7	78.25 ± 3.7	58.67 ± 12.2	95.76 ± 7.4	
30	0.129	0.94	1.67	2.55	7.42	80.57 ± 2.7	78.09 ± 2.7	60.06 ± 8.8	96.0 ± 5.3	
40	0.187	0.75	1.31	2.33	6.51	85.46 ± 0.9	82.98 ± 0.9	45.55 ± 3.4	96.57 ± 1.8	
50	0.256	0.58	0.89	1.99	5.76	98.49 ± 4.9	96.01 ± 4.9	5.32 ± 16	97.61 ± 9.7	
60	0.341	0.46	0.79	1.69	4.50	91.42 ± 4.8	88.94 ± 4.8	29.62 ± 15.9	97.77 ± 9.6	

Table 2 First order rate constant k_{obs} at different temperatures and activation parameters at 25 °C for the reaction of 2-chloroquinoline with OH^- (0.1 mol·dm $^{-3}$) in DMSO–H $_2$ O mixtures

V-%	x (DMSO)	$10^5 k_{\text{obs}}$, s $^{-1}$				Activated parameters at 25 °C			
		25 °C	30 °C	35 °C	45 °C	E_a kJ·mol $^{-1}$	ΔH^\ddagger kJ·mol $^{-1}$	$-\Delta S^\ddagger$ J·mol $^{-1}$ ·K $^{-1}$	ΔG^\ddagger kJ·mol $^{-1}$
10	0.027	1.99	3.00	5.17	10.90	67.78 ± 3.1	65.31 ± 3.07	96.71 ± 10.0	94.141 ± 6.1
20	0.060	2.18	3.60	6.58	16.50	80.512 ± 2.4	78.03 ± 2.4	53.29 ± 7.8	93.92 ± 4.7
30	0.098	4.27	7.00	9.58	24.08	67.21 ± 3.4	64.73 ± 3.4	92.28 ± 11.1	92.24 ± 6.7
40	0.126	12.70	16.33	20.10	32.08	36.43 ± 0.75	33.95 ± 0.75	186.49 ± 2.4	89.55 ± 1.4
50	0.203	26.60	33.30	40.20	60.58	32.27 ± 0.52	29.70 ± 0.54	194.25 ± 1.7	87.71 ± 1.06
60	0.275	51.00	65.20	97.08	151.08	43.74 ± 3.3	43.26 ± 3.3	150.38 ± 10.8	86.10 ± 6.5
70	0.372	173.00	226.00	326.00	526.67	44.5 ± 2.3	42.04 ± 2.3	137.6 ± 7.4	83.07 ± 4.5
80	0.538	302.10	312.92	673.00	804.40	103.97 ± 2.7	101.49 ± 2.7	61.26 ± 8.9	83.22 ± 5.4

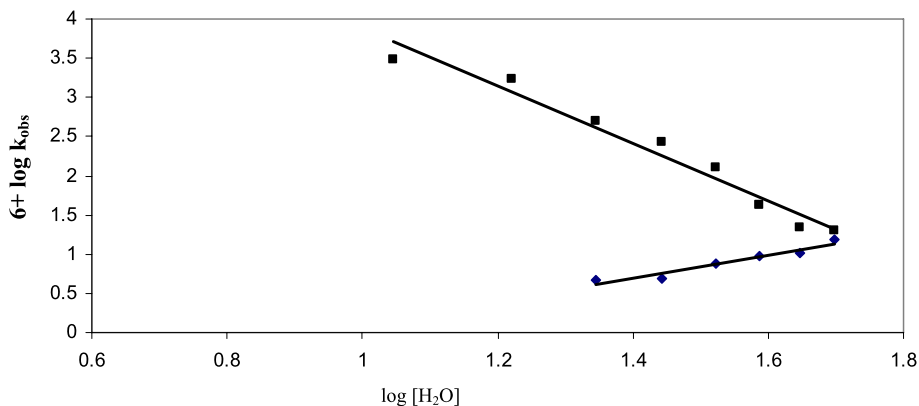


Fig. 1 Variation of the rate constant with water concentration/ ϵ for the reaction of compound **1** with OH^- at 25 °C in: ■ DMSO–water; ◆ ACN–H₂O

these mixtures exhibit microheterogeneity. The acidity, basicity and dipolarity/polarizability of ACN–H₂O mixtures must be the result of molecular interactions in their bulk phase. Consequently a change in their physical properties with mole fraction changes can be observed.

On the other hand, the increase of k_{obs} with progressive addition of the dipolar aprotic DMSO, a powerful hydrogen bonded acceptor, weakens hydrogen bonding to the base (OH^-) [27]. Thus, the large increase in kinetic activity of the hydroxide anion in DMSO is reasonably attributed to: (i) the hydroxylic solvent and may also have a thermodynamic origin, and (ii) increasing kinetic reactivity because DMSO is known to solvate the cation (e.g., Na^+ making OH^- susceptible to attacking the substrate **1**). Hence, the medium affinity leads to increasing the reaction rate upon progressive addition of DMSO. (iii) Another reason is the possible liberated free water molecules that can solvate the intermediate **I** and/or the substrate, Scheme 1.

Variations in reaction rates with solvent composition can be observed in the $\log_{10} k_{\text{obs}} - \log_{10} [\text{H}_2\text{O}]$ correlation, Fig. 1. These plots for the ACN–H₂O and DMSO–H₂O systems at 25 °C give straight lines with a positive slope equal to ~ 2 for ACN–H₂O mixtures and a negative slope equals to ~ -4 in DMSO–H₂O media. These behaviors indicate that the number of free water molecules involved in the activation process in DMSO may be higher than in the case of CAN, and consequently the values of k_{obs} increase in DMSO rather than in ACN [25]. This should be the controlling factor if a number of free water molecules are involved in the transition state for the slow kinetic step.

The plot of $\log_{10} k_{\text{obs}}$ versus $1/\epsilon$, Fig. 2, was found to be nonlinear for the reaction under investigation. The deviation from linearity is essentially due to preferential solvation between the initial and transition states. This nonlinearity is due to neglecting solvent structural effects. Also, accounting the molecular interactions are not adequate and the polarity of the bulk phase is not the main parameter to account for changes in the values of k_{obs} . In addition, the strong electrostatic force developed in the activated state restricts the freedom of motion of the solvent molecules in the neighborhood of the activated species.

The solvent effect was also analyzed using the Reichardt solvent parameter $E_{\text{T}}(30)$ which is defined as the solvent micropolarity. Plots of $\log_{10} k_{\text{obs}}$ versus $E_{\text{T}}(30)$ for water/organic co-solvent mixtures were nonlinear, Fig. 3. This observation, together with the dependence of the rate on the dielectric constant, is parallel to that previously discussed [27], presumably due to the specific solvation effect of the mixed solvent. It was found that the $E_{\text{T}}(30)$ values for

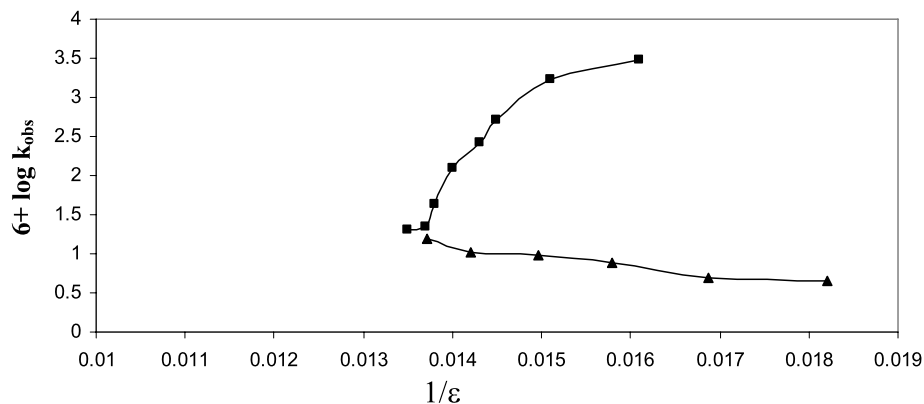


Fig. 2 Variation of $\log_{10} k_{\text{obs}}$ with $1/\epsilon$ for the reaction of compound 1 with OH^- at 25 °C in: ■ DMSO–water; ▲ ACN– H_2O

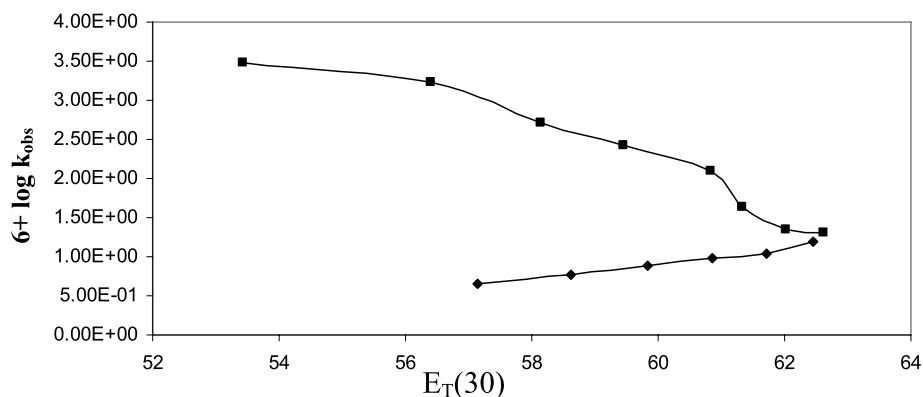


Fig. 3 Variation of $\log_{10} k_{\text{obs}}$ with $E_T(30)$ for the reaction of compound 1 with OH^- at 25 °C in: ■ DMSO–water; ◆ ACN– H_2O

both binary mixed solvents decreased with progressive addition of the organic solvent. This shows a decrease in the rate constant in the ACN– H_2O binary solvent and, in contrast, an increase the rate constant in the DMSO– H_2O binary solvent. These results indicate that correlations between $\log_{10} k_{\text{obs}}$ and microscopic solvent parameters, such as dielectric constant or micro polarity are poor, i.e., no single parameters can completely explain the effect of the solvent on reactivity.

5.2 Variation of Activation Parameters with Solvent Composition

The thermodynamic activation parameters ΔG^\ddagger , ΔH^\ddagger and ΔS^\ddagger under different experimental conditions were calculated by applying least-squares procedures to the reaction kinetics of 2-chloroquinoxaline with hydroxide ion in AN– H_2O and DMSO– H_2O . The variations of the activation parameters with x_{ACN} and x_{DMSO} are shown in Figs. 4 and 5, respectively. The variations of ΔH^\ddagger and ΔS^\ddagger with solvent composition are nonlinear and this may be due to specific solvation [28]. On the other hand, ΔG^\ddagger gradually increased in ACN– H_2O

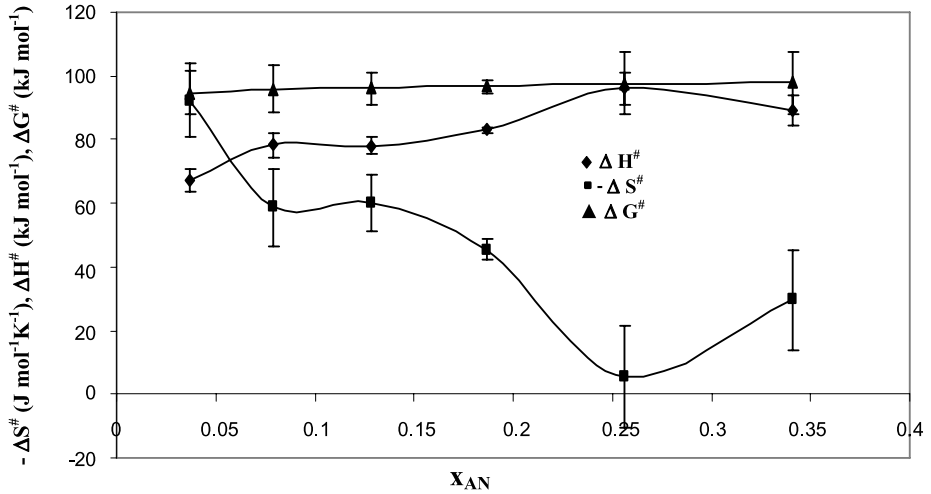


Fig. 4 Dependence of the thermodynamic parameters of activation on the composition fraction of DMSO in DMSO–H₂O mixtures for the reaction of compound 1 with OH⁻ at 25 °C

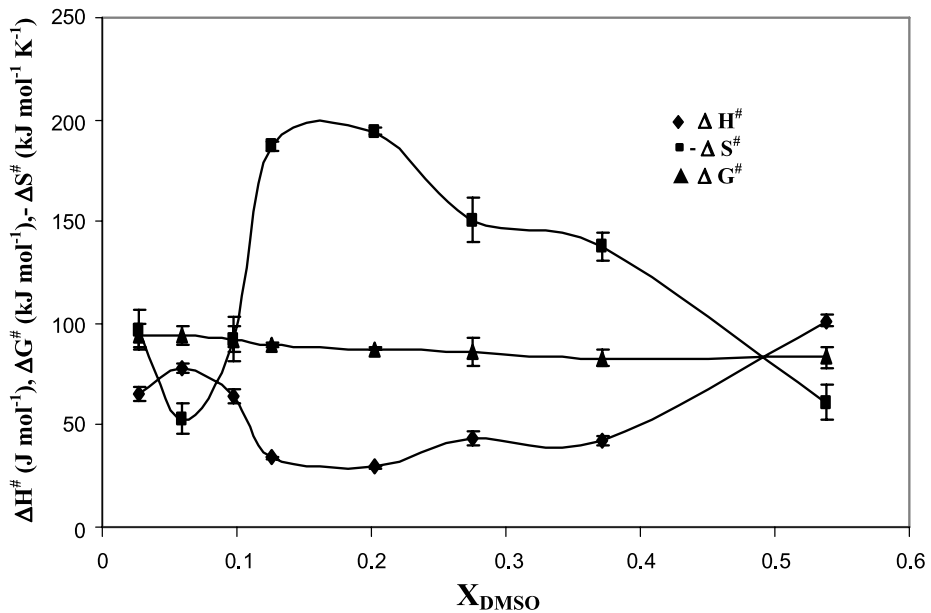


Fig. 5 Dependence of the thermodynamic parameters of activation on the composition fraction of DMSO in DMSO–H₂O mixtures for the reaction of compound 1 with OH⁻ at 25 °C

but decreased in DMSO–H₂O as functions of increasing mole fractions, due to a quasi-mirror image compensation of ΔH^\ddagger and ΔS^\ddagger , Figs. 3 and 5. Both the ΔH^\ddagger and ΔS^\ddagger curves showed a maximum at $x_{org} = 0.256$; this is in a good agreement with previously reported results in ACN–H₂O mixtures [29]. In contrast, in DMSO–H₂O mixtures a maximum is found at $x_{org} = 0.06$ and a minimum at $x_{org} = 0.1–0.2$ [28]. The maxima or minima seem to be due

to general changes in the physicochemical properties of the solvent's structure [30]. These extrema can be visualized in the light of changes of the water structure in the presence of the organic solvent. It known from viscosity and density measurements that ACN–H₂O and DMSO–H₂O mixtures, at any given temperature, have maxima at about 0.15 and 0.3 of x_{org} , respectively. Minima in the divergence from linear mixing of the molar viscosity $\Delta\eta_{12}$ was found to be at the same positions as their maxima [31].

As can be readily seen from these data, adduct complexes are formed at these maxima or minima compositions for ACN–H₂O and DMSO–H₂O. This behavior has led us to suggest that both organic solvents, along with their mixtures with water, belong to the class of solutions possessing numerous solute–water bonds that are stronger than hydrogen bonds among water molecules.

Tables 1 and 2 show that the minimum ΔS^\ddagger values for ACN–H₂O and DMSO–H₂O mixtures are -60.06 and $-194.25 \text{ J}\cdot\text{K}^{-1}\cdot\text{mol}^{-1}$ corresponding to $x_{\text{AN}} = 0.129$ and 0.203 , respectively. The maxima in ΔH^\ddagger are 78.1 and $29.7 \text{ kJ}\cdot\text{mol}^{-1}$, respectively.

Referring to the higher ΔS^\ddagger and ΔH^\ddagger values found at 10% organic solvent in both mixtures, which correspond to 0.037 and 0.027 for x_{AN} and x_{DMSO} , respectively, this gives evidence that water molecules in these media are predominately attached by hydrogen bonds among its molecules when traces of organic solvents are not contributing to the reaction between OH⁻ and substrate.

Among the thermodynamic data, the activation energy E_a values at 25 °C (Tables 1 and 2) are, firstly, found to be smaller in ACN–H₂O at $x_{\text{ACN}} = 0.0368$ giving $69.71 \text{ kJ}\cdot\text{mol}^{-1}$ (where water molecules provide good solvation for OH⁻ or around substrate). Secondly, lower E_a values are found at $x_{\text{ACN}} \sim 0.129$ giving $80.57 \text{ kJ}\cdot\text{mol}^{-1}$, which is consistent with larger $-\Delta S^\ddagger$ values, which indicate that the reaction at this composition is more easily completed. It can be seen again in the corresponding E_a data with respect to DMSO–H₂O, that E_a has a lower value equal to $32.3 \text{ kJ}\cdot\text{mol}^{-1}$ at $x_{\text{DMSO}} = 0.2029$ that is related to the larger $-\Delta S^\ddagger$ value as mentioned before.

The plots of ΔH^\ddagger against ΔS^\ddagger in both of ACN and DMSO gave isokinetic temperatures of 334 and 347 K, respectively, suggesting that the titled reaction are enthalpically controlled and the reaction for both solvent systems proceeds by the same mechanism.

Furthermore, the highly negative values of ΔS^\ddagger for entire range of solvent compositions supports the formation of a charged transition state. The low negative values obtained in the binary aqueous solvent DMSO–H₂O, compared to those obtained in ACN–H₂O, indicates that: (i) the order of the transition state is sensitive to changes of the solvent structure, and (ii) the formed transition state is dipolar and its solvation in DMSO–H₂O and ACN–H₂O arises from ion-dipole interactions. This suggests that the transition state is strongly solvated by a basic solvent.

5.3 Correlation between ΔG^\ddagger and the Preferential Solvation $E_T(30)$ Values

The correlation between rate constant for the reaction of alkaline hydrolysis of **1** by hydroxide ion with solvent polarity is of considerable interest [32]. Figure 6 shows the variation of ΔG^\ddagger versus the Reichardt solvent parameter $E_T(30)$, which is a measure of the solvent polarity in ACN–H₂O and DMSO–H₂O. It can be seen that there is a resemblance of the nonlinear correlations for the two solvent mixtures. In spite of the fact that the $E_T(30)$ values change quite rapidly as organic co-solvent is added to water, the behavior of the reaction with regard to preferential solvation is similar to that found in pervious studies [27, 33].

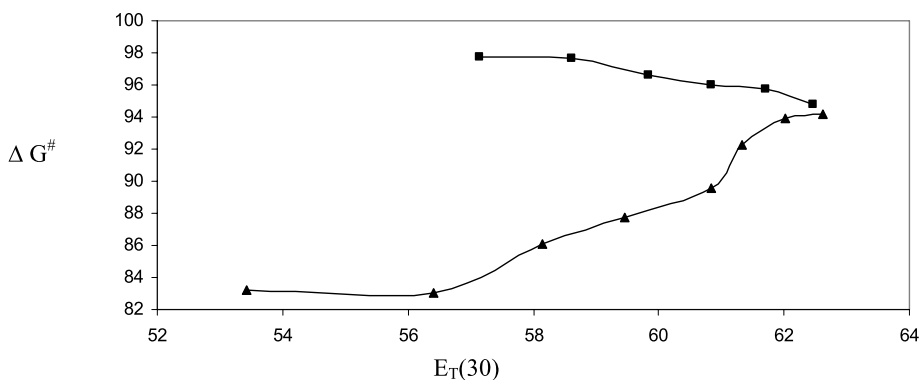
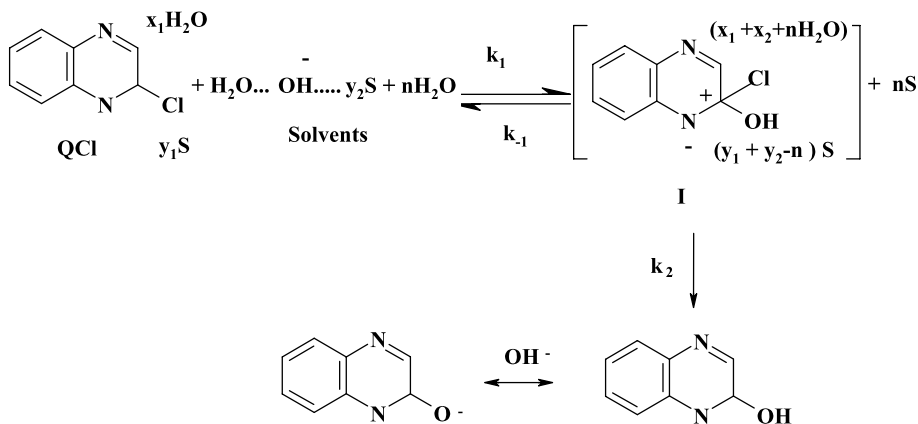


Fig. 6 Variation of Gibbs energy with $E_T(30)$ for the reaction of compound 1 with OH^- at 25 °C in: \blacktriangle DMSO–water; \blacksquare ACN–H₂O



Scheme 2 Mechanism of the reaction of 2-chloro-quinoxaline with hydroxide ion in presence of solvents-water mixtures

5.4 Proposed Reaction Mechanism

The hydrolysis reaction of 2-chloroquinoxaline with sodium hydroxide in water takes place through the cleavage of the C–Cl bond and formation of a C–OH bond through a substitution reaction. This mechanism is similar to that proposed earlier [30] and may be outlined in the form shown in Scheme 2.

Assuming that steady-state concentration is attained in the mixed solvent system for intermediate I

$$\begin{aligned}
 [I] &= \frac{k_1[\text{QCl}][\text{H}_2\text{O}]^n[\text{OH}^-]}{k_{-1}[\text{S}]^n + k_2} \\
 \text{rate} &= k_2[I] \\
 \text{rate} &= \frac{k_1 k_2 [\text{QCl}][\text{H}_2\text{O}]^n [\text{OH}^-]}{k_{-1}[\text{S}]^n + k_2}
 \end{aligned}
 \tag{1}$$

It well known that Cl is good leaving group and thus $k_2 \gg k_{-1}$, which then gives

$$\begin{aligned} \text{rate} &= \frac{k_1 k_2 [\text{QCl}][\text{H}_2\text{O}]^n [\text{OH}^-]}{k_2} \\ &= k_1 [\text{QCl}][\text{H}_2\text{O}]^n [\text{OH}^-] \quad (2) \\ k_1 = k_{\text{obs}} &= \frac{\text{rate}}{[\text{QCl}][\text{H}_2\text{O}]^n [\text{OH}^-]} \end{aligned}$$

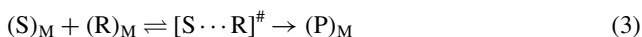
5.5 Multiparameter Analysis

A number of solvent polarity scales like the relative permittivity, solvent polarity, etc., have been established to quantify the influence of solvents on reactivity. In spite of the observation that single empirical parameters can be used as good approximations for solvent polarity, multiple solvent effects on kinetic processes are revealed only by using linear combinations of solvent parameters. Although separation of solvent effects into various solvent–solvent and solvent–solute interaction mechanisms is purely formal, a multi-parameter approach to solvent effects has been shown to work well [11]. The relation between reaction rate and composition of aqueous binary solvent is clearly too complex to be interpreted in terms of any single solvent parameter [11].

In order to obtain a deeper insight into specific co-solvent interactions that influence the reactivity, an attempt was made to adopt the solvatochromic comparison method developed by Kamlet and Taft. This method may be used to unravel, quantify, correlate and rationalize multiple interacting solvent effects on reactivity. The kinetic data were correlated with the solvatochromic parameters using the linear solvation energy relationship (LSER)

$$\log_{10} k = A_0 + a\alpha + b\beta + c\pi^*$$

where π^* is an index of the solvent dipolarity/polarizability, which measure the ability of the solvent to stabilize a charge by its dielectric effect, α is the solvent hydrogen bond donor acidity, β is the hydrogen bond acceptor basicity, and A_0 is the regression values of the solute property relative to the reference solvent cyclohexane. LSER relationships involve empirical relationships between rates or equilibria of a series of chemical reactions. Considering a chemical reaction between a substrate S, **1** and a reagent R (OH^-) in a medium M (ACN and DMSO), leads, via an activated complex, to a product p according to Eq. 3



By introducing small changes in order to establish a reaction series, one can change the surrounding solvent medium, while leaving all other reaction partners unchanged. In the case of sufficiently solvent-dependent chemical reactions, only a multiparameter approach is likely to allow any sort of realistic analysis of the data. Multiple linear regressions were performed on the data for the binary mixtures of both DMSO and ACN with water. Values of the Kamlet-Taft solvatochromic parameters α , β and π^* for ACN– H_2O and DMSO– H_2O over the entire range of composition are known [34–36] and give the relevant solvatochromic parameter values. For the studied mixtures the correlation results obtained are, for ACN– H_2O mixtures,

$$\begin{aligned} \log_{10} k &= -14.233 + 1.956\alpha + 9.87\beta + 2.31\pi^* \\ (n = 6, r = 0.99, F = 51.59, S = 0.0426) \end{aligned}$$

Table 3 The percentage contributions of various solvent parameters to the reactivity in different aqueous organic solvent mixtures

Solvent mixtures	Kamlet-Taft equation		
	α	β	π^*
ACN–H ₂ O	13.83	69.83	16.34
DMSO–H ₂ O	33.21	58.66	8.43

and in DMSO–H₂O mixtures

$$\log_{10} k = 8.908 - 8.736\alpha - 15.411\beta + 2.124\pi^*$$

$$(n = 8, r = 0.952, F = 13.05, S = 0.421)$$

From the above values of the regression coefficients, the contribution of each parameter on a percentage basis was calculated and are listed in Table 3. Examination of this systematic multiple regression analysis leads to the following conclusions: i) in ACN–H₂O solutions the contribution of hydrogen bond acceptor to the total solvent effect predominates and the sign of this coefficient means that the reaction rate decreases with decreasing polarity of the solvent, since ACN is a HBA solvent. Also in DMSO–H₂O solutions the contribution of HBA to the total solvent effect is also predominant, and the negative sign of coefficient β suggests that specific interaction between the activated complex and solvent through HBA properties are larger than those between reactant and solvent. Also, the contribution of the coefficient β in the case of DMSO–H₂O, compared to that of π^* , suggested that specific solvation occurs between the activated state and solvent through HBA.

It is concluded that the rate data indicated a substantial solvent effect on the title reaction, showing a strong dependence on the nature and amount of organic solvent added to the reaction medium.

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