Solvent Effects on the Kinetic and Mechanism of N-Mannich Bases of 3-Hydrazonoindole-2-one

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N-Mannich base reaction of 3-hydrazonoindolin-2-one with piperidine in presence of formaldehyde was followed spectrophotometrically in a wide range of water-acetonitrile and water ethanol (10-70 v/v) and at different temperatures (40-60 ºC). The reaction obeys pseudo-first order kinetics. Addition of organic solvent to water decreases the rate of the reaction. A non-linear relation was observed for the plot of log k_{obs} *versus* the reciprocal of the dielectric constant for the solvent used which suggested that there is a selective solvation by the higher polar solvent, *i.e*., by water molecules. The thermodynamic parameters ΔH^*, ΔS^* and ΔG^* were calculated and discussed in terms of solvation effects. The determined isokinetic temperatures in both systems, revealed the existence of compensation effect arising from the strong solute-solvent interaction. Finally a suggested mechanism was proposed.

Keywords: Solvent effects, Kinetics, Mechanism, N-Mannich base, 3-Hydrazonoindole-2-one.

INTRODUCTION

Isatin is present in the brain and other tissues in humans and the oxindole moiety is also found in natural products in some plants[1]. The metabolism of isatin in humans is not yet well elucidated. It has been suggested that tryptophan and/or phenylalanine is converted by intestinal bacteria into indole, which is then absorbed and metabolized in the liver to isatin *via* 3-hydroxyindole[2]. N-Mannich bases have gained importance due to their application in pharmaceutical chemistry. Isatin, chemically known as 1*H*-indole-2,3-dione, has become a popular topic due to its various uses. The chemistry of isatin and its derivatives is particularly interesting because of their potential application in medicinal chemistry. Isatins are very important compounds due to their antifungal properties[3]. Schiff and Mannish bases of isatin derivatives were reported to show variety of biological activities like antibacterial[4], antifungal[5], anticonvulsant[6], anti HIV[7], antidepressant[8] and antiinflammatory[9] activities. Because of the importance of the subject and as our continuation studies in the field of solvent effect on reaction rate[10-18], it was, therefore, as a matter of interest to submit this reaction to kinetic studies. The kinetics were measured in mixed solvent media of water with ethanol and water with acetonitrile (up to 70 %), where, pH of the medium was *ca.* 9 at different temperatures. This type of study will assist in highlighting on the correlations based on thermodynamic and extra-thermodynamic analysis of the kinetic data obtained; in addition, on the linear free energy relationships (LFER). 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 (ΔG^o_{solv}). This thermodynamic function is the result of superimposition of principle components of energy of different nature concerning the solute and the solvent[19]. The situation with respect to aqueous mixtures is usually more complicated, since there are inter-and intra-component interactions to consider in the solvent mixtures.

A recent study[20] has been done and revealed a deep 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.

EXPERIMENTAL

3-Hydrazonoindole-2-one was prepared as a recommended method[21]. Formaldehyde (B.D.H grade), piperidine (B.D.H grade) and pure solvents (spectroscopic grade) were used. The solvent water binary mixtures were prepared by using double distilled water.

Spectophotometric measurements: The spectra of the substrate (3-hydrazonoindole-2-one) in ethanol and in acetonitrile were recorded at 25 ºC. 3-Hydrazonoindole-2-one gave no reaction with piperidine only or with formaldehyde only (Fig. 1). The reaction of 3-hydrazonoindole-2-one performed efficiently using piperidine in presence of formaldehyde. The full UV-visible spectrum of the reaction mixture was recorded in wavelength range 200-600 nm at different intervals of time as shown in Fig. 2. It is shown from this figure that the reaction proceeds at 332, 324 nm, (in ethanol and acetonitrile, respectively) the spectrum of 3-hydrazonoindole -2-one suffers a gradual decrease in its intensity (hypochromic shift).
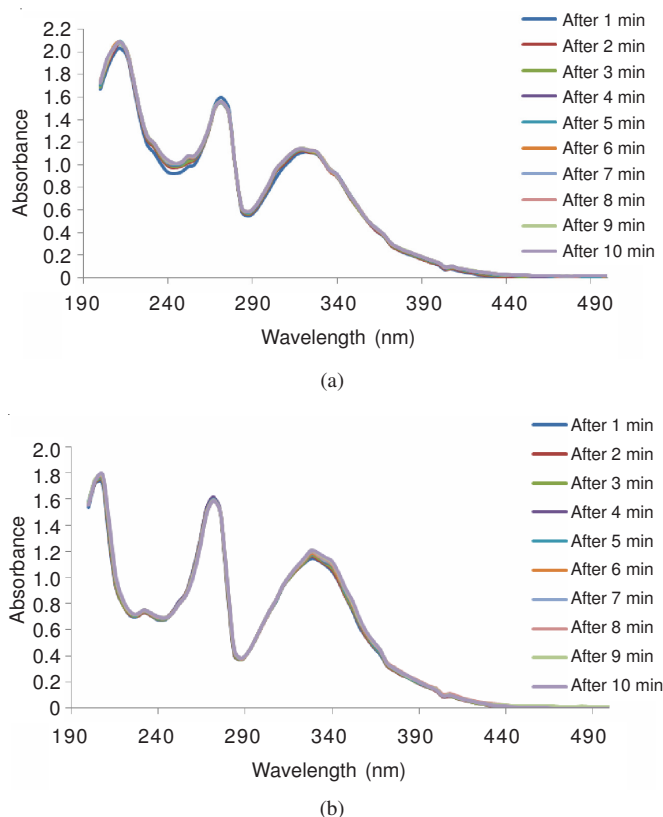

Fig. 1.   Absorption spectra of 3-hydrazonoindole -2-one in the presence of (a) piperidine (b) formaldehyde in 30 % ethanol-water at 40 ºC

Kinetic measurment: The rate of N-Mannich base of 3-hydrazonoindole-2-one was carried out by preparing solutions of 3-hydrazonoindole-2-one (in the solvent used ethanol or acetonitrile), formaldehyde and piperidine with concentrations 4×10^{-3}, 1 and 0.1 mol dm^{-3}, respectively. Solutions were kept in a thermostat at the required temperature till the thermal equilibrium was reached. The substrate with formaldehyde was added in flask and piperidine in another one then quickly and thoroughly the two flasks were mixed. The initial concentrations after mixing were 4×10^{-4}, 1×10^{-2} and 0.1 mol dm^{-3} for substrate, piperidine and formaldehyde, respectively .The zero time was recorded and the hypochromic shift of the optical density with time was recorded on a computerized Unicam Heλiosα spectrophotometer. The temperature was set automatically to ± 0.05 °C using Raypa thermostat temperature control. The reaction was carried under pseudo-first order condition. The progress of the reaction was followed spectrophotometrically at $\lambda_{max} = 332$ and 324 nm, respectively.
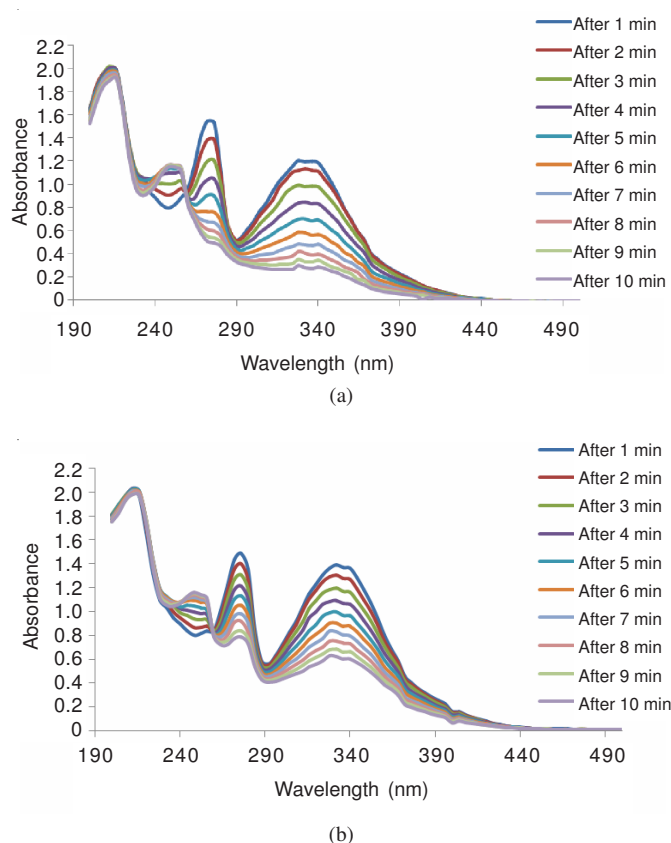

Fig. 2.   Spectra of N-Mannich base reaction of 3-hydrazonoindole 2-one in (a) 30 % ethanol-water mixture (b) 30 % acetonitrile-water mixture at 40 ºC

RESULTS AND DISCUSSION

Rate constant and the effect of temperature: Under pseudo-first-order conditions[16] in which [3-hydrazonoindole-2-one]$_0$ << [piperidine]$_0$ and at constant [formaldehyde], plots of log log $(A_t$ -$A_\infty)$ *versus* time t gave straight lines follows the pseudo- first order kinetics.

The reaction rates were also studied in aqueous ethanol and aqueous acetonitrile of varying compositions (10-70 % v/v) within the temperature range (40-60 ºC). Table-1 collects the obtained values of the rate constants and their corresponding activation energies. It is readily seen from Table-1 that reaction rate constant k_{obs} is decreasing with the progress addition of both ethanol and acetonitrile over the whole range of compositions. Table-1 shows that the reaction rate constant in presence of acetonitrile is greater than that in case of ethanol, the significant differences in rate constants of the reaction under investigation are presumably attributed to the differential competition for water molecules between the substrate and organic cosolvent[22].

Effect of base: Comparing the data obtained in this study Table-1 and previous one[16] showed that the rate in our study is greater as twice as the previous one where the base used is morpholine.

In general, base catalysis is more observed in less polar solvents. Unusually, when amines of the same nature and under the same experimental conditions react by different mechanism, there is considerable difference in their basicities which has been described to an increase in the value of k_{obs} with decreasing basicity of the nucleophile[23-25].

<table>
<tr><td colspan="8">TABLE-1
PSEUDO-FIRST ORDER RATE CONSTANT $k_{obs} \times (10^4 \, s^{-1})$ FOR N-MANNICH BASE OF
3- HYDRAZONOINDOLE-2-ONE USING PIPERIDINE IN PRESENCE OF FORMALDEHYDE IN MIXED
AQUEOUS SOLVENTS AND THEIR CORRESPONDING ACTIVATION ENERGY (E_a kJ/mol)</td></tr>
</table>

t (°C)	v/v (%)						
	10	20	30	40	50	60	70
	EtOH						
40	56.16	41.85	25.81	16.65	7.85	3.51	1.85
45	69.36	54.55	34.25	21.68	11.35	4.88	3.16
50	94.30	78.21	50.13	32.50	17.41	8.53	4.35
55	140.51	109.05	64.35	48.25	23.21	12.06	6.33
60	144.15	116.06	79.01	47.73	28.66	14.10	7.16
E_a	40.01	48.18	51.50	51.77	56.35	58.76	55.58
	± 4.93	± 5.37	±3.13	±4.80	±3.58	± 6.67	± 3.77
	Acetonitrile						
40	59.76	42.73	35.80	24.66	18.23	13.01	9.96
45	70.88	59.03	53.35	36.35	27.31	19.35	15.33
50	96.93	96.31	67.65	55.25	42.76	31.31	21.86
55	142.95	124.43	95.65	70.25	68.28	47.78	37.20
60	205.61	209.80	181.10	102.75	85.81	80.73	50.95
E_a	54.31	59.81	61.89	60.01	70.36	73.50	70.11
	±4.67	±3.35	±3.29	±2.35	±3.64	±2.06	±3.23

Effect of water concentration: It has been noted that the rate constant increases with increasing water concentration in both ethanol-water and acetonitrile-water mixtures. So water plays an important role in the kinetics of the reaction.

On plotting log k_{obs} *versus* log [H$_2$O], linear plots were obtained with different positive slopes. This may be due to different percent composition of the solvent molecules in the solvation sheath, indicating preferential solvation. When acetonitrile as an organic co-solvent is added to water, the former disrupts water structure over the whole range of the composition[26]. So the substrate may have a high chance to be preferentially solvated by water molecules. While when small amounts of ethanol are added to water, usually 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.

Thermodynamic parameters of activation: Thermodynamic parameters of activation ΔH*, ΔS* and ΔG*, under different experimental condition, were calculated by applying the least-squares procedures program and are collected in Table-2. The variation of activation parameters with the mole fraction χ_2 of ethanol and acetonitrile were depicted in Fig. 3. The figure shows that there is a maximum at $\chi_2 = 0.12$ and another broad one in the range $\chi_2 = 0.29 - 0.35$ for both ΔH* and ΔS* in the case of ethanol-water and there is a minimum at $\chi_2 = 0.17$ which nearly close to the values obtained from the partial molal volume V_t[27,28] while in case of acetonitrile there is a maximum at $\chi_2 = 0.13$ and another broad one in the range $\chi_2 = 0.26$-0.45 for both ΔH* and ΔS* and there is a minimum at $\chi_2 = 0.19$ which nearly close to the values obtained from other studies[29].

Over the whole solvent composition range, N-Mannich base of 3-hydrazonoindole-2 one in ethanol is associated with much more negative entropy of activation than in acetonitrile. This may be due to the large number of water molecules in the transition state[30].

<table>
<tr><td colspan="4">TABLE-2
ACTIVATION PARAMETERS FOR N-MANNICH BASE
OF 3- HYDRAZONOINDOLE-2-ONE USING PIPERIDINE
IN PRESENCE OF FORMALDEHYDE IN MIXED
AQUEOUS SOLVENTS AT 25 °C</td></tr>
</table>

[W] (mol L^{-1})	ΔH$^{\neq}$ (k J mol^{-1})	-ΔS$^{\neq}$ (J mol^{-1} deg^{-1})	ΔG$^{\neq}$ (k J mol^{-1})
	EtOH		
8.07	37.54 ± 4.90	167.75 ± 15.28	87.55 ± 9.49
16.49	45.70 ± 5.37	144.91 ± 16.62	88.90 ± 10.32
25.29	49.02 ± 3.13	138.35 ± 9.69	90.27 ± 6.02
34.5	49.29 ± 4.80	141.31 ± 14.85	91.43 ± 9.23
44.13	53.87 ± 3.58	132.42 ± 11.09	93.35 ± 6.89
54.23	56.28 ± 6.67	130.71 ± 20.64	95.26 ±12.82
64.83	53.10 ± 3.77	146.22 ± 11.66	96.70 ± 7.24
	Acetonitrile		
8.03	51.83 ± 4.68	123.06 ±14.48	88.52 ± 8.99
16.42	57.34 ± 3.36	107.47 ± 10.40	89.38 ± 6.46
25.19	59.42 ± 3.30	102.85 ± 10.21	90.09 ± 6.34
34.38	57.54 ± 2.35	111.27 ± 7.28	90.71 ± 4.52
44.01	67.89 ± 3.65	80.98 ± 11.29	92.03 ± 7.01
54.11	71.03 ± 2.07	73.91 ± 6.41	93.06 ± 3.98
64.71	67.64 ± 3.23	86.80 ± 10.0	93.52 ± 6.21

The highly negative ΔS* supports the formation of highly restricted transition state, the strong electrostriction developed in the activated state restricts the freedom of motion of solvent molecules in the neighborhood of the activated species and cause loss of entropy. 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 an 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 acetonitrile is less than the corresponding values in aqueous ethanol. This explains that why the reaction in the later solvent is slower than in the former one. ΔG* gradually decreases as a function of increasing [H$_2$O] due to a complex quasi-mirror image compensation of ΔH* and ΔS*.

This interpretation was supported by a recent work[20], where a reaction was started by reactants differ in their solvation
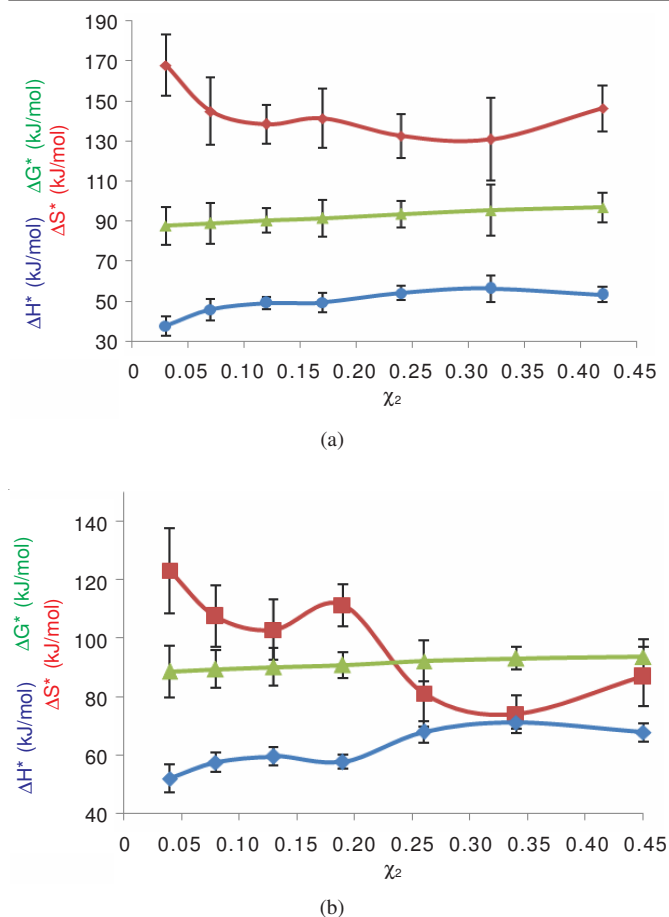
(a)

(b)

Fig. 3. Dependence of thermodynamic parameters of activation on the mole fraction of (a) ethanol-water (b) acetonitrile-water mixtures for N-Mannich base of 3-hydrazonoindole -2-one

sheath. Two channels of association reaction were studied, one was started by dissolving the reaction partners 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.

Effect of dielectric constant: The effect of dielectric constant on the N-Mannich base of 3-hydrazonoindole-2-one in ethanol and acetonitrile was investigated in the light of the correlation of log k *versus* the reciprocal of the dielectric constant. The values of the dielectric constant of ethanol-water mixtures at 40 ºC were interpolated from (Akerlöfs) data[31] and dielectric constant of acetonitrile-water mixtures at 40 ºC were interpolated from Leonardo *et al.*[32]. Plots of log k_{obs} *versus* $1/\varepsilon$ for various ethanol-water and acetonitrile-water composition at 40 ºC, revealed non-linear relationship (for both solvents), this deviation from linearity led to the conclusion that the electrostatic part of the solvent overcomes the nonelectrostatic part. In such case the differential solvation of the initial and transition state is the controlling factor for changes in the rate constant values with the solvent composition. This was shown from the extension of the equation of Laidler and Landskroaner[33] which allows for the changes in solvent structure with varying solvent composition[34]:

$$\Delta G^{o}_{t}(Tr.) \gg \Delta G^{o}_{t}(In.) \text{ or } \Delta G^{o}_{t}(In.) \gg \Delta G^{o}_{t}(Tr.)$$

where $\Delta G^{o}_{t}(Tr.)$ and $\Delta G^{o}_{t}(In.)$ are the free energy of transfer of the transition state and initial state, respectively.

Isokinetic relationship: Plot of ΔH^{*} *versus* ΔS^{*} gave a linear relation enclosed all the points of two solvents ethanol and acetonitrile indicates the two systems follow the same mechanism and the slop β (isokinetic temperature) was found to be 317 K. This value is located within the range of experimental temperature (313-333 K).

Proposed reaction mechanism: Mechanism proposed for (N-Mannich base) of 3-hydrazonoindole -2-one by piperidine in the presence of formaldehyde include two major steps: The first step is the nucleophilic attack of lone pair of electron on nitrogen to the carbonyl group, and the second step is nucleophilic addition of piperidine.
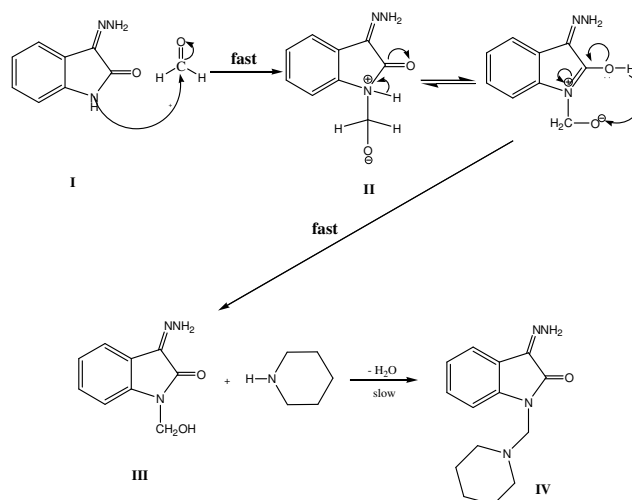
Scheme-I: Mechanism for N-Mannich base of 3-hydrazonoindole-2-one

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