

Solvent Effect on the Kinetics of the Basic Hydrolysis of Isatin

Hamed M. ABU EL-NADER* and Mahmoud N. H. MOUSSA

Chemistry Department, Faculty of Science, Mansoura University, Mansoura, Egypt.

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The kinetics of the basic hydrolysis of isatin in the presence of ethanol and ethylene glycol has been investigated spectrophotometrically. The rate of the reaction decreases with increasing ethanol content and it passes through a minimum at about 30% ethylene glycol. The effects of dielectric constant of the solvent mixture and the solvent composition on the reaction rate were studied, and the thermodynamic activation parameters were calculated and discussed. A mechanism for the base hydrolysis of isatin was proposed.

Key words isatin; kinetics; solvent; hydrolysis

Isatin and its derivatives exhibit a broad spectrum of biological activities.^{1–3} It was also used as a colourimetric reagent for quantitative determination of proline in maize and wheat after its separation by paper chromatography.⁴ Isatin is further employed as an inhibitor for glucose influx into human erythrocytes,⁵ and inhibited the activity of rabbit brush border sucrase by about 60% at pH 5.⁶

It is well known that isatins are stable substances in acidic media, but in basic media they hydrolyze quite rapidly depending on the basicity of the medium.⁷ The kinetics of ring opening processes of isatin and its analogues was studied in aqueous solution. The observed rate constants for these compounds are of the same order of magnitude as for isatin, making the importance of the hydrolyzed forms of isatins obvious.⁸ The pH dependence of the rate of hydrolysis of isatin and its *N*-carboxymethyl derivatives has recently been reported.⁹ However, little attention was given to the effects of the solvents on the kinetics of the basic hydrolysis of isatin. It is the aim of this investigation to shed light on the role of mono- and dihydric alcohols as solvents on the rate of this basic hydrolysis of isatin.

Experimental

Pure isatin (Merck) was used after recrystallization from benzene (mp 200 °C). Ethanol and ethylene glycol (B.D.H.) were further purified by distillation. Carbonate free sodium hydroxide solution was prepared and standardized against standard hydrochloric acid solution. Double distilled water was used throughout. The rate of hydrolysis was followed spectrophotometrically with absorption change at 370 nm using a UNICAM UV2-100 UV/visible spectrometer. All reacting solutions were allowed to equilibrate at the desired temperature before mixing in the temperature range 25–40 ± 0.1 °C. Measurements were usually carried out to about 90% completion of the reaction. Equal volumes of isatin and the alkali solutions were prepared in two different measuring flasks and were kept in a water bath at the desired temperature till thermal equilibrium was attained. The contents of the two flasks were then quickly and thoroughly mixed to provide initial concentrations of 4 × 10^{−4} and 4 × 10^{−3} mol·l^{−1} for isatin and sodium hydroxide, respectively. The zero time was recorded and the changes in absorbance with time were followed at λ = 370 nm. A typical plot of change in absorption *A* with time *t* is given in Fig. 1. The rate constants were calculated from the straight lines obtained on plotting log[*A*_∞/(*A*_∞ − *A*)] vs. time where *A* and *A*_∞ represent absorbance at time *t* and infinity, respectively. The values of dielectric constants were obtained by interpolation from Akerlof's data.¹⁰

Results and Discussion

The rate of the basic hydrolysis reaction of isatin was

found to be first order with respect to isatin and sodium hydroxide concentrations. However, the kinetics of the reaction were followed under pseudo first order conditions using ten fold excess of [NaOH] over [isatin]. Typical plot of absorption curves at different times for the reaction at 25 °C are illustrated in Fig. 1. The observed pseudo first order rate constants *k*_{obs} for the base hydrolysis of isatin in ethanol–water and glycol–water solvent mixtures were determined graphically and are given in Table 1. The system was found to obey Arrhenius equation (Fig. 2). From the slopes of Arrhenius plots the activation energies of hydrolysis of isatin (*E*_a) were calculated and are also listed in Table 1. It is evident that (*k*_{obs}) decreases gradually with successive addition of ethyl alcohol while the energy of activation increases. In ethylene glycol the rate constant passes through a minimum whereas the activation energy reaches a maximum after about 30%. The rate of the hydrolysis reaction will decrease due to a decrease in the stoichiometric concentration of the hydroxide ion by the addition of the alcohol component, according to the following equation:



The effective base in water rich mixtures is the hydroxide ion and not the alkoxide ions¹¹ formed in the presence of the alcohol. In ethanol water mixtures the rate of hydrolysis is influenced by a decrease in both dielectric constant and basicity. It is proposed that the latter factor is predominant leading to a continual decrease in rate. On the other hand, the anion of ethylene glycol may be stabilized by intermolecular hydrogen bonding of an unreacted hydroxyl group and the alkoxide oxygen atom¹²; the activity of such anion may be enhanced at the lower dielectric constant region, since the charge is somewhat dispersed through this hydrogen bonding.

The influence of the dielectric constant of the medium on the rate of hydrolysis can be visualised by application of the Laidler–Landskroener equation¹³ which predicts a straight line relation between log *k* and the reciprocal of the dielectric constant. In the studied reaction, no linear relation was observed on plotting log *k* vs. 1/*D* which suggests a large differential effect of solvent structure on the initial and transition state.¹⁴ However, plots of log *k* vs. *D* gave good straight lines¹⁵ as shown in Fig. 3. The increase in rate constant with the increase in dielectric constant can be ascribed to the formation of an activated

* To whom correspondence should be addressed.

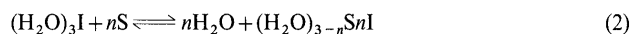
Table 1. Observed Pseudo First-Order Rate Constants and Activation Energies for Isatin Hydrolysis in Presence of Ethanol- and Ethylene Glycol-Water Mixtures

Wt (%)	$10^4 k \text{ (s}^{-1}\text{)}$				E (kJ mol ⁻¹)
	25 °C	30 °C	35 °C	40 °C	
Ethanol-water					
0	12.22	15.51	18.93	23.62	34.81
10	5.41	6.18	7.79	11.11	41.17
20	3.92	5.11	6.91	9.51	46.05
30	3.11	4.03	5.54	7.87	53.61
40	2.32	3.02	4.48	6.91	56.01
50	1.83	2.59	3.69	5.38	58.40
60	1.54	2.11	3.15	4.84	63.19
70	1.21	1.84	2.66	3.99	66.06
Ethylene glycol-water					
10	5.28	6.84	8.99	12.25	40.2
20	4.38	5.82	7.53	10.79	44.52
30	3.72	4.91	6.58	9.23	48.83
40	4.03	5.25	6.86	9.73	46.91
50	4.63	6.08	7.96	11.19	45.18
60	5.77	7.45	9.95	12.91	42.18
70	7.33	9.21	11.78	14.72	39.25

complex more polar than the reactants; so its formation is promoted by media of high dielectric constant.

To treat the results more precisely, the temperature dependence of the dielectric constant should be eliminated. Interpolated rate constants at constant dielectric constant, 40, 50, 60, 70 in case of ethanol and 55, 60, 65, 70 in case of ethylene glycol, k_d , were estimated at different temperatures. Arrhenius plots at constant dielectric constant were constructed and the isodielectric activation energies, E_d , were obtained (Table 2). It was observed that the isodielectric activation energy values increase with the increase in alcohol content. This may be attributable to a lesser extent of solvation of the activated complex than to the reactants¹⁵⁾ under these conditions.

The variation in reaction rate with solvent composition at constant base concentration, can be attributed primarily to changes in the solvent system through the equilibrium¹⁶⁾:



involving substitution of water by the organic solvent molecules in the ion clusters by a multi-step solvation

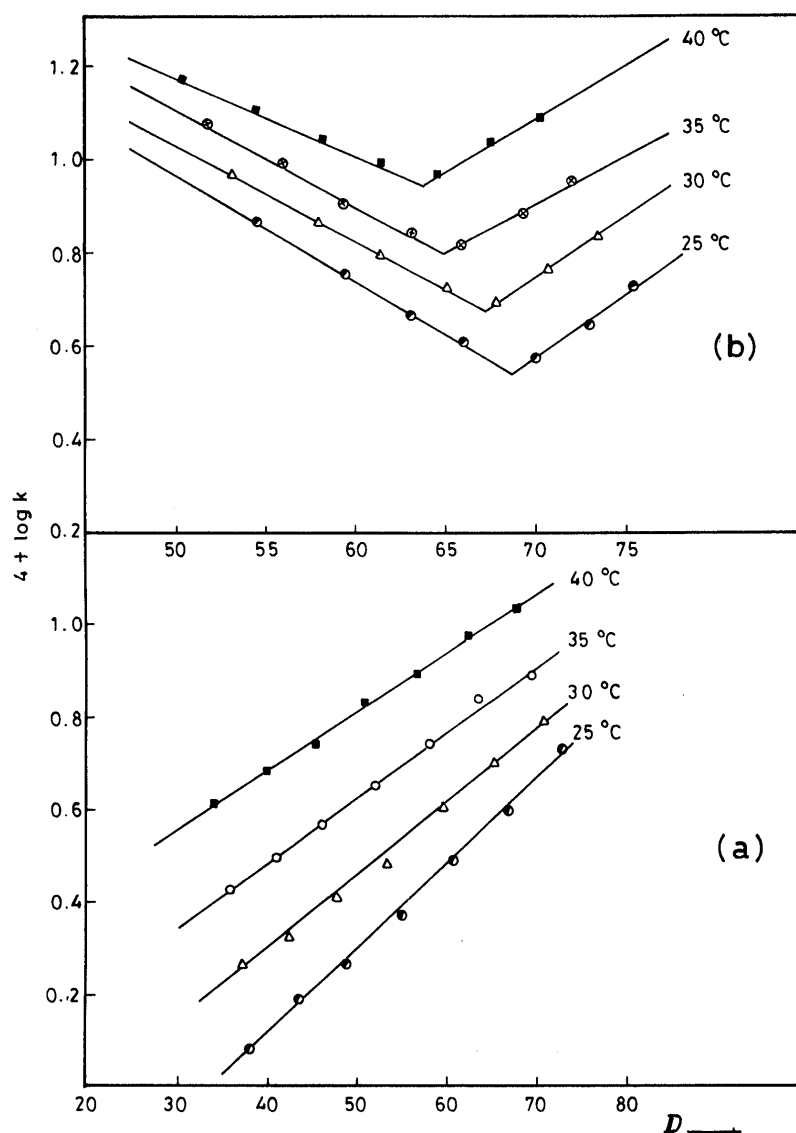


Fig. 3. Influence of Dielectric Constant on the Reaction Rate in the Presence of a) Ethanol b) Ethylene Glycol

mechanism. I stands for an OH^- ion and S for solvent molecules. Therefore, the number of free water molecules increases with progressive addition of the alcohols, and this plays an important role in the dependence of the

Table 2. Interpolated Rate Constant Values (k_d) and Isodielectric Activation Energies (E_d)

Wt (%)	$10^4 k \text{ (s}^{-1}\text{)}$				E_d (kJ mol ⁻¹)
	25 °C	30 °C	35 °C	40 °C	
Ethanol-water					
40	1.31	2.01	3.04	4.81	69.89
50	1.99	2.86	4.18	6.38	62.23
60	3.03	4.12	5.78	8.63	54.09
70	4.63	5.91	7.93	11.53	45.96
Ethylene glycol-water					
55	7.16	8.35	10.47	12.25	29.67
60	5.37	6.61	7.76	10.23	33.60
65	4.16	5.25	6.17	9.12	49.78
70	3.72	5.51	8.13	12.02	61.27

reaction rate on solvent composition. Plots of $\log k$ against $\log c_w/c_s$, where c_w and c_s represent the concentration of water and solvent, respectively, gave straight lines (Fig. 4) confirming the dependence of reaction rate on solvent composition. The dependence of reaction rate on water concentration ($\text{mol} \cdot \text{l}^{-1}$) is also illustrated in Fig. 5 by a plot of $\log k$ against $\log[\text{H}_2\text{O}]$. Two linear portions were obtained corresponding to water- and alcohol-rich mixtures. Thus the reaction rate is proportional to the concentration of water as expected.

Solvation effects can be understood from a study of the thermodynamic properties of the activated complex, *i.e.*, the enthalpy of activation (ΔH^*), the free energy of activation (ΔG^*) and the entropy of activation (ΔS^*). These properties were calculated for different ethanol- and ethylene glycol-water mixtures and are collected in Table 3. It is seen that the free energy of activation increases gradually with ethanol to obtain a maximum around 30% glycol, then decreases. This increase in ΔG^* is a sign of solvation of the reacting species and is parallel to

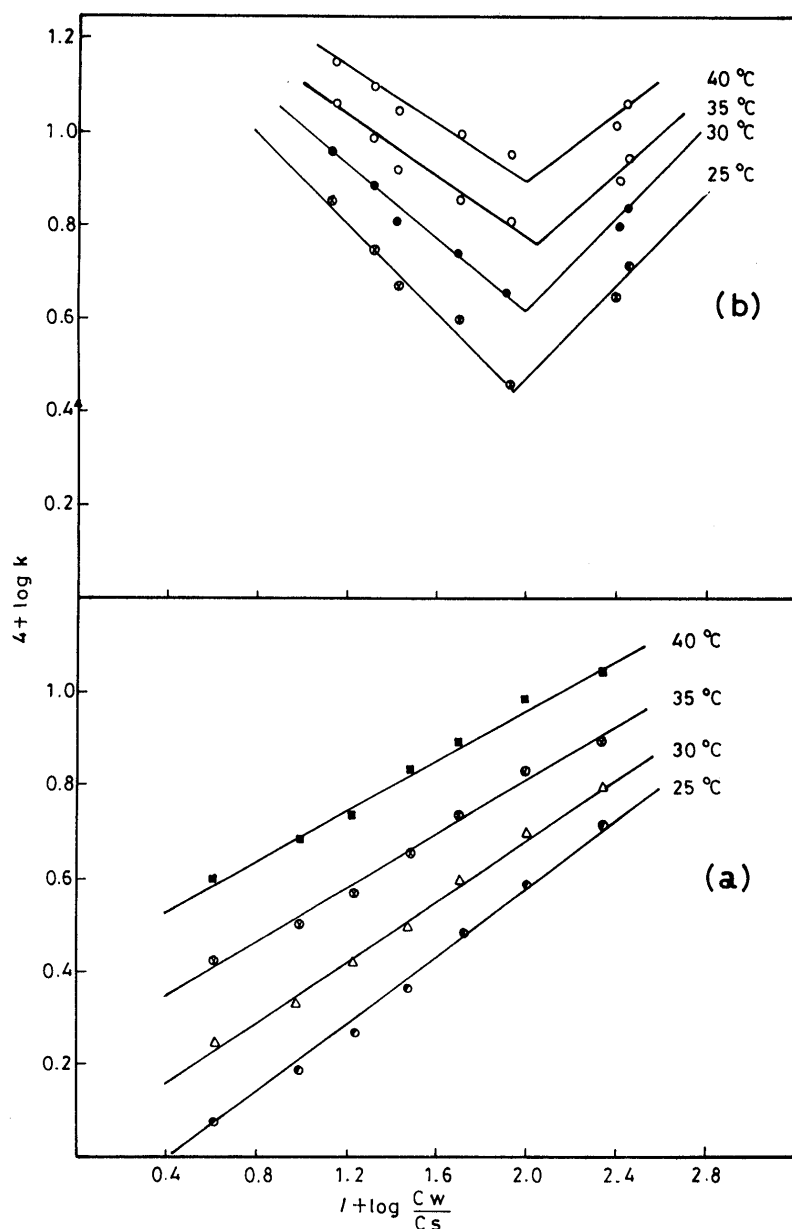


Fig. 4. Effect of Solvent Composition on the Reaction Rate in the Presence of a) Ethanol b) Ethylene Glycol

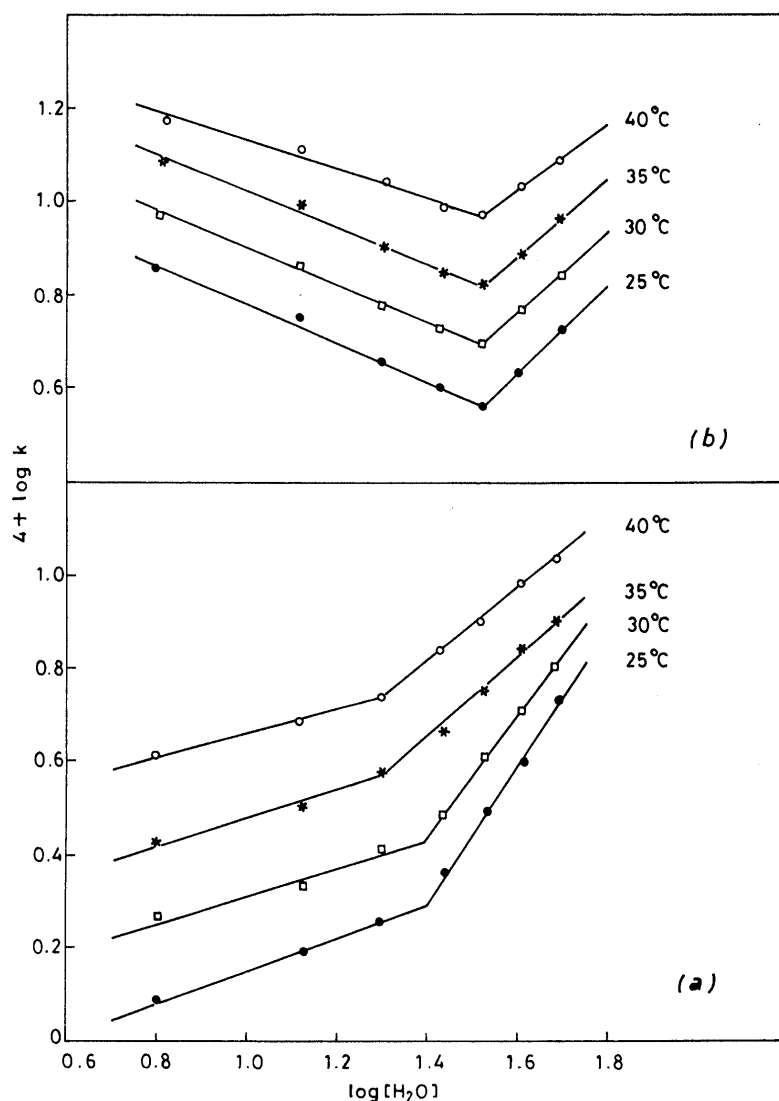


Fig. 5. Effect of Water Concentration on the Reaction Rate in the Presence of a) Ethanol b) Ethylene Glycol

Table 3. Thermodynamic Parameters of Activation for Isatin Hydrolysis in Different Ethanol- and Ethylene Glycol-Water Mixtures at 25 °C

Wt (%)	Ethanol-water			Ethylene glycol-water		
	ΔG^*	ΔH^*	$-\Delta S^*$	ΔG^*	ΔH^*	$-\Delta S^*$
0	89.65	32.33	192.26	89.65	32.33	192.26
10	91.68	38.69	177.72	91.73	37.72	181.15
20	92.48	43.57	164.05	92.21	42.04	168.24
30	93.05	51.13	140.61	92.61	46.35	155.12
40	93.79	53.53	135.04	92.41	44.43	160.93
50	94.37	55.92	128.97	92.06	42.70	165.54
60	94.79	60.71	114.29	91.52	39.71	173.77
70	95.38	63.58	106.67	90.92	36.77	181.62

ΔH^* and ΔG^* in kJ mol^{-1} , ΔS^* in $\text{J mol}^{-1} \text{K}^{-1}$.

the behaviour of the energy of activation. Therefore, solvation of reactions is expected to be more pronounced in the presence of the alcohols under investigation. The enthalpy change of activation behaves identically like ΔG^* . In both solvents the variation of ΔS^* is not linear, which is a criterion of specific solvation. From the slope of the plots of ΔH^* vs. ΔS^* (Fig. 6) the isokinetic

temperature was calculated (353 K).

Based on these results the following mechanism could be proposed. Since equilibrium (1) predominates, the overall reaction rate may be represented by the following equation

$$\text{rate} = k[\text{isatin}][\text{Base}] \quad (3)$$

From equilibrium (1) we have

$$[\text{Base}] = [\text{OH}^-] + [\text{RO}^-] \quad (4)$$

and

$$K = \frac{[\text{H}_2\text{O}][\text{RO}^-]}{[\text{ROH}][\text{OH}^-]} \quad (5)$$

Accordingly,

$$\text{rate} = [\text{isatin}]\{k'[\text{OH}^-] + k''[\text{RO}^-]\} \quad (6)$$

substituting in Eq. 6 from Eq. 5 and rearranging then we have,

$$\text{rate} = [\text{isatin}][\text{OH}^-] \left\{ k' + \frac{K[\text{ROH}]}{[\text{H}_2\text{O}]} k'' \right\} \quad (7)$$

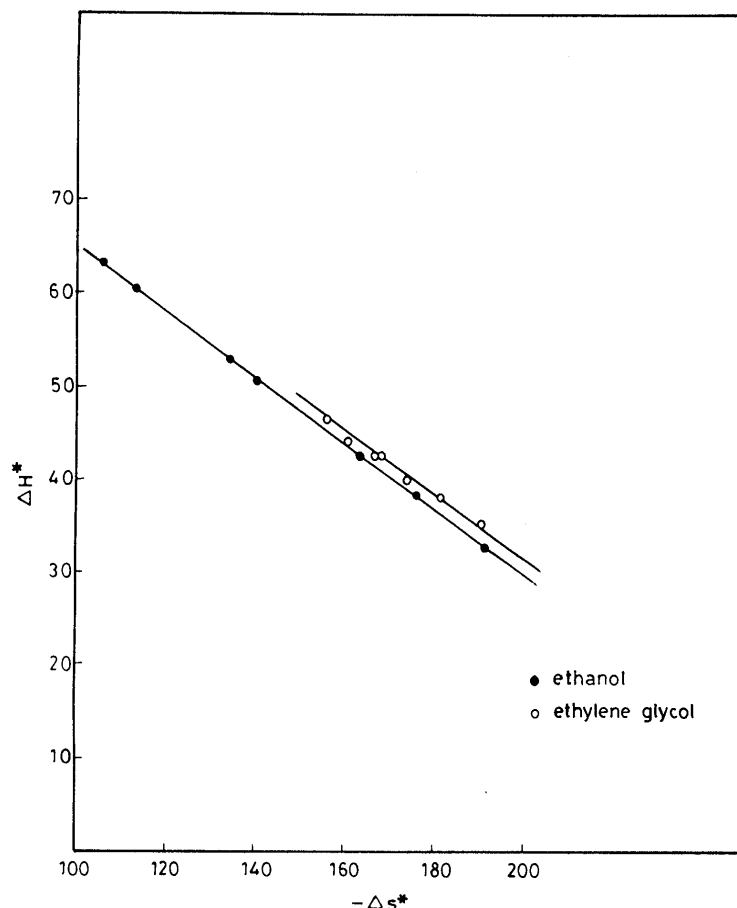


Fig. 6. Relation of ΔH^* and ΔS^* at 25°C

Therefore,

$$k_{\text{obs}} = [\text{OH}^-] \left\{ k' + \frac{K[\text{ROH}]}{[\text{H}_2\text{O}]} k'' \right\} \quad (8)$$

where k' and k'' are the specific rate constants for the reaction involving OH^- and RO^- ions, respectively, K is the equilibrium constant for Eq. 1 and k_{obs} is the observed pseudo first order rate constant.

In the case of ethanol, the increase in ethanol content will cause a decrease in k'' and hence k_{obs} will also decrease, while in the case of ethylene glycol k'' is still small at the region of high dielectric constant due to the specific solvation of the anion by the highly polar solvent, water. At the low dielectric constant region, the increase in k'' results in an increase in the value of k_{obs} at these regions, (i.e. at higher contents of ethylene glycol) as was observed in the present case.

References and Notes

- 1) Maysinger D., Birus M., Movrin M., *Acta Pharmac. Jugosl.*, **29**, 15 (1979).
- 2) Morvin M., Saric M. M., *Europ. J. Med. Chem.*, **13**, 309 (1978).
- 3) Varma R. S., Mobles L. W., *J. Pharmac. Sci.*, **83**, 881 (1975).
- 4) Divakar N. G., Rao U. N., Nagaraja S., Hartman C. P., *J. Inst. Chem., Calcutta*, **47**, 87 (1975).
- 5) Kumar P., *Enzyme*, **24**, 152 (1979).
- 6) Glover V., Halket G. M., Watkins P. J., Clow A., Goodwin B. L., Sandler M., *J. Neurochem.*, **51**, 656 (1988).
- 7) Coffey S., "Rodd's Chemistry of Carbon Compounds, Heterocyclic Compounds," Vol. IV, Elsevier Sci. Publ. Comp., 1973, Part A, p. 460.
- 8) Maysinger D., Birus M., Movrin M., *Pharmazie*, **37**, 779 (1982).
- 9) Lorraine C. A., Ron G., Michael P. I., *J. Chem. Soc., Perkin Trans. 2*, **1993**, 23.
- 10) Akerlof C., *J. Am. Chem. Soc.*, **54**, 4125 (1932).
- 11) Caldin E. F., Long G., *J. Chem. Soc.*, **1954**, 3737.
- 12) Gould E. S., "Mechanism and Structure in Organic Chemistry," Holt, Rinehart and Winston, Inc. New York, 1959.
- 13) Laidler K. J., Landskroener P. A., *Trans. Faraday Soc.*, **52**, 200 (1956).
- 14) Wells C. F., *J. Chem. Soc., Faraday Trans. 1*, **73**, 185 (1977).
- 15) Elsemongy M. M., Amira M. F., *Ind. Chem. Soc.*, **37**, 506 (1980).
- 16) Elsemongy M. M., Abu El-Nader H. M., *Ind. J. Chem. Soc.*, **LIV**, 1055 (1977).