Solvent Effect on Amide Hydrolysis. III—Kinetics of Formamide Hydrolysis in isoPropanol-Water Mixtures

M. M. ELSEMONGY and H. M. ABU ELNADER

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

Solvent effects on the acid and base hydrolysis of formamide were investigated in isopropanol-water mixtures, up to 75.06 wt % of the alcohol, at the temperature range 25-60°. Both reactions are retarded by increasing the concentration of isopropanol, but in case of the base hydrolysis the rate increases on further progressive addition of the alcohol passing through a minimum at about 34 wt % of isopropanol. Temperature, dielectric constant, solvent composition, activation parameters, acidity function and medium effects on reaction rates and mechanisms are briefly discussed.

THE kinetics and mechanisms of formamide hydrolysis were recently studied in this laboratory, in acidic and basic dioxane- and n.propanol-water mixtures[1]. The results were analysed and discussed in the light of our proposed mechanisms of the acid and base hydrolysis. In the present work we have studied the solvent effects on the kinetics and mechanism of formamide hydrolysis in isopropanol-water solutions of different compositions. This was undertaken to decide also the validity of our previously proposed correlations of reaction rate[1].

Experimental

Materials and Kinetic Procedure

The purification of formamide or isopropanol was described before[2]. AnalaR or B D H materials were generally used. Boiled deionised water was used throughout all the experimental work. The rate of the acid or base hydrolysis of formamide in isopropanol-water mixtures, up to 75.06% by weight of the alcohol, was determined by the same procedure mentioned in our previous work[3,4]. The initial concentrations of both amide and acid or base were always constant and equal to $0.1M$. The temperature was held constant within $\pm 0.05°$. Measurements were repeated at least two times and all rate constants listed are the mean of at least three completely independent determinations.

Results and Discussion

Temperature Effect on Reaction Rate

The effect of temperature on the rate of acid or base hydrolysis of formamide was investigated in five isopropanol-water mixtures (7.95, 16.25, 34.08, 64.32 and 75.06 wt % of isopropanol). Rate constants in liter mole^{-1} second^{-1} were measured at five different temperatures (25, 35, 40, 50 and 60°). The results are collected in Table 1. Both re-

TABLE 1—KINETIC RESULTS OF FORMAMIDE HYDROLYSIS IN ISO-PROPANOL-WATER MIXTURES

Iso-Propanol wt %		7.95	16.25	34.08	53.49	64.32	75.06
log $C_{solvent}$		0.115	0.417	0.718	0.894	0.961	1.015
log C_{water}		1.701	1.639	1.517	1.342	1.232	1.051
I—Acid Hydrolysis							
25°	D	72.79	66.80	53.91	39.88	32.42	26.16
	22+L	3.906	3.696	3.203	2.699	2 305	1.641
	5+log k_2	1.246	1.146	1.053	0.989	0 932	0.901
35°	D	69.36	63.54	51.28	37.77	30.58	24.55
	5+log k_2	1.621	1.520	1.475	1.382	1.339	1.310
40°	D	67.62	62 01	49.94	36.78	29.79	23.93
	5+log k_2	1.803	1.707	1.665	1.589	1.534	1.516
50°	D	64.59	59.12	47.41	34.78	28.14	22.52
	5+log k_2	2.155	2.065	2.013	1.959	1.922	1.901
60°	D	61.82	55.66	44.19	32.44	26.68	21.24
	5+log k_2	2.485	2.401	2.362	2.319	2.279	2.258
E_c		16.06	16.43	16.92	17.28	17.53	17.76
log A		8.02	8.17	8 45	8.64	8.78	8.91
II—Base Hydrolysis							
25°	D	72.79	66.80	53.91	39.88	32.42	26.16
	22+L	5.005	4.716	4.325	3.652	3.857	2.449
	5+log k_2	2 269	2.206	2.145	2.160	2.177	2.229
35°	D	69.36	63.54	51.28	37.77	30.58	24.55
	5+log k_2	2.606	2.523	2.461	2.476	2.498	2.545
40°	D	67.62	62.01	49.94	36.78	29.79	23.93
	5+log k_2	2.764	2.672	2.611	2.623	2.641	2.699
50°	D	64.59	59.12	47.41	34.78	28.14	22.52
	5+log k_2	3.066	2.961	2.892	2.903	2.928	2.989
60°	D	61.82	55.66	44.19	32.44	26.68	21.24
	5+log k_2	3.345	3.238	3.162	3.183	3.201	3.266
E_c		14.03	13.66	13.58	13.51	13.44	13.35
log A		8.15	7.12	7.09	7.06	7.04	7.01

actions are inhibited by increasing the concentration of the organic component, but in case of the base hydrolysis the rate increases on further progressive addition of isopropanol passing through a minimum at about 34 wt % of isopropanol. The isocomposition (E_c) and isodielectric (E_d) activation energies were calculated (Tables 1 and 2) from the very good followed Arrhenius plots in this wide range of temperatures. It can be seen that both activation energies increase with successive addition of isopropanol in the acid hydrolysis, *whereas they decrease in the base hydrolysis*. This may reflect the dependence of the reaction rate on the solvent composition.

TABLE 2—REFINED $a_{\neq}$ VALUES (in A) AND ISODIELECTRIC ENERGIES OF ACTIVATION (IN KCAL/MOLE) AT CHOSEN D VALUES.

Dielectric Constant		10	20	40	60	80
		I—*Acid Hydrolysis*				
$a_{\neq}$ at	25°	7.3	7.7	8.0	8.2	8.5
	35°	7.3	7.7	8.0	8.2	8.5
	40°	7.3	7.7	8.0	8.2	8.5
	50°	7.4	7.8	8.1	8.3	8.6
	60°	7.4	7.8	8.1	8.3	8.6
E_d		18.88	18.53	17.84	17.07	16.75
		II—*Base Hydrolysis*				
$a_{\neq}$ at	25°	6.2	6.4	6.6	6.7	6.8
	35°	6.2	6.4	6.6	6.7	6.8
	40°	6.2	6.4	6.6	6.7	6.8
	50°	6.3	6.5	6.7	6.8	6.9
	60°	6.3	6.5	6.7	6.8	6.9
E_d		14.19	13.85	13.31	14.67	15.43

Dielectric Constant Effect on Reaction Rate

Both the Laidler-Landskroener equation of ion-neutral molecule interaction[5] and Amis equation of ion-dipole interaction[6] involve a linear correlation of the logarithm of the velocity constant (log k_2) with reciprocal of the dielectric constant (1/D) in aqueous-organic solvents. However, the plots of log k_2 versus 1/D for the various isopropanol-water compositions reveal that the rate decreases first linearly with decrease of the dielectric constant, then a curvature occurs specially at low dielectric constants. This behaviour, generally found with electrostatically influenced rates, is due to selective solvation by the higher dielectric constant component (water) of the mixed solvent[7]. The dielectric constant values of isopropanol-water mixtures were obtained by interpolation from sufficiently large-scale plots of Åkerlöf's data[8].

The effect of dielectric constant on rate of hydrolysis of formamide in isopropanol-water mixtures can best be described by the Elsemongy's equation[7].

$$k = k' \ e^{\alpha(D-1)} \ ,$$

where k is the rate constant, k' is the rate constant under the conditions of the standard state (D = 1), and α is a constant. This equation predicts a linear dependence of log k_2 on D at any temperature. Fig. 1 shows that the plots of log k_2 versus D gave very good straight lines. The rate constants, k', for the acid (k'_a) and base (k'_b) hydrolysis of formamide in isopropanol-water mixtures were deter-
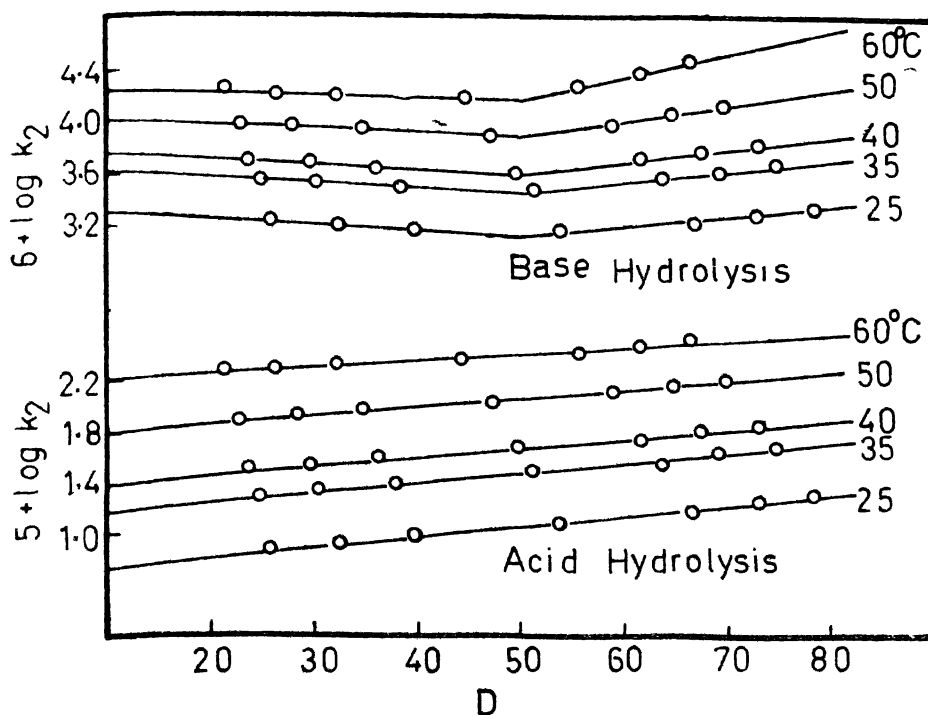

Fig. 1. Influence of dielectric constant on reaction rate.

mined[7] at different temperatures (Table 3). These were used to calculate the refined values of distances of closest approach for the activated complexes $(a_{\neq})$ at chosen values of D (10, 20, 40, 60 and 80). The

TABLE 3—VALUES OF k' (in liter/mole/sec).

Temperature	25°	35°	40°	50°	60°
5+log k'$_a$	0.679	1.182	1.328	1.731	2.159
5+log k'$_b$	2.336	2.668	2.811	3.102	3.389

results are given in Table 2. It can be seen that the values of $a_{\neq}$ decrease with progressive addition of isopropanol. This is in agreement with the fact that successive additions of any organic solute must obviously disrupt the three-dimensional hydrogen-bonded structure of water and cause stronger interactions between the solvent molecules than occur in pure water. As a result, the reacting species might become closer to each other and so the distance of closest approach should be decreased.

However, the $a_{\neq}$ values are reasonable and may account for the solvation of the activated complex. Also they give an idea about the extent of solvation. The $a_{\neq}$ value is equal to, considering the mechanism of the reaction which is given below, the radius of the activated complex plus the radius of a water molecule.

Considering the hydration number for each of the hydrogen ion (4) and the hydroxide ion (3), one should expect large separation between the reactants in the transition state in the case of acid hydrolysis. Actually, the $a_{\neq}$ values were found to be higher in acid hydrolysis than that in base hydrolysis.

It is noteworthy that the radius of the activated complex in the acid or base hydrolysis of carboxylic amides of simple structure in aqueous-organic solvents seems to be almost independent of temperature and increases with increase in the dielectric constant and is, in general, dependent on the amide or the medium. This generalisation can be considered in the light of our results for formamide[1] and acetamide[3,4,7,9,10] hydrolysis in aqueous-organic solvents.

Solvent Composition Effect on Reaction Rate

In reactions in mixed solvents specific interactions of the solvent with the reactants and with the transition state can be of major importance in controlling reaction rate. Properties of the solvent alone do not necessarily predict the reaction rate and generalisation involving the structure of water also have no predictive value[11].

The variation of reaction rate with solvent composition, at constant acid or base concentration, may be ascribed primarily to changes in the solvent system through the equilibrium[1,12]

$$(H_2O)_3I + nS \rightleftharpoons nH_2O + (H_2O)_{3-n}S_nI$$

where I stands for a H_3O^+ or OH^- ion, involving substitution of water by the organic solvent molecules in the ion clusters by a multi-step solvation mechanism[12]. Therefore, the number of free water molecules increases on progressive addition of isopropanol and this plays an important role in the dependence of reaction rate on solvent composition. Also, the ratio $(a_{hyd\ 1}/a_{solv\ 1})$ will be directly proportional to $(a_w/a_s)^n$, and the reaction rate should be dependent on each of these two terms.
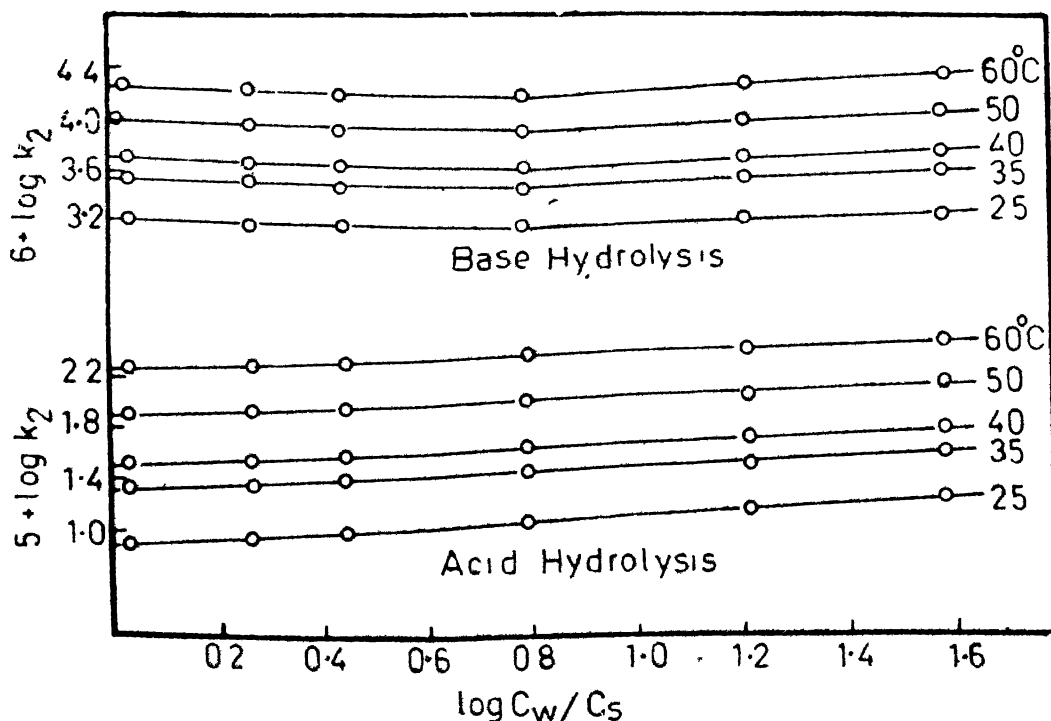

Fig. 2. Dependence of reaction rate on solvent composition.

In absence of the activities data for solutions of the binary alcohol-water mixtures, the values of molar concentrations may be used. It is reasonable to expect that the variation in the ratio C_w/C_s with solvent composition, in solutions of fixed acid or base concentration, is directly proportional to the variation in the a_w/a_s ratio. This may be actually true since the rate constants of the reactions were always determined under a constant ionic strength (u=0.1). However plots of log k_2 against log C_w/C_s gave good straight lines (Fig. 2), in acid hydrolysis and two linear portions corresponding to isopropanol- and water-rich mixtures in base hydrolysis, indicating the operation of the above equilibrium.

The dependence of reaction rate on water concentration (mole/liter) was also illustrated by a plot of log k_2 against log C_w. Two linear portions were obtained corresponding to water- and isopropanol-rich mixtures in acid and base hydrolysis. The slopes of these lines varied with temperature and amounted to 1.4-1.2 and 0.48-0.34 in the acid hydrolysis, and 1.10-1.90 and 0.21-0.31 in the base hydrolysis, at 25-60° respectively. These slopes, as generally known, represent the number of water molecules involved in the formation of the activated complex. The rate is thus proportional to the concentration of water in agreement with the expected bimolecular mechanism.

Solvation Effects and Activation Parameters

The increase of activation energy with successive addition of the organic solvent may be due to solvation of the activated complex to a less extent than of the reactants. However, the enthalpy ($\Delta H^{\neq}$) and entropy ($\Delta S^{\neq}$) of activation could be more sensitive indicators of effects of solvent structure than the rate constant directly[11]. The activation parameters were calculated and are listed in Table 4.

In the acid hydrolysis the enthalpy of activation increases gradually with increasing isopropanol content, whereas it decreases in base hydrolysis in the same direction. This behaviour may be a direct consequence of the variation of the isocomposition activation energy with the dielectric constant.

The free energy of activation, $\Delta F^{\neq}$, increases also gradually with increasing isopropanol content in acid hydrolysis, whereas it increases slightly at first and then decreases also slightly by further successive addition of the solvent in base hydrolysis. This weak dependence is due largely to the general linear compensation between the enthalpy and entropy of activation for a given temperature. According to the theory of absolute reaction rates, an increase in $\Delta F^{\neq}$ is indicative of the solvation phenomena[3,4]. This agrees with the observed increase of energy of activation in the same direction. Therefore, solvation is expected to be more pronounced in presence of isopropanol.

A major determinant of $\Delta S^{\neq}$ for reaction in solution is solvation change between reactants and

TABLE 4—THERMODYNAMIC PARAMETERS OF THE ACTIVATED COMPLEX

($\Delta F^{\neq}$ and $\Delta H^{\neq}$ in Kcal/mole, $\Delta S^{\neq}$ in Cal/mole/degree)

iso-Propanol wt %		7.95	16.25	34.08	53.49	64.32	75.06
			I—Acid Hydrolysis				
25°	$\Delta F^{\neq}$	22.58	22.71	22.84	22.93	23.00	23.05
	$\Delta H^{\neq}$	15.47	15.84	16.33	16.68	16.94	17.16
	$-\Delta S^{\neq}$	23.84	23.06	21.81	20.94	20.34	19.73
35°	$\Delta F^{\neq}$	22.82	22.97	23.03	23.16	23.22	23.26
	$\Delta H^{\neq}$	15.45	15.82	16.31	16.66	16.92	17.14
	$-\Delta S^{\neq}$	23.94	23.20	21.83	21.06	20.46	19.85
40°	$\Delta F^{\neq}$	22.94	23.08	23.14	23.25	23.33	23.36
	$\Delta H^{\neq}$	15.44	15.81	16.30	16.65	16.90	17.13
	$-\Delta S^{\neq}$	23.97	23.23	21.85	21.09	20.51	19.87
50°	$\Delta F^{\neq}$	23.17	23.31	23.39	23.47	23.52	23.55
	$\Delta H^{\neq}$	15.42	15.78	16.28	16.63	16.88	17.11
	$-\Delta S^{\neq}$	23.99	23.28	21.99	21.15	20.53	19.92
60°	$\Delta F^{\neq}$	23.41	23.54	23.60	23.66	23.72	23.76
	$\Delta H^{\neq}$	15.39	15.76	16.25	16.61	16.86	17.09
	$-\Delta S^{\neq}$	24.05	23.32	22.03	21.19	20.58	19.99
			II—Base Hydrolysis				
25°	$\Delta F^{\neq}$	21.18	21.27	21.35	21.33	21.31	21.24
	$\Delta H^{\neq}$	13.44	13.07	12.99	12.92	12.85	12.76
	$-\Delta S^{\neq}$	25.96	27.50	28.05	28.22	28.37	28.44
35°	$\Delta F^{\neq}$	21.39	21.55	21.64	21.62	21.59	21.52
	$\Delta H^{\neq}$	13.42	13.05	12.97	12.90	12.83	12.74
	$-\Delta S^{\neq}$	25.86	27.60	28.14	28.30	28.43	28.50
40°	$\Delta F^{\neq}$	21.57	21.70	21.79	21.77	21.74	21.66
	$\Delta H^{\neq}$	13.41	13.04	12.96	12.89	12.82	12.73
	$-\Delta S^{\neq}$	26.06	27.66	28.19	28.36	28.50	28.52
50°	$\Delta F^{\neq}$	21.83	21.98	22.09	22.07	22.03	21.94
	$\Delta H^{\neq}$	13.39	13.02	12.94	12.87	12.80	12.71
	$-\Delta S^{\neq}$	26.12	27.75	28.31	28.48	28.57	28.59
60°	$\Delta F^{\neq}$	22.10	22.26	22.38	22.35	22.32	22.22
	$\Delta H^{\neq}$	13.39	13.00	12.92	12 85	12.78	12.69
	$-\Delta S^{\neq}$	26.21	27.81	28.40	28.52	28.61	28.62

transition state. The incorporation of solvent into the transition state entails a loss of entropy. The entropy of activation varies with solvent addition in a non-linear manner. This behaviour indicates specific solvation[13] and hence a non-random distribution of the solvent molecules. The sudden variation of the entropy of activation noticed at about 34 wt % of isopropanol in the base hydrolysis may reflect the variation of reaction kinetics with solvent composition.

Medium Effects on Reaction Rate

The correlation between the rate of formamide hydrolysis and medium effects[14] has also been investigated in isopropanol-water mixtures. This correlation involves a linear dependence of the rate function L ($L = \log k_{obs} - pK_w$, where k_{obs} is the observed rate constant and k_w is the water ionisation constant) on the logarithm of the molar concentration of the water which is present as a component of the solvent system ($\log C_w$). On the other hand, it was pointed out[1] that the variation of the reaction rate may be determined by the variation of the water ionisation constant with water concentration of the solvent system. This conclusion can also be proved by plotting the rate function L versus $\log C_w$, at constant temperature, where very good straight lines with positive slopes (n) were obtained (Fig. 3). The slopes of the lines obtained amounted to $n_a = 3.22$ and $n_b = 4.01$ for the acid and base hydrolysis of formamide, in isopropanol-water mixtures at 25°, respectively.

Here again we find that $n_b = n_a + 1$. This should be expected since the value of n could be looked upon as the change in number of solvated water molecules in passing from reactants to the transition

state in the rate determining step[14], and the H^+ or OH^- ion, in aqueous medium, is hydrated by four or three water molecules respectively. The values of the water ionisation constant in isopropanol-water mixtures were obtained at 25°, by interpolation, from the recently published data[15]. Unfortunately, their values at temperatures other than 25° were not reported in the literature. However, it is evident[1] that the n values are almost independent on temperature.

These results lend also further evidence to the validity of the correlation between the reaction rate and medium effects through the water ionisation constant and therefore Elsemongy's hypothesis[14] may be generally applicable.

Solvent Effect on Reaction Mechanism

The study of formamide hydrolysis in isopropanol-water mixtures was also made in a wider temperature range (25-60°) so as to examine the effect of temperature on the mechanism of the reaction. Successive addition of isopropanol alters the rate without influencing the mechanism and so the mechanism is the same for the different solvent compositions.

These data are consistent with our previously reported mechanisms for the acid[4] and base[7] hydrolysis of amides in aqueous-organic solvents. The analogies between the kinetic behaviour of formamide in acidic and basic isopropanol-water mixtures and that in acidic and basic dioxane-water mixtures[1] support our previous proposed mechanisms. Other evidences for these bimolecular mechanisms are the large negative values of the activation entropy and the values of energy of activation together with the
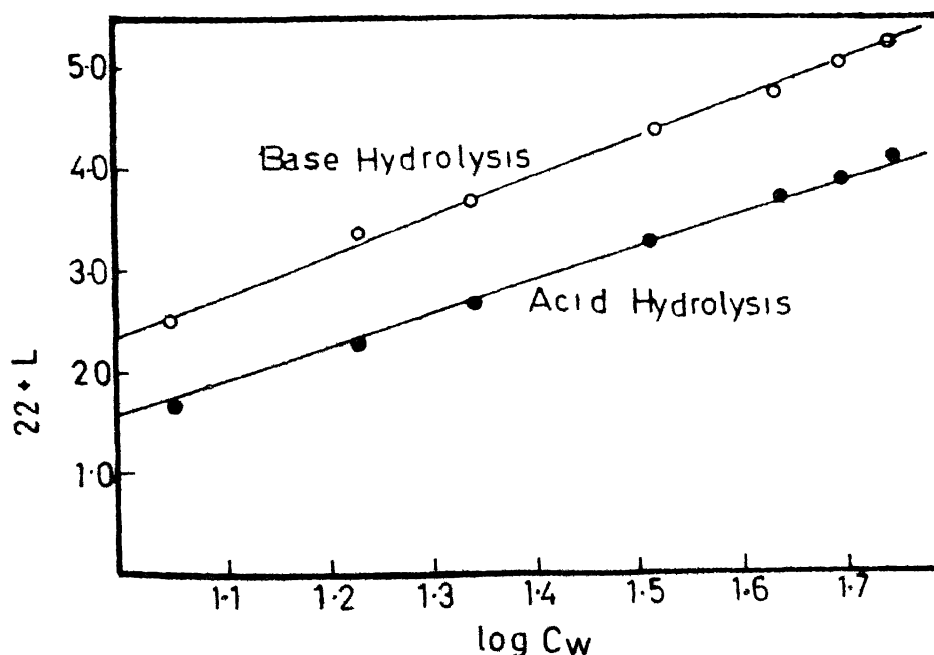

Fig. 3. Rate function and water concentration.

values of the frequency factor. These values are in excellent agreement with our previous proposed bimolecular mechanisms and thus they lend further support to the validity of these mechanisms.

Kinetics of Formamide Hydrolysis in Aqueous-Organic Solvents

Comparison of the kinetics of hydrolysis of formamide in isopropanol-water mixtures and in other aqueous organic mixed solvents[1, 16] (dioxane- and n.propanol-water mixtures) might therefore yield information about the role of the solvent. In the acid hydrolysis of formamide the velocity constant decreases with progressive addition of dioxane or n.propanol and then increases passing through a minimum at concentrations characteristic of the organic solvent (50 wt % of dioxane and 34.5 wt % of n.propanol). On the other hand, in the base hydrolysis, the rate decreases in presence of dioxane and n.propanol. The reverse is observed here in isopropanol-water mixtures.

In acid hydrolysis, the reaction rate decreases in the order : dioxane>n.propanol>isopropanol. In base hydrolysis the reaction rate first decreases in the order : n.propanol>isopropanol>dioxane, then the rate increases on progressive addition of isopropanol. However, the reaction rate is generally much higher than that in acid hydrolysis.

These results may be clarified in the light of Oakenfull suggestion[11] that addition of the organic solvent might change the rate-determining step. The organic solvent molecule is more tightly bound in the transition state for formation of the intermediate than in the transition state for breakdown to products. Consequently the transition state for formation is the more polarizable and hence the more stabilized by addition of the organic solvent. Addition of the organic solvent would therefore tend more to increase the rate of formation of the intermediate than its rate of breakdown to products and large concentrations of the organic solvent would change the rate-determining step. This explanation is supported by the sharpness of the sharp change of variation of log k_2 with D or with log C_w/C_s at concentrations characteristic of the organic solvent.

On the other hand, previous studies have shown that the N- and O-protonated amides are in equilibrium and that the concentration of N-protonated species increases with the electron-withdrawing character of the substituent on the nitrogen atom[4, 17]. It was also shown that the equilibrium is solvent-dependent and that the concentration of N-protonated amide varies in the same way as the rate profile.

Recently a kinetic study, based on a reaction mechanism in which water attacks N-protonated conjugate acid in the rate-determining step, has been successfully carried out for the acid hydrolysis of amides. Thus the relative rates of hydrolysis can, however, be readily explained if one considers the N-protonated form to be kinetically favourable[4, 18]. As the organic solvent concentration is increased the activity of water decreases simultaneously and, when this effect becomes more important than the increase in protonated intermediate, the rate of reaction decreases.

References

1. M. M. ELSEMONGY and H. M. ABU ELNADER, J. Indian Chem. Soc., in press.

2. A. I. VOGEL. "A Text Book of Practical Organic Chemistry", 3rd Ed. 1971.

3. M. M. ELSEMONGY, M. S. ABU ELAMAYEM and M. MOUSSA, Z. physik. Chem. Neue Folge 1975, 94, 69.

4. M. M. ELSEMONGY, M. S. ABU ELAMAYEM and M. MOUSSA, Z. physic. Chem. Neue Folge 1975, 95, 215.

5. K. J. LAIDLER and P. A. LANDSKROENER, Trans. Faraday Soc. 1956, 52, 200.

6. E. S. Amis, J. Chem. Education, 1953, 30, 351.

7. M. M. ELSEMONGY, Z. physik. Chem. Neue Folge 1973, 84, 294.

8. G. ÅKERLÖF, J. Amer. Chem. Soc. 1932, 54, 4125.

9. M. M. ELSEMONGY, M. S. ABU ELAMAYEM and M. MOUSSA, J. Indian Chem. Soc. 1975, 52, 321.

10. M. M. ELSEMONGY, M. S. ABU ELAMAYEM, M. MOUSSA and M. GOUDA, J. Indian Chem. Soc. 1975, 52, 1130.

11. D. G. OAKENFULL, Aust. J. Chem. 1974, 27, 1423.

12. Y. KONDO and N. TOKURA, Bull. Chem. Soc. Jap. 1972, 45, 818.

13. R. F. HUDSON and B. SAVILLE, J. Chem. Soc. (London), 1955, 4114.

14. M. M. ELSEMONGY, Z. physik. Chem. Neue Folge, in press

15. E. M. WOOLLEY, D. G. HURKOT and L. G. HEPLER, J. Phys. Chem. 1970, 74, 3908.

16. M. M. ELSEMONGY and H. M. ABU ELNADER, J. Indian Chem. Soc. in press.

17. S. RYSMAN DE LOCKERENTE, O. B. NAGY and A. BRUYLANTS, Org. Magn. Reson. 1970, 2, 179.

18. C. J. GIFFNEY and C. J. O' CONNOR, Aust. J. Chem. 1976, 29, 307.

65