

# Solvent Effect on Amide Hydrolysis I—Formamide Hydrolysis in Dioxane-Water Mixtures

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The kinetics of formamide hydrolysis was studied in acidic and basic dioxane-water mixtures at temperatures within the range 25-60°. The variation of rate constant with temperature, dielectric constant, acidity function and solvent composition was discussed. The refined distances of closest approach for the activated complexes and the thermodynamic parameters of activation were calculated and discussed as further evidences for the solvation effects. The results were explained by the proposed mechanisms of the acid and base hydrolysis. Water ionisation constants in several dioxane-water mixtures up to 80% by weight of dioxane were also determined at eight temperatures ranging from 25 to 60° at 5° intervals. An excellent linear dependence of  $pK_w$  on the mole fraction of water in the solvent was recorded. This can be represented by an equation which facilitate the calculation of any unknown  $pK_w$  value. Plots of  $pK_w$  versus  $\log C_w$ , at any temperature, give two excellent linear portions separated by a sharp boundary at a water concentration corresponding to 50 wt% of dioxane. As a surprising result, this solvent composition was coincident with the minimum in the reaction rate. The reaction rate was thus correlated with the ionisation constant of the water which is present as a component of the solvent system.

FEW investigations have been carried out on the hydrolysis of amides in aqueous-organic solvents.

The propionamide hydrolysis has earlier been investigated in ethanol-water mixtures<sup>1</sup>. The hydrolysis of acetamide has also been studied in mixtures of water with ethanol<sup>1</sup>, acetone<sup>2</sup>, dioxane<sup>3,4</sup>, methanol, glycol and glycerol<sup>5,6</sup>, *t*-butanol<sup>7</sup> and isopropanol<sup>8</sup>. The effects of amide structure, medium and temperature on the rate constants were discussed. The mechanisms of the acid and base hydrolysis of acetamide have recently been investigated<sup>3,4,6</sup> in terms of the role and the effect of the solvent on the reaction rate. However, no kinetic study of the hydrolysis of formamide has been undertaken from the standpoint of solvent effects.

A new correlation between reaction rate and medium effect through water ionisation constant in aqueous-organic solvents was recently proposed<sup>9</sup>. The ionisation of water has been investigated in aqueous-organic solvents<sup>10,11</sup>. The status of measurements is not nearly so satisfactory<sup>11</sup>. The uncertainty in the determination of the water ionisation constant in dioxane-water mixtures<sup>10</sup> increases with the dioxane content of the solvent. This is caused<sup>10</sup> by the change in relative solubility of silver chloride and hydroxide in passing from pure aqueous solutions to those containing the higher percentages of dioxane and cannot be remedied as long as silver-silver chloride electrodes are employed<sup>10</sup>. Therefore, the silver-silver iodide electrode is the most convenient one for this purpose.

This investigation was planned to study the

solvent effects on the kinetics and mechanism of the hydrolysis of formamide in dioxane-water mixtures. The correlation between reaction rate and medium effects was also investigated. This needs a precise measurement of the water ionisation constant for the various dioxane-water mixtures at different temperatures.

## Experimental

### Materials and apparatus

Pure formamide and 1,4 dioxane of "Prolabo" quality were further purified as described before<sup>4,12</sup>. Potential measurements were made with an Orion model 801 digital pH meters. Glass electrodes used with these meters were the Beckman 39004 pH 0-14 electrodes. The Ag, AgI electrode was prepared according to recommended procedures<sup>13</sup>. All the chemicals used are of the B. D. H. grade. All solutions were made up in boiled de-ionised water.

### Procedure

Rates of hydrolysis were measured as mentioned before<sup>4</sup>. The initial concentrations of both amide and acid or base were always 0.1 M. The temperature was held constant within  $\pm 0.05^\circ$ . All rate constants listed are the mean of at least two completely independent determinations.

The technique of determination of water ionisation constant was that employed recently for measurements of this kind<sup>11</sup>. The two cells used

are represented as

glass electrode/soln A :



and

glass electrode/soln B :



The advantage of this procedure is to make use of the difference in two potentials, thereby eliminating the often unknown standard potential from the calculations<sup>11,13</sup>. The largest source of error in the absolute magnitude of  $pK_w$  is caused by the error in determining the standard potential<sup>10</sup>. In all cases, the cells were maintained at the given temperature ( $\pm 0.05^\circ$ ) and the potential readings were recorded when they became constant to  $\pm 0.1$  mV. Measurements were repeated at least two times. Average deviations in  $pK_w$  values derived from these independent measurements were always less than 0.007 for solutions up to 50% by weight of dioxane and increased with dioxane content and reached to 0.065 for 80% by weight of dioxane.

## Results and Discussion

### Rate constant and energy of activation

Acid and base hydrolysis of formamide were studied in water and in dioxane-water mixtures at temperatures within the range 25–60°. The solvent composition was chosen to cover the range up to about 80.0 and 40.5% by weight of dioxane in the acid and base hydrolysis respectively. Unfortu-

nately, dioxane has a very limited range of miscibility with aqueous sodium hydroxide which limits the significance of the results. The hydrolysis of formamide in these media is a complete reaction. The infinity values obtained were found to be constant and the same in pure water and in different dioxane-water mixtures. This assured the complete hydrolysis even in the presence of dioxane. The system was found to obey the Arrhenius equation in this wide range of temperatures. This proves that dioxane alters the reaction rate without influencing the mechanism. Second order rate constants in liter mole<sup>-1</sup> second<sup>-1</sup> were measured in the various solutions. These are collected in Table I together with the isocomposition activation energies  $E_a$  and frequency factors (log A). The rate constant decreases slightly on successive addition of dioxane in both acid and base hydrolysis, then increases passing through a minimum in case of the acid hydrolysis at about 50 wt % of dioxane. The acidity is appreciably reduced by the first additions of dioxane, passes through a minimum and finally increases again. The tetrahedral structure of water has been largely broken by successive addition of dioxane and so the proportion of free water molecules increases as the water activity decreases. In light of these effects the variation of rate constant with solvent composition can be understood. In addition, the increase in the rate constant of the acid hydrolysis at higher dioxane contents may be due to changes in ion pair formation by protonated formamide or to the breakdown of the dimer structure of formamide<sup>14</sup> on successive addition of dioxane. However, the effect of solvent is more pronounced on decreasing the temperature. Similar behaviour was recently observed, in this laboratory,

TABLE I—VARIATION OF RATE CONSTANT WITH DIELECTRIC CONSTANT AND SOLVENT COMPOSITION

		I—Acid Hydrolysis								II—Base Hydrolysis					
		00.00	10.28	20.47	30.51	40.69	60.68	70.52	79.38	00.00	5.16	10.14	20.37	30.36	40.50
	Dioxane wt %	1.745	1.699	1.623	1.590	1.517	1.388	1.200	1.066	1.745	1.732	1.699	1.648	1.591	1.529
	log $\epsilon_{\text{water}}$	1.000	0.973	0.944	0.922	0.881	0.756	0.661	0.561	1.000	0.984	0.974	0.945	0.925	0.892
	$\epsilon_{\text{dioxane}}$	0.000	0.092	0.205	0.326	0.477	0.686	0.751	0.792	0.000	0.045	0.075	0.189	0.316	0.462
25°	D	78.45	69.21	60.42	51.38	42.88	25.55	17.29	11.18	78.45	73.95	69.42	60.48	51.72	42.60
	23+L	5.339	5.002	4.621	4.301	3.699	2.458	1.426	0.880	6.382	6.146	5.943	5.531	5.080	4.556
	4+log $k_2$	0.329	0.291	0.251	0.236	0.200	0.298	0.386	0.470	1.322	1.286	1.238	1.161	0.100	0.046
	$\epsilon_{\text{water}}$	0.000	0.092	0.205	0.326	0.477	0.686	0.751	0.792	0.000	0.045	0.075	0.189	0.316	0.462
35°	D	74.89	66.01	57.49	48.84	40.16	28.89	16.36	10.60	74.89	70.52	66.01	57.55	49.00	40.34
	23+L	5.963	5.668	5.398	4.888	4.403	3.090	2.220	1.100	6.996	6.828	6.620	6.224	5.782	5.240
	4+log $k_2$	0.693	0.658	0.628	0.608	0.593	0.660	0.790	0.910	1.676	1.648	1.600	1.554	1.492	1.430
	$\epsilon_{\text{water}}$	0.000	0.092	0.205	0.326	0.477	0.686	0.751	0.792	0.000	0.045	0.075	0.189	0.316	0.462
40°	D	73.12	64.39	55.98	47.56	39.04	28.16	15.90	10.27	73.12	68.70	64.50	56.00	47.74	39.26
	23+L	6.274	5.989	5.601	5.312	4.717	3.403	2.551	1.442	7.295	7.128	6.935	6.532	6.090	5.556
	4+log $k_2$	0.359	0.329	0.291	0.278	0.267	0.833	0.991	1.122	1.852	1.807	1.755	1.702	1.659	1.606
	$\epsilon_{\text{water}}$	0.000	0.092	0.205	0.326	0.477	0.686	0.751	0.792	0.000	0.045	0.075	0.189	0.316	0.462
45°	D	71.44	62.91	54.56	46.34	38.11	22.58	15.47	9.99	71.44	67.15	63.00	54.64	46.56	38.20
	23+L	6.628	6.382	5.927	5.508	5.012	3.715	2.833	1.775	7.607	7.430	7.232	6.830	6.380	5.863
	4+log $k_2$	1.018	0.992	0.967	0.947	0.932	0.995	1.143	1.305	1.996	1.964	1.921	1.870	1.810	1.773
	$\epsilon_{\text{water}}$	0.000	0.092	0.205	0.326	0.477	0.686	0.751	0.792	0.000	0.045	0.075	0.189	0.316	0.462
50°	D	69.85	61.42	52.26	45.14	36.98	21.95	15.05	9.82	69.85	65.61	61.56	53.25	45.90	37.12
	23+L	6.903	6.604	6.237	5.824	5.358	4.016	3.157	2.102	7.892	7.718	7.524	7.135	6.681	6.168
	4+log $k_2$	1.190	1.164	1.147	1.134	1.123	1.166	1.337	1.512	2.152	2.126	2.084	2.038	1.991	1.937
	$\epsilon_{\text{water}}$	0.000	0.092	0.205	0.326	0.477	0.686	0.751	0.792	0.000	0.045	0.075	0.189	0.316	0.462
60°	D	66.62	58.49	50.48	42.58	34.69	20.68	14.25	9.21	66.62	62.41	58.49	50.54	42.82	34.81
	23+L	7.484	7.151	6.806	6.405	5.908	4.573	3.716	2.689	8.433	8.253	8.085	7.684	7.255	6.751
	4+log $k_2$	1.494	1.471	1.469	1.465	1.448	1.478	1.676	1.889	2.453	2.428	2.395	2.354	2.315	2.281
	$\epsilon_{\text{water}}$	0.000	0.092	0.205	0.326	0.477	0.686	0.751	0.792	0.000	0.045	0.075	0.189	0.316	0.462
$E_a$		15.22	15.36	15.74	15.84	15.90	16.02	16.66	18.56	14.38	14.80	15.19	15.56	15.94	16.29
log A		7.48	7.55	7.79	7.84	7.87	8.02	8.60	10.07	7.89	8.13	8.36	8.56	8.77	8.96

during the study of hydrolysis of acetamide in dioxane-water mixtures<sup>4</sup>.

The experimental activation energies involve a highly mixed dependence of the rate constant and of the dielectric constant of the medium on temperature<sup>1,5</sup>. In order to obtain a more precise treatment of the results the temperature dependence of the dielectric constant should be eliminated. This is achieved by calculating the isodielectric activation energies,  $E_d$ , from the corresponding rate constants in isodielectric solutions. These were obtained by interpolation, at chosen values of  $D$ , from plots of  $\log k$  against  $D$ . The values of  $E_d$  were then obtained from the Arrhenius plots, and hence the contribution due to solvation phenomena will be more or less minimised. The values of  $E_d$  for the acid and base hydrolysis of formamide are listed in Table 2. The increase of both isocomposition and isodielectric energies of activation with the addition of dioxane may be due to solvation of the activated complex to a less extent than of the reactants.

#### *Influence of dielectric constant*

The increase in rate constant with increase in dielectric constant can be ascribed to the formation of an activated complex more polar than the reactants. The influence of the dielectric constant on the rate of the hydrolysis of formamide can be visualised by application of both Laidler-Landskroener equation of ion-neutral molecule interaction<sup>1</sup> and Amis equation of ion-dipole interaction<sup>1,6</sup>. Both equations involve a linear correlation of the logarithm of the velocity constant with reciprocal of the dielectric constant in aqueous-organic solvents. The dielectric constant,  $D$ , values of dioxane-water mixtures were obtained by interpolation from sufficiently large-scale plots of Åkerlöf's data<sup>17</sup>. However, the plots of  $\log k_s$  versus  $1/D$  for the various water-dioxane compositions (Table 1) reveal that the rate decreases first linearly with decrease of the dielectric constant, then a curvature occurs specially at low dielectric constants.

The variation of velocity constant with dielectric constant can best be investigated on the basis of Elsemongy's equation<sup>8</sup>,

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

where  $k$  is the velocity constant,  $k'$  is its value at  $D=1$ , and  $\alpha$  is a constant. This equation predicts a linear dependence of  $\log k$  on  $D$  at any temperature<sup>4,8-9</sup>. Actually, the plots of  $\log k_s$  versus  $D$  gave very good straight lines. Following the same procedure mentioned before<sup>8</sup>, the values of  $k'$  for the acid and base hydrolysis of formamide and the refined values of  $a_{\neq}$ , the distances of closest approach for the activated complexes at chosen values of  $D$  (10, 20, 40, ..., etc.), were calculated and the results are given in Table 3. The values of  $a_{\neq}$  decrease with progressive addition of dioxane. This is in agreement with the fact that on progressive addition of dioxane, the structure of water would be destroyed progressively and the reacting species might become closer to each other and so the distance of closest approach should decrease<sup>8</sup>. However, these reasonable values account for the solvation of the activated complex and give an idea about the extent of solvation.

It is noteworthy that the radius of the activated complex in the acid or base hydrolysis of carboxylic amides of simple structure in dioxane-water mixtures 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 understood in the light of our results for acetamide<sup>4-8</sup> and formamide<sup>1,8</sup> in various aqueous-organic solvents.

#### *Thermodynamic data of the activated complex*

Now, it is well generally known that the role of the effect of change in solvent composition on the rate and mechanism of the reaction is conveniently expressed in terms of the thermodynamic parameters of activation, namely, the free energy change

TABLE 2—ISODIELECTRIC ENERGIES OF ACTIVATION  $E_d$  (IN K CAL/MOLE)

$D$	I—Acid Hydrolysis					II—Base Hydrolysis				
	10	20	40	55	75	40	50	60	70	80
$E_d$	18.949	16.955	16.716	16.477	16.238	17.327	17.053	16.870	16.474	15.985

TABLE 3—VALUES OF  $k'$  (IN LITER/MOLE/SEC) AND  $a_{\neq}$  (IN Å)

$t^\circ$	I—Acid Hydrolysis						II—Base Hydrolysis					
	$4 + \log k'$	$D=10$	Refined values of $a_{\neq}$ at				$4 + \log k'$	$D=40$	Refined values of $a_{\neq}$ at			
			$D=20$	$D=40$	$D=60$	$D=80$			$D=50$	$D=60$	$D=70$	$D=80$
25	0.601	6.2	6.5	6.6	6.7	6.8	0.719	5.8	5.9	6.0	6.1	6.2
35	1.078	6.2	6.5	6.6	6.7	6.8	1.109	5.8	5.9	6.0	6.1	6.2
40	1.314	6.2	6.5	6.6	6.7	6.8	1.327	5.8	5.9	6.0	6.1	6.2
45	1.552	6.2	6.5	6.6	6.7	6.8	1.473	5.9	6.0	6.1	6.2	6.3
50	1.724	6.2	6.5	6.6	6.7	6.8	1.648	5.9	6.0	6.1	6.2	6.3
60	2.148	6.2	6.5	6.6	6.7	6.8	2.071	5.9	6.0	6.1	6.2	6.3

TABLE 4—THERMODYNAMIC PARAMETERS OF ACTIVATION ( $\Delta F^\ddagger$  AND  $\Delta H^\ddagger$  IN K CAL/MOLE,  $\Delta S^\ddagger$  IN E.U.)

DIOXANE wt %		I—ACID HYDROLYSIS								II—BASE HYDROLYSIS					
		00.00	10.23	20.47	30.51	40.69	60.68	70.52	79.38	00.00	5.16	10.14	20.37	30.26	40.50
25°	$\Delta F^\ddagger$	22.46	22.51	22.57	22.59	22.64	22.50	22.88	22.27	21.10	21.15	21.23	21.32	21.41	21.48
	$\Delta H^\ddagger$	14.62	14.76	15.15	15.25	15.31	15.42	16.06	17.96	13.79	14.20	14.60	14.96	15.35	15.70
	$-\Delta S^\ddagger$	26.30	25.99	24.87	24.61	24.58	23.76	21.20	14.45	24.53	23.31	22.23	21.33	20.33	19.39
35°	$\Delta F^\ddagger$	22.72	22.77	22.81	22.84	22.86	22.77	22.58	22.41	21.34	21.38	21.44	21.54	21.60	21.68
	$\Delta H^\ddagger$	14.60	14.74	15.13	15.23	15.29	15.40	16.04	17.94	13.77	14.18	14.58	14.94	15.33	15.68
	$-\Delta S^\ddagger$	26.35	26.05	24.92	24.70	24.57	23.90	21.23	14.51	24.55	23.34	22.28	21.40	20.35	19.49
40°	$\Delta F^\ddagger$	22.86	22.91	22.96	22.97	22.99	22.90	22.69	22.48	21.44	21.51	21.58	21.66	21.72	21.79
	$\Delta H^\ddagger$	14.59	14.73	15.12	15.22	15.28	15.39	16.08	17.93	13.76	14.17	14.57	14.93	15.32	15.67
	$-\Delta S^\ddagger$	26.41	26.10	25.03	24.76	24.64	23.97	21.27	14.55	24.52	23.41	22.39	21.47	20.44	19.56
45°	$\Delta F^\ddagger$	23.01	23.05	23.09	23.12	23.14	23.05	22.83	22.60	21.59	21.62	21.69	21.77	21.86	21.91
	$\Delta H^\ddagger$	14.58	14.72	15.11	15.21	15.27	15.38	16.02	17.92	13.75	14.16	14.56	14.92	15.31	15.66
	$-\Delta S^\ddagger$	26.50	26.17	25.08	24.84	24.74	24.09	21.40	14.68	24.64	23.45	22.42	21.52	20.58	19.65
50°	$\Delta F^\ddagger$	23.12	23.16	23.19	23.21	23.22	23.16	22.91	22.65	21.70	21.76	21.80	21.88	21.94	22.02
	$\Delta H^\ddagger$	14.57	14.71	15.10	15.20	15.26	15.37	16.01	17.91	13.74	14.15	14.55	14.91	15.30	15.65
	$-\Delta S^\ddagger$	26.46	26.14	25.03	24.78	24.65	24.10	21.36	14.65	24.64	23.50	22.45	21.54	20.60	19.70
60°	$\Delta F^\ddagger$	23.39	23.43	23.44	23.45	23.47	23.42	23.11	22.79	21.94	21.98	22.02	22.09	22.15	22.20
	$\Delta H^\ddagger$	14.55	14.69	15.08	15.18	15.24	15.35	15.99	17.89	13.72	14.13	14.53	14.89	15.28	15.63
	$-\Delta S^\ddagger$	26.53	26.23	25.08	24.79	24.70	24.22	21.38	14.69	24.67	23.53	22.49	21.59	20.62	19.72

$\Delta F^\ddagger$ , enthalpy change  $\Delta H^\ddagger$  and entropy change  $\Delta S^\ddagger$ . The thermodynamic properties of the activated complex are usually taken as a measure of the solvation effects. These properties have been calculated (Table 4) and are shown in Fig. 1. It is evident that solvation of one or more of the reactants will result in an increase of the activation energy and the reaction will be retarded<sup>4,7,8</sup>. If the solvation of the activated complex is less than that of the reactants, then the energy of activation should increase with the successive addition of dioxane. This is the case for the hydrolysis of formamide in

dioxane-water mixtures. The heat content change,  $\Delta H^\ddagger$ , increases gradually with increasing dioxane content which may be a direct consequence of the increase of the isocomposition activation energy with decrease of dielectric constant.

It is seen that  $\Delta F^\ddagger$  increases slightly with increase of dioxane concentration and then decreases also slightly by further successive addition of the organic solvent in acid hydrolysis. This weak dependence is due largely to the general linear compensation between  $\Delta H^\ddagger$  and  $\Delta S^\ddagger$  for a given temperature.

A major determinant of  $\Delta S^\ddagger$  for reactions in solution is solvation change between reactants and transition state. The incorporation of solvent into the transition state entails a loss of entropy.  $-\Delta S^\ddagger$  decreases with solvent addition in a non-linear manner. This behaviour indicates specific solvation and hence a non-random distribution of the solvent molecules. The sudden decrease of  $-\Delta S^\ddagger$  noticed at about 50 wt % of dioxane in the acid hydrolysis reflects the variation of reaction kinetics with solvent composition. As mentioned above, minimum rate constants were observed at about 50 wt % of dioxane.

#### Water ionisation constant

To investigate the correlation between the rate of hydrolysis of formamide and medium effects<sup>9</sup>, precise measurements of water ionisation constant were taken up.

Results of  $pK_w$  determinations in several dioxane-water mixtures (containing 10, 20, 30, 40, 50, 60, 70 and 80% by weight of dioxane) are shown in Table 5 at eight temperatures ranging from 25 to 60°. The increasing values of  $pK_w$  with increasing dioxane in the solvent system are to be expected on the basis of the decreasing dielectric constant of the medium and have been observed before<sup>10,11</sup> for aqueous dioxane in agreement with our results. These results are also in excellent agreement with those values at the

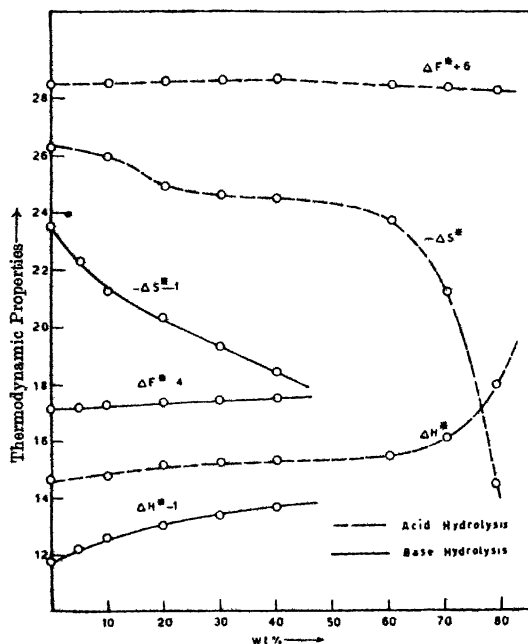


Fig. 1. Dependence of Thermodynamic properties on the composition of the solvent at 25°C.

TABLE 5—IONISATION CONSTANT OF WATER IN DIOXANE-WATER MIXTURES

t°	Dioxane wt %									m	c
	0	10	20	30	40	50	60	70	80		
25	13.997	14.284	14.618	15.007	15.462	16.011	16.782	17.795	19.199	11.573	25.610
30	13.833	14.122	14.459	14.833	15.293	15.882	16.663	17.640	19.062	11.645	25.518
35	13.680	13.971	14.310	14.698	15.157	15.741	16.524	17.502	18.910	11.651	25.379
40	13.535	13.823	14.157	14.550	15.019	15.602	16.391	17.377	18.781	11.707	25.286
45	13.397	13.694	14.026	14.425	14.883	15.453	16.241	17.241	18.639	11.710	25.125
50	13.262	13.553	13.892	14.285	14.742	15.299	16.098	17.119	18.518	11.716	25.020
55	13.137	13.439	13.762	14.153	14.615	15.187	15.974	16.996	18.404	11.735	24.913
60	13.017	13.308	13.647	14.041	14.505	15.088	15.862	16.882	18.305	11.778	24.837

same solvent compositions obtained by interpolation of the previous data<sup>10,11</sup> up to about 25 wt % of dioxane. As the dioxane content increases, our  $pK_w$  values become less than the corresponding previous data<sup>10</sup>, with differences up to 0.06 for a mixture of water with 70 wt % dioxane. The results of our  $pK_w$  determination are displayed graphically in different forms. Plots of  $pK_w$  versus mole fraction of water in the solvent  $X_w$  showed an excellent linear dependence and this can be expressed, at any temperature, by the equation

$$pK_w = c - mX_w \quad \dots (4)$$

The  $pK_w$  values of any dioxane-water mixture over the temperature range 25–60° can be computed by using equation (4). The least square values of the slopes,  $m$ , and intercepts,  $c$ , of these lines are presented in Table 5. These values facilitate the calculation of any unknown value of  $pK_w$ . Equation (4) with these numerical constants reproduces the observed values of  $pK_w$  with an average accuracy better than  $\pm 0.008$ .

Plots of  $pK_w$  versus  $\log C_w$  (Fig. 3) as suggested by Marshall's treatment<sup>10</sup> give, at any temperature, two excellent linear portions separated by a sharp boundary at a water concentration of 27.75 moles/liter (50 wt % of dioxane). According to this treatment, which was intended to apply only in the case of inert cosolvents such as dioxane, the slopes of the lines provide evidence about the difference between hydration numbers of  $H^+$  (S) +  $OH^-$  (S) and  $H_2O$  (S). However, the slope of the lines amounts to +7 in the water-rich mixtures, in excellent agreement with that obtained before<sup>11</sup> through the same solvent region, and reaches to +8 in the dioxane-rich mixtures. This means and proves that the internal structure of the medium suffered serious changes on addition of dioxane to water and this has recently been discussed<sup>4</sup>.

A surprising result can be seen from the above  $pK_w - \log C_w$  relation. The minimum in the reaction rate is coincident with the above mentioned water concentration of 27.75 moles/liter corresponding 50 wt % of dioxane. Above or below this water content the rate increases but the solvent effect on the kinetic behaviour is much different in these two regions. As a conclusion, the minimum of the

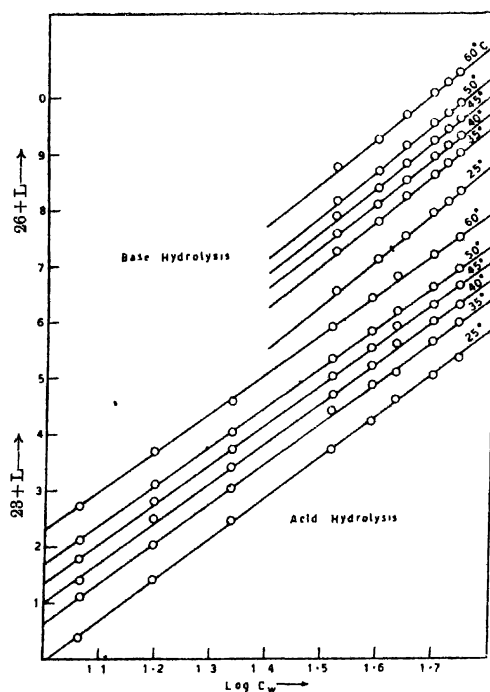


Fig. 2. Correlation of reaction rate with water ionisation constant.

reaction rate may be determined by the variation of the water ionisation constant with water concentration of the solvent system. Plots of the rate function  $L(L = \log k_{obs} - pK_w)$  versus  $\log C_w$ , at constant temperature, are very nicely linear (Table 1 and Fig. 2). Elsemongy's hypothesis<sup>9</sup> is therefore applicable.

$$\log k_{obs} - pK_w = n \log C_w + \text{constant} \quad \dots (5)$$

$C_w$  is the molar concentration and  $K_w$  is the ionisation constant of the water which is present as a component of the solvent system and  $k_{obs}$  is the observed rate constant. The slope of any of these straight lines,  $n$ , constitutes a parameter which describes the manner in which the particular reaction responds to acid or base catalysis<sup>9</sup>.

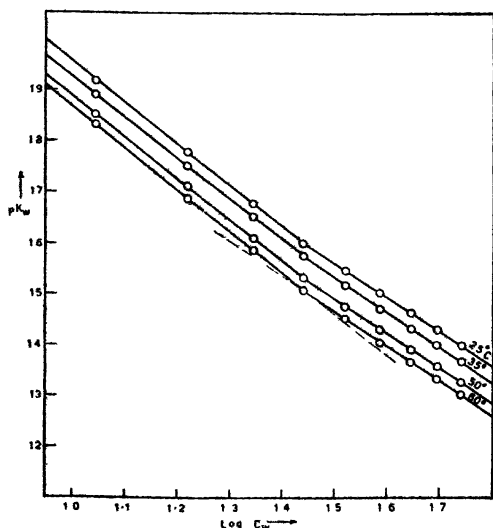


Fig. 3. Effect of water concentration on water ionisation constant in dioxane-water mixtures.

The interesting phenomenon of a rate minimum in a plot of  $\log k_{\text{obs}}$  against  $\log C_w$  is encountered. Such rate minima have been known for the acid hydrolysis of amides in aqueous-organic solvents<sup>2,4,18</sup>. Nevertheless success has been claimed in treating the phenomenon with reference to Elsemongy's hypothesis<sup>9</sup> and indeed for formamide hydrolysis the agreement is very good. This lends further strong support to the validity of the hypothesis.

In general, very good linear plots were obtained and the slopes  $n$  could be defined with certainty. These are collected in Table 6 for the acid ( $n_a$ ) and

TABLE 6—VALUES OF  $n$  AT VARIOUS TEMPERATURES

$t^\circ$	25	35	40	45	50	60
$n_a$	7.33	7.23	7.15	7.13	7.11	7.09
$n_b$	8.32	8.20	8.15	8.11	8.01	7.92

base ( $n_b$ ) hydrolysis of formamide at the various temperatures. No great dependence of  $n$  on temperature is evident and it is clear 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<sup>9</sup> and the  $H^+$  or  $OH^-$  ion, in aqueous medium, is hydrated by four or three water molecules respectively<sup>4,6,9</sup>.

#### Acidity function and reaction mechanism

The results of Hammett's acidity function studies in dioxane-water<sup>20,21</sup> mixtures show the acidity falling to a minimum with first additions of the organic component and, then, increasing with further addition. Graphical representation of the correlation between  $-H_0$  and medium composition

for any fixed acid concentration in dioxane-water mixtures shows that the proton availability is appreciably reduced by the first additions of either water or dioxane. Minima are exhibited at solvent compositions (about 80 wt % dioxane for 0.1M HCl) depending on the fixed acid concentration through the whole solvent system. This was explained<sup>21</sup> in terms of a gradual breakdown of a quasi-crystalline tetrahedral structure of water on progressive addition of dioxane. The aqueous solvation shell will be gradually dispersed as the proportion of non-aqueous component is increased and the aqueous solvates ( $n H_2O, H^+$ ) will be replaced by  $H_2O^+$  ions at the minima of the plots relating  $-H_0$  to medium composition. Reaching the minima, the increase in  $-H_0$  with further addition of the organic solvent was supposed to result from the replacement of the  $H_2O^+$  ions by the  $SH^+$  ions<sup>21</sup>.

Application of Zucher-Hammett or Bunnett treatments<sup>20</sup> showed that the kinetic behaviour is not parallel to the changes in acidity function<sup>21,22</sup> with change in solvent composition. Our calculations have shown that the rates of hydrolysis of formamide in dioxane-water mixtures are not consistent with any of these previous treatments which correlate rates with acidity functions. This may be due to the fact that the concept of the acidity function loses some of its generality on passing from aqueous solutions to media of lowest dielectric constants<sup>9</sup>. The observed deviations, in the acid hydrolysis, are probably due to the fact that the maximum in  $H_0$  is not coincident with the minimum in the reaction rate. The bimolecular rate constant follows a trend which is far from linear indicating the operation of our proposed bimolecular addition mechanism.

All previous results reveal that the recently proposed mechanisms for the acid<sup>4</sup> and base<sup>6</sup> hydrolysis of acetamide in dioxane-water mixtures are the operating mechanisms. Thus in acid hydrolysis a mechanism involving a rapid protonation pre-equilibrium on either the oxygen or nitrogen atom by solvated protons followed by a slow bimolecular addition of water to the solvated protonated amide may be proposed. An equilibrium was established between O- and N-protonated transition states. The positive charge that is distributed over the oxygen and nitrogen atoms of the amide in the initial state is further partly distributed to the other oxygen atoms arising from the solvating water molecules on water-rich mixtures. The changes in polarity are then small and only a small solvent effect would be expected, in agreement with our observations in these regions. In the dioxane-rich region, the transition state is probably involved in a proton transfer reaction in which the proton is transferred from the oxygen atom to the nitrogen atom. The reaction between nitrogen-protonated formamide and water is accompanied by an increase in polarity and the transition state then decomposes to the products at a relatively high rate which is in agreement with the

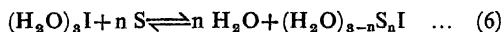
observed relatively high rates in dioxane-rich regions. In base hydrolysis, a fast pre-equilibrium nucleophilic attack of solvated hydroxyl ions on the amide molecule proceeds the slow bimolecular addition of a water molecule to the solvated transition state.

Energies and entropies of activation together with the frequency factors ( $\log A$ ) given in Tables 1 and 4 are further evidences supporting the validity of our proposed bimolecular mechanisms.

#### Solvent composition and reaction rate

An explanation for the decrease of the reaction rate would be that a water molecule bound by a hydrogen bond to a dioxane molecule is less nucleophilic than a water molecule bound by a hydrogen bond to another water molecule. The variation of the reaction rate with water concentration is illustrated by a plot of  $\log k_2$  against  $\log C_w$ . In acid hydrolysis, two linear portions were obtained corresponding to water- and dioxane-rich solvent mixtures. Their slopes vary with temperature and have the values 0.6-0.4 and 0.7-1.4 at 25-60° respectively. In base hydrolysis, straight lines were obtained and their slopes vary also with temperature and have the values 1.2-0.9 at 25-60°. 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 mechanisms.

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



where  $I$  stands for a  $H_3O^+$  or  $OH^-$  ion. This can be considered in the light of the assumption of a multi-step solvation mechanism<sup>23</sup>. A  $H_3O^+$  or  $OH^-$  ion, that is hydrated by three water molecules in pure aqueous solvents, can be expected to exist as such clusters as  $(H_2O)_{3-n}S_nI$  in mixed solvents<sup>4,6,9,20,23</sup>. However, the net reaction actually taking place is the substitution of water by dioxane in the cluster. Therefore the number of free water molecules increases on progressive addition of dioxane and this plays an important role in the dependence of reaction rate on solvent composition. In addition, this may explain the increase of acidity, at high dioxane content in dioxane-water mixtures, at a fixed acid concentration, through the formation of the more acidic non-solvated  $H_3O^+$  ions. Thus, the decrease in  $-H_0$  with addition of dioxane may also attributed to the shift of equilibrium (6) to the right. The protonated species were supposed changing from  $(H_2O)_4H^+$  to water solvated  $SH^+$  ions. At the minimum of  $-H_0$ , the protonated species changes from water solvated  $SH^+$  ions to  $H_3O^+$ , and only at very high concentrations of dioxane they change to dioxane solvated  $SH^+$  ions resulting in the increase of  $-H_0$ .

Presumably, the water solvated  $SH^+$  ion exists as  $[S(H_2O)_3]H^+$ , or possibly  $SH^+(H_2O)_2$ , with all species solvated by iceberg-like structure of water. The equilibrium constant is given, in terms of activities, by the equation

$$K = \frac{(a_{H_2O})^n a_{solv \cdot I}}{(a_S)^n a_{hyd \cdot I}} \quad (7)$$

Thus the ratio  $(a_{hyd \cdot I}/a_{solv \cdot I})$  is directly proportional to  $(a_{H_2O}/a_S)^n$  and the reaction rate would be dependent on each of these two terms. This can be proved by plotting  $\log k_2$  against  $\log (a_{H_2O}/a_S)$  where very good straight lines were obtained (Fig. 4). Activities of water and dioxane were

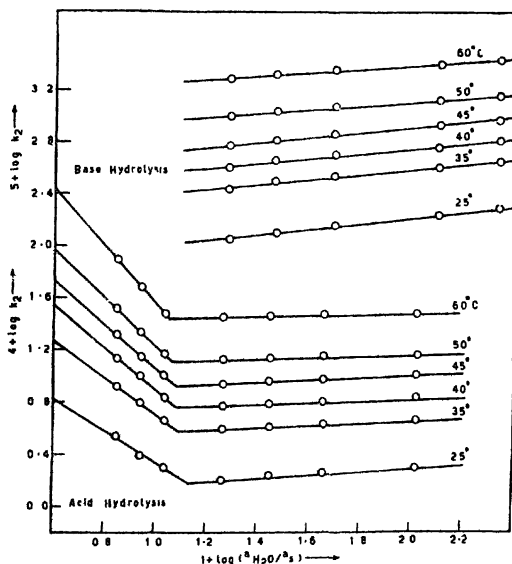


Fig. 4. Dependence of reaction rate on solvent composition.

obtained by interpolation from the previously published data<sup>24</sup>. At 25-60°, the slopes range from 0.21 to 0.13 in the base hydrolysis; from 0.10 to 0.04 and from 1.21 to 2.16 in water- and dioxane-rich solvent mixtures respectively in the acid hydrolysis. As the relative concentrations of the solvent components change, preferential solvation of the activated complex will also vary. The dependence of the number of water molecules involved in the activated complex on solvent composition is again a strong evidence of the continuous substitution of water by dioxane molecules as dioxane is increased.

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