KINETICS OF THE HYDROLYSIS OF ANILIDES

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The hydrolysis of anilides has mainly been studied from the points of view of (i) the kinetics, and (ii) the influence of structure on the ease and the velocity of hydrolysis. The work carried out so far has been mainly confined to the ease of saponification with regard to the position of the substituted groups in anilides, and the pH of the reacting medium. One of the major difficulties experienced in these studies is that investigations on all the anilides could not be conducted in the same solvent for want of solubility.

The authors have attempted a detailed study of the hydrolysis of sixteen anilides under varying conditions of temperature, solvent, concentration of catalyst, etc.

Experimental Technique

Among the anilides investigated, formanilide, form-o-toluidide, form-p-toluidide, p-nitroacetanilide, p-bromoacetanilide and benzoyl-p-toluidide were prepared in the laboratory according to standard methods. Acet-o-toluidide, acet-m-toluidide, acet-p-toluidide, acet-α-naphthalide, acet-β-naphthalide, propionanilide, benzanilide and benzoyl-o-toluidide were products of the British Drug House. Acetanilide was a product of Schering-Kahlbaum, whereas o-nitroacetanilide was a product of Messrs. E. Merck. All these compounds were tested for their purity before use.

The alcohol used was a product of the Government Distillery, Nasik, and it was distilled with alkaline permanganate, the portion between 77° and 78° C. being used in this investigation. Sulphuric acid used was an extra-pure compound. Barium hydroxide, used in the estimation of acid liberated during the reaction, was a product of the British Drug House.

The hydrolysis was carried out in flasks fitted with ground-glass reflux condensers placed in a thermostat maintained at a constant temperature with a variation of 0·1° C. Equal volumes of anilide solutions and sulphuric acid solutions (catalyst) were mixed at any required temperature and the liberated acid was estimated from time to time by titrating 25 c.c. of the reaction mixture against 0·1 N barium hydroxide solution, using methyl red as an indicator. Where acetic acid was used as a solvent, separate test-tubes, fitted with reflux condensers, were used for carrying out the reactions,

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the amine liberated at definite intervals of time being estimated in the contents of each test-tube. The infinity reading was calculated from the initial concentration of the anilide when alcohol was used as the solvent, while in other cases it was obtained experimentally.

As many of the anilides were insoluble or not sufficiently soluble in water, absolute alcohol, water-alcohol mixtures or acetic acid were used as solvents. The introduction of alcohol in the reaction system caused ester formation with the acid liberated by hydrolysis of the anilides to some extent.

The values of K_1, the velocity constants for the hydrolytic reactions carried out under different conditions, were calculated from the equation for a uni-molecular reaction. In the case of reactions in 50% alcohol, the values of $(a - x)$ were corrected for the amount of the acid esterified and the values of K_1 are the corrected values excepting those marked with an asterisk. The various results obtained are given in the following tables under four different headings. The reactivity of the different anilides has been taken to be proportional to the velocity constant.

RESULTS

(A) HYDROLYSIS OF ANILIDES IN WATER

TABLE I. *Effect of Catalyst Concentration*

Temperature 30 °C.   Concentration of Anilide 0·05 M

Anilide	Concentration of catalyst (H_2SO_4)	$K_1 \times 10^4$	$K_2 \times 10^4$
Formanilide ..	0·05 N	13·2	26·4
	0·10 N	24·7	24·7
	0·25 N	61·3	24·6
Form-*o*-toluidide ..	0·05 N	5·3	10·6
	0·25 N	27·3	10·9

TABLE II. *Effect of Temperature*

Formanilide in aqueous medium (0·05 M)

Temp. (°C.)	$K_1 \times 10^4$ at different concentrations of catalyst		
	0·05 N	0·10 N	0·25 N
30	13·2	24·7	61·3
35	19·7	38·0	..
40	27·2	51·8	126·8
45	40·4	78·5	..
Q (calories)	13,820	14,840	13,860

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TABLE III. *Effect of Temperature*

Form-*o*-toluidide in aqueous medium (0·05 M)

Temp. (°C.)	$K_1 \times 10^4$ at different concentrations of catalyst	
	0·05 M	0·25 N
30	5·35	27·3
35	7·68	..
40	11·43	59·16
45	16·24	..
Q (calories)	14,230	14,730

TABLE IV. *Effect of Temperature*

Concentration of catalyst 0·25 N   Concentration of anilide (0·10 M)

Temp. (°C.)	Values of $K_1 \times 10^4$ for			
	Acetanilide	Acet-*o*-toluidide	Acet-*m*-toluidide	*o*-Nitro-acetanilide
65	14·36	..	..	..
70	20·10	7·4	..	..
75	29·40	..	..	..
80	41·22	13·6	39·2	76·2
85	59·00	..	..	105·3
90	83·00	24·6	78·7	155·7
95	120·00	..	..	211·2
Q (calories)	17,940	15,020	18,110	17,730

TABLE V. *Reactivity of Different Anilides*

Concentration of anilide 0·05 M   Concentration of catalyst 0·15 N

Anilide		Temperature	$K_1 \times 10^4$
Formanilide	..	40	126·8
Form-*p*-toluidide	..	40	102·5
Form-*o*-toluidide	..	40	59·2
o-Nitroacetanilide	..	80	76·2
Acetanilide	..	80	41·2
Acet-*m*-toluidide	..	80	39·2
Acet-*o*-toluidide	..	80	13·6

(B) HYDROLYSIS OF ANILIDES IN 50% ALCOHOL

TABLE VI. *Effect of Catalyst Concentration*

Concentration of anilide 0·05 M

Anilide	Temperature (°C.)	Concentration of catalyst (H_2SO_4)	$K_1 \times 10^4$	$K_2 \times 10^4$
Formanilide ..	30	0·045 N	7·1	158
		0·100 N	16·5	165
		0·250 N	40·25	161
		0·300 N	47·32	158
Form-*o*-toluidide ..	30	0·050 N	4·1	82
		0·100 N	8·6	86
		0·250 N	19·0	76
		0·300 N	22·8	76
Form-*p*-toluidide ..	30	0·050 N	5·8	116
		0·100 N	12·1	121
		0·250 N	28·0	112
		0·300 N	36·0	120
Acetanilide ..	70	0·150 N	7·0	46
		0·250 N	12·0	48
		0·350 N	16·5	47

TABLE VII. *Effect of Temperature*

Concentration of Anilide 0·05 M   Concentration of catalyst 0·25 N

Temp. (°C)	Values of $K_1 \times 10^4$				
	Formanilide	Form-*o*-toluidide	Form-*p*-toluidide	Acetanilide	*o*-Nitro-acetanilide
20	21·9	9·7	14·6	..	..
25	33·3	14·9	22·0	..	..
30	47·2	21·0	31·6	..	..
35	73·7	31·5	46·0	..	..
40	103·1	44·0	67·2	..	..
45	161·3	64·5	96·6	..	..
60	..	..	..	8·7	16·8
70	..	..	..	17·78	35·5
Q (calories)	12,720	13,660	12,990	14,560	15,310

TABLE VIII. *Effect of Concentration of Anilide*

Concentration of catalyst 0·25 N   Temperature 70° C.

Concentration of acetanilide (M)	0·025	0·050	0·10	0·15	0·20
$K \times 10^4$ ..	12·8	12·0	10·3	9·4	8·9

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TABLE IX. *Reactivity of Different Anilides*

Concentration of anilides 0·05 M   Concentration of catalyst 0·25 N

Anilide	Temperature (°C.)	$K_1 \times 10^4$
Formanilide	40	103·1
Form-*p*-toluidide	40	67·0
Form-*o*-toluidide	40	44·0
p-Nitroacetanilide	70	42·1
o-Nitroacetanilide	70	33·4
Acet-*α*-naphthalide	70	30·6
Propionanilide	70	20·6
Acet-*β*-naphthalide	70	18·8
Acetanilide	70	17·8
Acet-*p*-toluidide	70	16·8
p-Bromacetanilide	70	16·5
Acet-*m*-toluidide	70	16·1
Acet-*o*-toluidide	70	7·4

(C) HYDROLYSIS OF ANILIDES IN ABSOLUTE ALCOHOL

TABLE X. *Reactivity of Different Anilides*

Temperature 65° C.   Concentration of catalyst 0·25 N

Anilide	Concentration of anilide	$K_1 \times 10^4$
	M	
Acetanilide	0·05	9·20
Benzanilide	0·01	3·91
Benz-*p*-toluidide	0·0125	2·52
Benz-*o*-toluidide	0·0125	2·07

(D) HYDROLYSIS OF ANILIDES IN ACETIC ACID

TABLE XI. *Effect of Temperature*

Concentration of catalyst 0·5 N   Concentration of acetanilide 0·1 M

Temperature °C.	$K_1 \times 10^4$
70	39·7
80	86·5
90	161·0

TABLE XII. *Effect of Change of Solvent on the Velocity of Hydrolysis*

Concentration of catalyst 0·25 N

Temp. (°C.)	Anilide	Concentration of anilide	$K_1 \times 10^4$	
			In water	In 50% alcohol
30	Formanilide	0·05 M	61·3	47·5
30	Form-*o*-toluidide	0·05 M	27·3	21·0
40	Form-*p*-toluidide	0·025 M	103·1	67·2
70	*o*-Nitro-acetanilide	0·025 M	38·1	33·5
70	Acetanilide	0·05 M	20·1	17·7
70	Acet-*m*-toluidide	0·025 M	19·8	16·5

TABLE XIII. *Effect of Change of Solvent on the Velocity of Hydrolysis*

Concentration of catalyst 0·25 N   Concentration of acetanilide 0·05 M

Temperature 65° C.

Solvent		$K_1 \times 10^4$
Water	..	14·36
10% alcohol	..	12·42
20% do	..	11·16
30% do	..	9·77
40% do	..	9·25
50% do	..	9·08
60% do	..	8·67
70% do	..	8·41
80% do	..	7·28
90% do	..	6·74
Absolute alcohol	..	5·73

DISCUSSION OF RESULTS

It will be seen from Table I that the velocity constant (K_1) increases as the concentration of the catalyst (b) is increased. The plots of K_1 against b show that the relation between the two is a linear one. The values of K_2, equal to K_1/b, were calculated and are given in the last column of Table I. They are very nearly equal to each other. A similar behaviour is noticed in the case of results given in Table VI.

Straight lines are obtained on plotting the values of log K_1 against those of the reciprocal of the absolute temperature (1/T), indicating that the Arrhenius equation $\left(\dfrac{d \ln K}{dt} = \dfrac{Q}{RT^2}\right)$ is applicable to the reactions studied in this investigation. The values of Q were calculated from the various straight lines and are given in Tables II, III, IV, VII and XI. It will be

seen that the values of Q for a particular anilide are very nearly independent of the concentration of the catalyst.

The effect of the concentration of the anilide was examined only in one case (*cf.* Table VIII). It will be seen that the values of K_1 decrease regularly as the concentration of acetanilide is increased.

The reactivity of different anilides in aqueous medium, 50%-alcohol and absolute alcohol are given in Tables V, IX and X, the order of reactivity being the same as given in these tables.

Experiments were made on the determination of the effect of the solvent on the velocity constant of the hydrolysis of some anilides. The results obtained are given in Table XII. It will be seen that invariably the values of K_1 in aqueous medium are greater than those in 50%-alcohol. Hence, a systematic investigation was made to determine the change in the value of K_1 with the addition of different amounts of alcohol to water. The results obtained in the case of acetanilide are given in Table XIII which show that the value of K_1 decreases systematically as the percentage of alcohol in alcohol-water mixtures is increased, the lowest value being obtained in absolute alcohol. Hence, it can be stated that the hydrolysis of anilides decreases in the following order:

$$\text{Water} > \text{alcohol-water mixture} > \text{Alcohol.}$$

SUMMARY AND CONCLUSIONS

From a detailed study of the hydrolysis of sixteen different anilides in the presence of different concentrations of the catalyst (sulphuric acid), at different temperatures and with varying concentrations of the anilides, and in different solvents, it has been shown that the hydrolysis of anilides is a uni-molecular reaction. Straight lines are obtained on plotting values of log K_1 against those of 1/T, indicating that Arrhenius equation is applicable to these systems; the values of Q have been calculated from these straight lines and are found to be nearly independent of the concentration of the catalyst employed. The effect of substituent groups in the anilides is in accordance with the electronic theory of valency. This is seen clearly if the velocity constants of acetanilide and benzanilide are compared. The slower hydrolysis of benzanilide, in spite of the presence of a donor group near the covalent linkage is probably to be explained by the proximity effect.