Kinetics of the Acid Hydrolysis of Acetamide in Dioxan-Water Mixtures

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The first-order rate constants of the hydrolysis of protonated acetamide were calculated from kinetic data and known [12] acid constants of the amide over a wide range of dioxan-water mixtures. In solvent mixtures containing small amounts of water the rate is approximately of first order in water. Bimolecular rate constants were obtained by dividing the first order rate constant by the water concentration. This rate constant changes only to a small extent by less than a factor or three, over the range of solvent mixtures from pure water to a 0.1 M solution of water in dioxan. Also the activation enthalpy $\Delta H^* \approx 18$ kcal and activation entropy $\Delta S^* \approx -26$ cal.deg.$^{-1}$ are approximately constant in these solvent mixtures. A reaction mechanism is proposed according to which a slow formation of an intermediate by the oxygen-protonated acetamide and water is followed by a fast transfer of proton from the oxygen to the nitrogen atom in the intermediate and a fast decomposition to products.

The acid hydrolysis of carboxylic acid amides has been studied recently by several authors and has been discussed in a review by Whalley.[1] Except for some data relating to extreme conditions [2] all the results obtained are in agreement with a bimolecular A-2 mechanism involving a fast proton transfer pre-equilibria in moderately strong acid solutions followed by slow reaction of the protonated amide with a water molecule. As the protonation of an acid amide is almost complete in highly acid solutions, it is possible to study separately the hydrolysis of the protonated amide.

The bimolecular mechanism is supported by the negative value of the activation entropy,[3] $\Delta S^* = -18.2$ cal. deg^{-1}, for acetamide in water containing 0.1 N HCl as catalyst, by the negative activation volume,[4] $\Delta V^* = -9.4$ and -11.3 cm^3 mole^{-1}, for acetamide at 55°C in aqueous 0.3 M and 4 M perchloric acid solutions, respectively, by the observed steric and polar substituent effects [5] in reactions of fully protonated substituted benzoic amides and by the decrease in the rate of hydrolysis of completely protonated amides in concentrated mineral acid-water mixtures with decreasing activity of water.[5] The mechanism of acid hydrolysis of acid amides has also been discussed [6,7]

in terms of the experimental values of w introduced by Bunnett.[7] It seems, however, doubtful[1] whether such a discussion has general validity and can be extended to the hydrolysis of acid amides as the degree of protonation of acid amides does not parallel the acidity function.[8,5]

The acid hydrolysis of acid amides has been studied in ethanol-water,[9] acetone-water,[10] and dioxan-water mixtures.[11] The interpretation of the results is difficult because of the simultaneous influence of the solvent on the acid-base equilibria and the rate of the subsequent slow reaction. In the present study the rates of acid hydrolysis of acetamide in dioxan-water mixtures and data[12] on the acid constants of the amide in the same solvent mixtures are employed to study the dependence of the rate of hydrolysis of protonated acetamide on changes in the solvent composition.

EXPERIMENTAL

Materials. Acetamide (E. Merck AG, guaranteed reagent) was purified by crystallisation from water. Dioxan (Fluka AG, purified by the method of Hess and Frahm) was retreated by the method of Hess and Frahm.[13] 70 % perchloric acid and 30 % hydrochloric acid (both guaranteed reagents from E. Merck AG) were used as received.

Method. The kinetic experiments were performed using ampoules or vapour-free reaction vessels[14] and electrically heated thermostats. The amounts of acetic acid produced in the reaction were determined by adding an excess of formaldehyde solution and titrating with 0.1 N sodium hydroxide solution potentiometrically using a glass electrode after an appropriate period of time. The final value was obtained by titrating a sample taken after at least ten times the half-life of the reaction or by calculation from the weight of the acetamide initially added to the reaction mixture.

Calculations. Acetamide is protonated by perchloric acid only to a small extent in water, about half protonated in dioxan-water containing 5 moles of water per litre, and almost completely protonated in dioxan containing only small amounts of water. In solvent mixtures containing more than 5 moles of water per litre the reaction is approximately first order in both acetamide and perchloric acid and hence the second-order rate equation was used to calculate the experimental rate constant. In solvent mixtures containing less than 5 moles of water per litre the rate constant was calculated from the first-order rate equation assuming complete protonation of acetamide by perchloric acid. The first-order rate constant of the hydrolysis of protonated acetamide can be calculated from these second-order and first-order experimental rate constants using known values[12] of the acid constants of acetamide.

An approximate method was used to calculate these rate constants. Calculations showed that when only a small fraction of acetamide is protonated and when the protonation is almost complete the fraction of the amide protonated remains practically constant during the reaction. The first-order rate constant of the hydrolysis of the protonated acetamide k_{BH+} is then obtained by multiplying the experimental rate constants k_1 or k_2 by appropriate correction factors a or β.

$$k_{BH+} = ak_1 \tag{1}$$
$$k_{BH+} = \beta k_2 \tag{2}$$

Values of a and β were calculated[12] separately for 0 % and 50 % change in each reaction mixture using the respective values of the acid constants.

$$a = [\text{acetamide}]_{\text{total}}/[\text{acetamide} \cdot H^+] \quad \text{when } [\text{HClO}_4]_{\text{total}} > [\text{acetamide}]_{\text{total}} \tag{3}$$
$$a = [\text{HClO}_4]_{\text{total}}/[\text{acetamide} \cdot H^+] \quad \text{when } [\text{HClO}_4]_{\text{total}} < [\text{acetamide}]_{\text{total}} \tag{4}$$

The values of a calculated for 0 % and 50 % change differed about 10 % for the reaction mixture containing about 2.4 moles of water per litre of dioxan and less than 2 % for reaction mixtures containing 1.3 moles of water per litre or less. The mean value of

a was used to calculate k_{BH+} from eqn. 1. At very low water concentrations $a \approx 1$, which indicates complete protonation of acetamide.

$$\beta = [HClO_4]_{total} \cdot [acetamide]_{total}/[acetamide \cdot H^+] \tag{5}$$

Values of β were calculated for both zero and 50 % change for each reaction mixture using known values [12] of the acid constant of acetamide. For solvent mixtures of high water content, $\beta \approx K_{BH+}$, in agreement with the fact that only a small fraction of acetamide is protonated.

The method gives values of k_{BH+} which are correct to about $\pm$ 2 % or less when the concentration of water in dioxan is higher than about 10 M or less than about 2 M for the ranges of concentrations acetamide and perchloric acid used in the experiments. For solvent mixture 2 M to 10 M in water the method of calculation is less satisfactory and the results are uncertain to the extent of about $\pm$ 10 %. At low water concentrations the correction is small because $a \approx 1$ and almost independent of the value of K_{BH+}, but at high water concentrations where $\beta \approx K_{BH+}$, the correction is sensitive to errors in the value of the acid constant. Except for one value at 55°C values of the acid constants in dioxan-water mixtures are known [12] only at 25°C; the effect of temperature on the value of K_{BH+} was found to be small, and therefore no large error was expected to result from the use of values of the acid constant determined at temperatures different from those at which the kinetic experiments were carried out.

The experimental first-order and second-order rate constants and the calculated first-order rate constants of the hydrolysis of protonated acetamide are given in Table 1. Table 2 contains experimental rate constants obtained with hydrochloric acid as catalyst. In water-rich solvent mixtures, the rate constants obtained with hydrochloric and perchloric acids as catalysts are identical within the experimental error. In dioxan 5 M and 10 M in water, the rate constants obtained using hydrochloric acid as catalyst have somewhat larger values than the rate constants with perchloric acid as catalyst. Values of the first-order rate constant k_{BH+} were not calculated as the values of the acid constant of acetamide in solvent mixtures containing hydrochloric acid are not known.

DISCUSSION

In the present work the first-order rate constants k_{BH+} of protonated acetamide were evaluated from the kinetic data and the known [12] acid constants of acetamide in dioxan-water mixtures. The results are shown in Table 1 and Fig. 1. The first-order rate constant decreases continuously as the con-
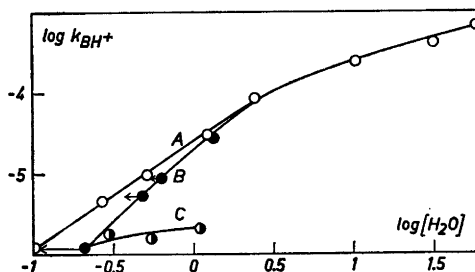

Fig. 1. Logarithm of the rate constant k_{BH+} of hydrolysis of protonated acetamide in dioxan-water mixtures at 60°. For further information, see discussion.

centration of water in dioxan decreases. When log k_{BH+} is plotted against log $[H_2O]$ in the dioxan-water mixtures the slope is approximately constant and equal to 1.3 at low water concentrations. The rate is thus proportional to the concentration of water, in agreement with the expected bimolecular mechanism.

Table 1. Experimental rate constants k_1 and k_2 of the hydrolysis of acetamide in dioxan-water mixtures catalysed by perchloric acid, calculated first-order ($k_{BH}+$) and second-order (k_2') rate constants of the hydrolysis of protonated acetamide, and activation enthalpies and entropies calculated from the values of $k_{BH}+$.

$t°$	[H_2O] M	[$HClO_4$] M	[amide] M	$10^6 k_1$ sec^{-1}	$10^4 k_2$ M^{-1}sec^{-1}	$10^6 k_{BH}+$ sec^{-1}	$10^5 k_2'$ M^{-1}sec^{-1}	ΔH^* cal.	ΔS^* cal.deg.$^{-1}$
60	0.101	0.0496	0.100	1.16		1.17	1.38		
	0.260	0.0507	0.100	4.55		4.68	1.89		
	0.513	0.0504	0.100	9.02		9.85	1.96		
	1.228	0.0513	0.100	22.2		35.9	2.25		
	2.34	0.0518	0.100	39.0		84.7	3.62		
	0.206	0.101	0.050	1.20		1.23			
	0.480	0.102	0.050	5.00		5.45			
	0.637	0.127	0.048	7.25		8.70			
	1.33	0.099	0.050	17.9		27.2			
	2.41	0.101	0.050	38.8		86.2			
	5.29	0.097	0.050		3.14				
	10.48	0.097	0.051		3.00	246	2.35		
	22.7	0.097	0.053		1.92				
	32.5	0.097	0.050		2.04				
	43.4	0.097	0.050		1.98				
	54.8	0.097	0.052		2.41	692	1.26		
	54.3	0.194	0.051		2.24	670	1.24		
	0.295	0.124	0.049	1.78		1.88			
	0.558	0.234	0.048	1.45		1.55			
	1.10	0.453	0.048	1.91		2.09			
	1.80	0.229	0.050	7.37		16.5			
40	0.274	0.050	0.100	0.714		0.735			
60	0.270	0.051	0.100	4.55		4.68		18.3	−28.2
80	0.274	0.052	0.100	21.1		21.7			
40	1.217	0.052	0.100	4.67		7.52			
60	1.228	0.051	0.100	22.2		35.9		16.8	−28.6
80	1.224	0.052	0.100	102		164			
21	1.420	0.094	0.050	0.335		0.447			
40	1.404	0.0940	0.049	2.43		3.24			
60	1.404	0.123	0.050	15.4		20.5		18.6	−24.5
80	1.390	0.088	0.051	81		108			
21	55.2	0.097	0.050		0.050	14.3			
40	55.0	0.097	0.050		0.390	112			
60	54.8	0.097	0.052		2.41	692		18.2	−19.0
80	54.6	0.097	0.051		11.0	3140			

In dioxan-water mixtures of low water content the hydrolysis of protonated acetamide is retarded by an increase in the concentration of perchloric acid at constant water concentration. This results can be compared [5] with the decrease of the rate of the reaction in strong mineral acid-water mixtures with increasing mineral acid concentration and decreasing activity of water. The activities of water in dioxan-water mixtures containing perchloric acid are not known. However, cryoscopic measurements [15] show that perchloric acid is associated with approximately two water molecules in dioxan containing small amounts of water. If the water molecules associated with perchloric acid are much less reactive than the water molecules present in excess, the

rate of hydrolysis of protonated acetamide should depend only upon the concentration of "free" water molecules. This assumption is to be regarded only as a first approximation as the increase in electrolyte concentration may cause other "salt effects".

When the molarity of acetamide is greater than that of perchloric acid (part A of the curve in Fig. 1), the protonation of acetamide is almost complete at low water concentrations and almost all the perchloric acid is consumed in the proton transfer reaction. Data for proton transfer equilibria in dioxan-water mixtures [12] show that approximately two water molecules are liberated in the transfer of proton from perchloric acid to acetamide. Protonated acetamide is hence not associated with water in dioxan-water mixtures of low water content. In dioxan-water mixtures of low water content that contain a greater number of moles of acetamide than of perchloric acid the concentration of free water is approximately equal to the total water concentration.

When perchloric acid is present in excess over acetamide, only a part of the acid is consumed in the protonation of acetamide and the excess of perchloric acid is associated with the water in the solvent mixture. For example, when the concentration of perchloric acid is increased but the ratio $[H_2O]/[HClO_4]$ is kept constant at 2.4 the concentration of free water and the rate of hydrolysis of protonated acetamide are not changed (part C, Fig. 1). Curve B of Fig. 1 plots the rates when perchloric acid was present in excess over acetamide and the ratio $[HClO_4]/[acetamide]$ was constant. An increase of the water concentration brings curve B closer to curve A, and the difference is negligible in dioxan containing 3 moles or more of water per litre. If the values of the rate constant evaluated in these experiments are plotted against the concentration of "free" water instead of the total water the points are shifted close to curve A as shown by the arrows in Fig. 1. These experiments show that the hydrolysis of protonated acetamide is approximately proportional to the concentration of free water in dioxan-water mixtures and that the water molecules associated with perchloric acid are less reactive than the "free" water molecules in dioxan-water mixtures.

As the hydrolysis is a bimolecular reaction between the protonated acetamide and water, the second-order rate equation should be used to calculate rate constants. Calculations show that the second-order rate constants k_2' (Table 1) change very little over the whole range of solvent mixtures from pure water to dioxan-water containing 0.1 mole of water per litre. As the reaction is one between an ion and a neutral molecule, the solvent effects should be small, in agreement with the observations.

The second-order rate constants increase somewhat when the water concentration increases from 0.1 M to 2 M in dioxan-water mixtures. The activity coefficient [16] of water decreases approximately by a factor of two with increasing water concentration in this solvent mixture range at 20°C. Cryoscopic measurements [15] show that the degree of association of water rapidly increases in this solvent mixture range. One explanation for the increase of the rate constant would be that a water molecule bound by a hydrogen bond to another water molecule is more nucleophilic than a free water molecule bound by a hydrogen bond to a dioxan molecule.

Table 2. Rate constants of the hydrolysis of acetamide catalysed by hydrochloric acid in dioxan-water mixtures at $t = 60°$.

[H_2O]	[HCl]	[amide]	$10^4 k_2$ 1 mole^{-1} s^{-1}
5.42	0.104	0.049	5.90
10.95	0.104	0.049	4.37
32.2	0.104	0.051	2.16
54.8	0.104	0.050	2.60
54.3	0.202	0.050	2.22
54.3	0.101	0.200	2.48

$$O-H\cdots O-H\cdots ORO \qquad\qquad (6)$$
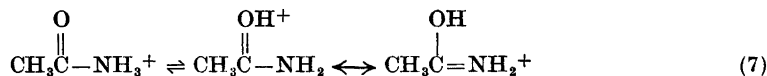$$\quad|\qquad\ |$$
$$\quad H\qquad H$$

It may be noted also that the products of the second-order rate constant and activity coefficient of water is approximately constant over the range of solvent mixtures in question.

The decrease of the second-order rate constant with increasing water concentration in dioxan-water mixtures containing from 2 to 55 moles of water per litre may be due to changes in hydrogen bonding, to changes in ion pair formation by protonated acetamide and perchlorate ion, or to the variation of the dielectric constant. Probably all these changes affect the rate, but it is difficult to estimate which of the effects predominates.

Values of the activation enthalpy calculated from the first-order rate constants vary only slightly with solvent composition. The variation of the first-order rate constant is hence mainly due to changes in activation entropy. Values of the activation entropy calculated from the second-order rate constants, however, remain almost unaltered at about $\Delta S^* = -26$ cal/degree. This negative value of the activation entropy is in agreement with the proposed bimolecular mechanism.

Several mechanisms may be proposed for the bimolecular reaction between protonated acetamide and water. Many authors have discussed possible mechanisms but it is difficult to decide between them on the basis of the available data.[1]

Recent NMR measurements [17],[18] have demonstrated that the protonation of acetamide involves mainly the oxygen atom of the amide, although protonation occurs at the nitrogen atom also as shown by the hydrogen exchange of the amide.[17],[18] An equilibrium is established between these forms:

$$\begin{array}{ccc} O & OH^+ & OH \\ \| & \| & | \\ CH_3C-NH_3^+ & \rightleftharpoons CH_3C-NH_2 & \longleftrightarrow CH_3C=NH_2^+ \end{array} \qquad (7)$$

Both forms of protonated amide may react with water. The reaction between protonated acetamide and water may be a onestep substitution reaction or may involve a slow formation of an addition intermediate followed by a rapid proton transfer and rapid decomposition to the products. The alternative

mechanism involving a rapid formation of an addition intermediate followed by a slow decomposition to products is not likely because oxygen exchange does not occur during the acid hydrolysis of benzamide.[19,20]

If the direct substitution mechanism is chosen, the nitrogen-protonated acetamide must be considered more reactive than the oxygen-protonated amide (mechanism 1). The bimolecular substitution reaction between oxygen-protonated acetamide and water has to be rejected also as it would involve an increase in polarity when the transition state is formed which is not in agreement with the observed small solvent effect in dioxan-water mixtures.

If the mechanism involves a slow intermediate formation, the reaction between nitrogen-protonated acetamide and water can be disregarded because it is accompanied by an increase in polarity which is in disagreement with the observed small solvent effect. The other alternative, the reaction of oxygen-protonated amide with water, presupposes no large change in polarity and is in agreement with the observed solvent effect (mechanism 2).

A choice between the two remaining mechanisms is difficult. Reactions at a carbonyl carbon atom take place usually by an addition mechanism, and the non-occurrence of oxygen exchange during the acid hydrolysis of amides [8,9] does not disprove this mechanism. The large negative values of the activation entropy, $\Delta S^* = -26$ cal.deg.$^{-1}$, and activation volume,[4] $\Delta V^* = -13.2$ cm^3 mole^{-1}, in the hydrolysis of protonated acetamide is in better agreement with the addition mechanism 2 than with the substitution mechanism 1. Somewhat less negative values are usually obtained [1,21], for bimolecular substitution reactions at a saturated carbon atom, e.g. $\Delta S^* = -9$ cal deg^{-1} and $\Delta V^* = -8.5$ cm^3 mole^{-1} for the hydrolysis of diethyl ether. Mechanism 2 can be postulated for the acid hydrolysis of acetamide on other grounds also.[1] The corresponding transition state is

$$
\begin{array}{c}
OH^{+\delta_1} \\
\| \\
CH_3-C-NH_2^{+\delta_2} \\
| \\
OH_2^{+1-\delta_1-\delta_2}
\end{array}
\tag{8}
$$

Before it decomposes, the intermediate formed from the transition state (8) is probably involved in a proton transfer reaction in which the proton is transferred from the oxygen atom to the nitrogen atom. The intermediate then decomposes to the products at a relatively high rate. When the transition state is formed, 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 atom. The changes in polarity are then small and only a small solvent effect would be expected, in agreement with the observations.

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