[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF PENNSYLVANIA]

Effect of Structure on Reactivity. X. Effect of α-Hydroxy Substituted Amides on the Ammonolysis and Hydrolysis of Methyl Acetate

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The effects of lactamide, N-methyllactamide, N-dimethyllactamide, α-hydroxyisobutyramide and ethylene glycol on the ammonolysis and hydrolysis of methyl acetate have been determined. The energies of activation and entropies of activation for these reactions have been calculated.

Earlier investigations have shown that hydroxylated solvents such as water, alcohols and glycols facilitate the ammonolysis of esters.[1] These studies showed that solvents or solutes containing the groupings O–C–C–O or O–C–C–N had a special effect on the rates of ammonolysis. It was postulated that a cyclic hydrogen bonded intermediate between the solvent or solute molecule and the ammonia molecule could best account for this effect. The present study concerns itself with the  $-O-C-\overset{\overset{\displaystyle O}{\|}}{C}-N-$ grouping and its effect upon the velocity constants, energies of activation and entropies of activation for the ammonolysis of methyl acetate. The following compounds, which have this grouping, were chosen for this work: lactamide, N-methyllactamide, N,N-dimethyllactamide and α-hydroxyisobutyramide. Ethylene glycol was included as a reference compound. For the experimental work the following system was adopted: 1 molar amide, 10 molar water, 2 molar ammonia, 1 molar ester and dioxane as the diluent to bring the solution to the proper volume. Water was necessary to obtain homogeneous solutions since the amides were insoluble in dioxane alone. The presence of water causes a competing hydrolysis reaction. This was taken care of by a procedure developed in a previous paper[1b] whereby the velocity constants for both ammonolysis and hydrolysis were determined. This involved the determination of both ammonia and ammonium ion concentrations.

Experimental

Reagents.—Dioxane, methyl acetate, methyl alcohol and ethylene glycol were purified as described previously.[1b]

Lactamide was obtained from the ammonolysis of ethyl lactate in anhydrous methanol. The crude product was recrystallized repeatedly from a dry ethanol–ether–petroleum ether mixture; m.p. 77–78°.

N-Methyllactamide and N,N-dimethyllactamide were prepared similarly, dry methylamine and dry dimethylamine being used in place of ammonia. N-Methyllactamide was repeatedly recrystallized from chloroform–benzene; m.p. 70–71°. N,N-Dimethyllactamide was purified by distillation *in vacuo*, b.p. 78.6–79.6° (4 mm.), $n^{25}\text{D}$ 1.4571.

α-Hydroxyisobutyramide was prepared in a similar manner from the corresponding ethyl ester. It was recrystallized from dry acetone until its melting point remained constant, 95–98°. Analyses showed no impurity in this product.

Procedure.—The procedure was the same as that used in previous work.[1a]

Analysis.—Unused ammonia and the ammonium ion concentration were determined by methods described earlier.[1b]

Calculations and Results

The ammonolysis of esters is a pseudo second-order reaction and the basic hydrolysis of esters is a second-order reaction. The rate equation for the second-order reactions may be written (as derived in ref. 1b) as

$$k_1 + k_2 = \frac{2.303}{t(a-b)} \log \frac{b(a-x)}{a(b-x)}$$

and by applying the Wegscheider principle, we may write

$$k_1/k_2 = CH_3CONH_2/CH_3COO^-$$

This term may be evaluated if it is assumed that $CH_3COO^- = NH_4^+$. Since both the sum and the ratio of k_1 and k_2 are measured, the individual values of k_1 and k_2 may be determined.

The average values for k_1 and k_2 were determined by taking the arithmetical mean of all values of k_1 and all values of k_2 for each catalyst used. These values are given in Table I. The values for the energies and entropies of activation were calculated, together with their errors, in the same way as reported previously[1c]

TABLE I

VELOCITY CONSTANTS FOR THE AMMONOLYSIS AND HYDROLYSIS OF METHYL ACETATE

(k_1 = ammonolysis, k_2 = hydrolysis, units = liters mole^{-1} second^{-1})

Amide used	Temp., °C.	$k_1 \times 10^7$		$k_2 \times 10^7$	
Lactamide	20	2.544	±0.031	0.294	±0.008
	30	4.206	.044	0.661	.019
	40	6.283	.008	1.247	.006
N-Methyllactamide	20	2.422	.014	0.289	.011
	30	4.217	.044	0.631	.033
	40	6.022	.014	1.219	.014
N-Dimethyllactamide	20	2.519	.019	0.281	.011
	30	4.542	.106	0.700	.025
	40	6.161	.008	1.161	.011
α-Hydroxyisobutyramide	20	1.989	.019	0.225	.008
	30	3.347	.067	0.522	.011
	40	5.044	.028	1.072	.011
Ethylene glycol	20	3.517	.014	0.394	.008
	30	5.650	.075	0.856	.022
	40	8.286	.050	1.697	.022

Discussion

The mechanism for the ammonolysis of esters involves a nucleophilic attack on the carbonyl carbon atom of the ester. The transfer of a proton is also involved, but it is not known with certainty at what point this transfer takes place.

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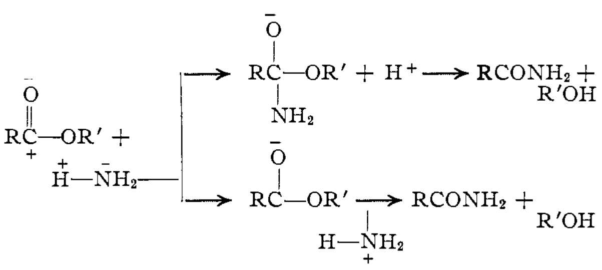
[1] (a) M. Gordon, J. G. Miller and A. R. Day, THIS JOURNAL, **71**, 1245 (1949); (b) T. A. Koch, J. G. Miller and A. R. Day, *ibid.*, **75**, 953 (1953); (c) F. H. Wetzel, J. G. Miller and A. R. Day, *ibid.*, **75**, 1150 (1953).

TABLE II

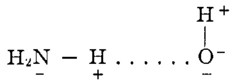
ENERGIES OF ACTIVATION AND ENTROPIES OF ACTIVATION

(E_{a_1} and $-\Delta S^*_1$ for ammonolysis and E_{a_2} and $-\Delta S^*_2$ for hydrolysis)

Amide used	E_{a1}, cal.		E_{a2}, cal.		$-\Delta S^*_1$, e.u.		$-\Delta S^*_2$, e.u.	
Lactamide	8232	±150	13,144	±387	62.63	±0.35	50.14	±0.92
N-Methyllactamide	8275	122	13,122	646	62.55	0.29	50.27	1.53
N-Dimethyllactamide	8106	778	12,884	502	63.02	1.84	51.04	1.19
α-Hydroxyisobutyramide	8475	230	14,229	384	62.29	0.54	46.99	0.91
Ethylene glycol	7806	153	13,304	340	63.45	0.36	49.05	0.81

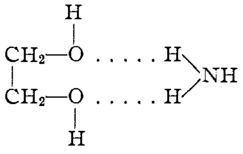


In previous publications,[1] it has been stated that hydroxylated solvents assist in the proton transfer through hydrogen bonding with the ammonia molecule.

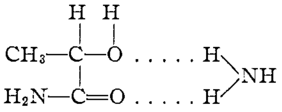


Such bonding would increase the negative charge on the nitrogen atom and lower, somewhat, the energy necessary for the ionization of the nitrogen–hydrogen bond. It is believed, therefore, that it is the hydrogen-bonded intermediate that is the activated nucleophilic intermediate. It is not necessary that a free amide ion be formed in this mechanism.

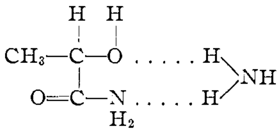
It was postulated also in previous work[1] that ethylene glycol owes its unique, promoting effects on ammonolysis rates to a cyclic hydrogen-bonded intermediate.



Similar cyclic, hydrogen-bonded systems can be written for the amides used in the present study. With lactamide, for example, the following may be postulated as possible intermediates.



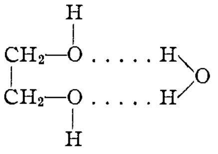
I



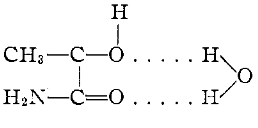
II

Of the two structures, I probably makes the larger contribution.

Similar structures may be written to explain the effects of the lactamides and ethylene glycol on the rates of hydrolysis.



III



IV

It will be noted, from the data, that the three lactamides differed very little in their effects on the ammonolysis and hydrolysis rates, and α-hydroxyisobutyramide had the smallest effect of the amides used. None of the four amides was equal to ethylene glycol in promoting reaction rates.

The large differences between the entropies of activation for ammonolysis and hydrolysis are rather surprising. This may suggest that the solvated ammonia molecule is more sterically hindered than the solvated water molecule.

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