

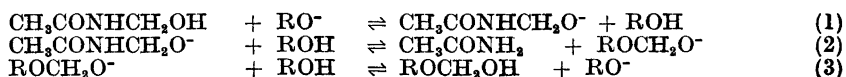
Kinetics of the Alcoholysis of Hydroxymethylacetamide and Proton Transfer Equilibria in Methanol, Ethanol and *iso*Propanol

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In a previous study¹ the kinetics of formation and hydrolysis of hydroxymethylacetamide were studied in alkaline aqueous solutions. The analogous alcoholysis reactions in a number of alcohols have now been investigated. In the alcoholysis of hydroxymethylacetamide in methanol, ethanol and *iso*propanol, similarly as in the hydrolysis, the role of a base is to produce the hydroxymethylacetamide anion which reacts with the solvent molecule to give acetamide and monoformal anion. The rate constant for the reaction between hydroxymethylacetamide anion and the solvent has been calculated in each case from the kinetic data obtained by varying the concentration of alcoholate. Also the equilibrium constants of the alcoholysis reactions were determined. The equilibrium is shifted further towards hydroxymethylacetamide in different alcohols in the following order: methanol, ethanol, *iso*propanol and *tert.*-butanol. Values of the equilibrium constants for the proton transfer between alcoholate ions and hydroxymethylacetamide were also derived from the kinetic data. The acidities of the various alcohols relative to that of the hydroxymethylacetamide anion were found to decrease in the order: methanol, ethanol, *iso*propanol. The heat of the proton transfer reaction was found to vary considerably in the different alcohols.

Similarly as the hydrolysis¹, the alcoholysis of hydroxymethylacetamide is a three-step process:



The proton transfer reactions (1) and (3) are fast, the alcoholysis reaction (2) being the slow, rate-determining step. The reaction product monoformal is believed to be stable in the alcohol solutions used, but if free formaldehyde (CH_2O) is formed, it will influence only the calculation of the equilibrium constant of reaction (3).

Fortunately the acidity of hydroxymethylacetamide does not differ very much from the acidities of the alcohols used as solvents, so that by varying the concentration of alcoholate ion (RO^-) the amount of ionized hydroxymethylacetamide can be altered, this will effect a change in the reaction rate

$$-\frac{dc_{\text{CH}_3\text{CONHCH}_2\text{O}^-}}{dt} = k_1 c_{\text{CH}_3\text{CONHCH}_2\text{O}^-} - k_2 c_{\text{CH}_3\text{CONH}_2} c_{\text{ROCH}_2\text{O}^-} \quad (4)$$

where k_1 is the first-order rate constant of the alcoholysis reaction and k_2 the second-order rate constant of the reverse reaction 2.

EXPERIMENTAL

Materials. Methanol, ethanol and isopropanol, all of the highest purity obtainable, were dried by adding the corresponding aluminium alcoholate² and distilling. Usually only about 0.1 g of water per liter was found to be present in the dried alcohols by the Fischer titration. *Tert.*-butanol was purified by crystallisation. The other compounds were prepared as described earlier¹.

Analytical. The kinetic measurements were performed as described in the previous paper¹. The amount of formaldehyde liberated during the reaction was analysed by the sulphite method¹ used previously except that phosphate buffer solution (0.5 M NaH_2PO_4 , 0.125 M K_2HPO_4) was added to the sample in order to reduce the standing period required after the addition of bisulphite solution³, since the reaction between bisulphite and formaldehyde is retarded by alcohols.

Calculations. The alcoholysis of hydroxymethylacetamide did not go to completion in the solvents studied. The rate eqn. (4) yields on integration

$$k_1 = \frac{2.303}{t} \cdot \frac{A_{\text{eq}} \cdot F_{\text{eq}}}{(M_0 + A)(M_0 + F_0)} \log \left[\frac{M_0 - M_{\text{eq}}}{M_t - M_{\text{eq}}} \cdot \frac{(M_0 + A_0)(M_0 + F_0) - M_t M_{\text{eq}}}{(M_0 + A_0)(M_0 + F_0) - M_0 M_{\text{eq}}} \right] \quad (5)$$

Table 1. Rate constants for the ethanolysis of hydroxymethylacetamide at 20° (eqn. (5)). Initial concentrations: hydroxymethylacetamide 0.0196 mole/l (which corresponds to 9.57 ml of 0.0246 N iodine solution), acetamide 0.200 mole/l and sodium ethylate 0.0482 mole/l.

Time min	0.0246 N iodine consumed ml	% reacted	$10^3 \times k_1$ sec. ⁻¹
0	0.12	0	
0.5	0.71	9.7	2.18
1	1.20	17.7	2.11
1.5	1.61	24.5	2.00
2	1.99	30.7	1.98
3	2.68	42.1	1.96
4	3.25	51.5	1.94
5	3.70	58.9	1.91
6	4.13	65.9	1.92
7	4.42	70.7	1.88
12	5.48	88.2	1.89
17	5.93	95.5	1.95
20	6.06	97.7	2.04
100	6.20	100	mean 1.96

Table 2. Equilibrium and first-order rate constants and activation energies for the alcoholysis of hydroxymethylacetamide in methanol.

t°	Concentrations mole/l						$K = \frac{c_M}{c_A c_F}$ l/mole	$10^3 \times k_1 \text{ sec.}^{-1}$		$E_{0^\circ-40^\circ}$ kcal
	initial			at equilibrium				exptl.	calc.*	
	c_{RO^-}	c_M	c_A	c_M	c_A	c_F				
0	0.0499	0.0091					1.42	0.00308	0.00315	
	0.201	0.0085						0.0126	0.0125	
	1.005	0.0097						0.0575	0.0568	
	0.975	0.0776	0.600	0.0370	0.641	0.0406				
20	∞								0.5	27.5
	0.0097	0.0088						0.0196	0.0189	
	0.0496	0.0091						0.098	0.093	
	0.202	0.0087						0.367	0.359	
	0.202	0.044						0.336	0.356	
	0.202	0.036	0.300	0.0268	0.327	0.0091	1.05	0.338	0.356	
	0.99	0.0094						1.46	1.42	
	1.00	0.044						1.36	1.42	
40	0.975	0.0776	0.600	0.0305	0.647	0.0471	1.00			21.1
	∞								6	
	0.0499	0.0091						1.98	2.00	
	0.201	0.0085						7.34	7.43	
	1.00	0.0096						26.5	26.2	
	0.975	0.0776	0.600	0.0247	0.653	0.0529	0.72			
	∞							70		

* Calculated using eqns. (7) and (8) with $K_1 = 7.84, 3.16$ and 1.68 at $0^\circ, 20^\circ$ and 40° , respectively.

where M, A and F denote the concentrations of hydroxymethylacetamide, acetamide and formaldehyde, respectively, and subscripts o, t and eq referring to times $t = 0, t$ and infinity, and k_1 is the first-order rate constant of the alcoholysis reaction. The rate constant of the reverse reaction is computed in the usual way from $k_2 = k_1 K$, where K is the equilibrium constant of the reaction 2

$$K = \frac{M_{eq}}{F_{eq} A_{eq}} = \frac{k_2}{k_1} \quad (6)$$

The rate constants were usually calculated from data for 15–90 % reaction. The first-order rate constant showed a slight tendency to decrease as the reaction proceeded. A typical run is shown in Table 1. The variation in the rate constant may be due to the incorrect substitution of total concentrations of hydroxymethylacetamide and formaldehyde for the concentrations of the respective ions in eqn. (5). The concentrations of the ionic forms could be obtained from eqns. (7) if the respective equilibrium constants of the proton transfer reactions (1) and (3), K_1 and K_3 , were known.

$$K_1 = \frac{c_{MH} c_{RO^-}}{c_{M^-}} \quad \text{and} \quad K_3 = \frac{c_{FH} c_{RO^-}}{c_{F^-}} \quad (7)$$

MH and M^- denote hydroxymethylacetamide and its anion, FH and F^- monoformal and its anion and RO^- the alcoholate anion. Because the values of K_1 and K_3 were not known, it was assumed that the decrease of the alcoholate ion concentration in reactions (1) and (3) can be neglected, *i. e.* $c_{RO^-} \gg c_{M^-}$ and c_{F^-} . This assumption proved to be a good approximation for methanol and ethanol but only approximately valid for *isopropanol*. The error can be diminished further by extrapolating rate constants obtained at a con-

Table 3. Equilibrium and first-order rate constants and activation energies for the alcoholysis of hydroxymethylacetamide in ethanol.

t°	Concentrations mole/l						$K_1 = \frac{c_M}{c_A c_F}$		$10^3 \times k_1 \text{ sec.}^{-1}$		$E_{0^\circ-40^\circ}$ kcal
	initial			at equilibrium			exptl.	calc.**	exptl.	calc.*	
	c_{M^-}	c_M	c_A	c_M	c_A	c_F					
0	0.0207	0.0202	0.200	0.0091	0.211	0.0111	3.88	4.76	0.0375	0.0395	
	0.0505	0.0198	0.200	0.0085	0.211	0.0112	3.60	4.25	0.0832	0.0810	
	0.104	0.0204	0.200	0.0095	0.211	0.0109	4.45	5.05	0.122	0.128	
	0.201	0.0200	0.201	0.0097	0.212	0.0107	4.29	4.69	0.183	0.177	
	0.504	0.0204	0.199	0.0098	0.210	0.0106	4.41	4.62	0.240	0.222	
	∞						mean	4.67		0.27	
20	0.0105	0.0198	0.200	0.0070	0.218	0.0127	2.54	3.46	0.573	0.547	24.6
	0.0204	0.0194	0.200	0.0071	0.212	0.0123	2.72	3.60	0.952	0.990	
	0.0482	0.0196	0.200	0.0069	0.213	0.0127	2.55	3.18	1.96	1.91	
	0.0485	0.0192	0	0.0010	0.018	0.0182	2.95	3.64	1.97	1.92	
	0.103	0.0194	0.200	0.0077	0.212	0.0117	3.11	3.64	2.90	2.96	
	0.207	0.0194	0.200	0.0076	0.212	0.0117	3.08	3.41	3.59	3.83	
	0.512	0.0194	0.200	0.0083	0.211	0.0110	3.57	3.75	5.27		
	1.04	0.0198	0.200	0.0075	0.212	0.0122	2.80	2.88			
∞						mean	3.43		5.26	22.3	
40	0.0207	0.0202	0.200	0.0091	0.211	0.0111	2.07	2.96	12.4	12.0	
	0.0505	0.0198	0.200	0.0061	0.214	0.0137	2.09	2.72	22.8	22.8	
	0.104	0.0204	0.200	0.0077	0.213	0.0127	2.85	3.44	31.5	32.9	
	0.201	0.0200	0.201	0.0067	0.214	0.0133	2.35	2.64	43.4	41.1	
	0.504	0.0204	0.199				2.57	2.72			
	∞						mean	2.76		52.6	

* Calculated using eqns. (7) and (8) with $K_1 = 0.104, 0.072$ and 0.054 at $0^\circ, 20^\circ$ and 40° , respectively.

** Calculated using eqn. (9) with $K_3 = 0.132, 0.102$ and 0.086 at $0^\circ, 20^\circ$ and 40° , respectively.

stant alcoholate concentration to zero hydroxymethylacetamide concentration. The rate constant k_1 is obtained by extrapolating the experimental k_1' values to infinite alcoholate concentration by the method described in the previous paper¹. Using the extrapolated value k_1 together with the different k_1' values c_{M^-} is calculated from

$$c_{M^-} = \frac{k_1'}{k_1} \cdot c_{M_{\text{total}}} \quad (8)$$

and K_1 from eqn. (7). The constancy of the K_1 values gives evidence for the validity of the assumptions made in the calculations. The mean value of K_1 was used to recalculate k_1 , but the latter was not found to be altered. Tables 2, 3 and 4 give the experimental first-order rate constants, the extrapolated values of the first-order rate constants, and the rate constants calculated using the values of k_1 and K_1 obtained by extrapolation (eqns. (7) and (8)). The agreement between the experimental and calculated values are satisfactory in methanol and ethanol, but in isopropanol only when the alcoholate concentration is greater than the concentration of hydroxymethylacetamide.

When total concentrations of hydroxymethylacetamide and formaldehyde are used in the calculations of the equilibrium constant K of reaction 2 (eqn. (6)), a considerable change in the values of K are obtained as the alcoholate concentration is altered. This

Table 4. Equilibrium and first-order rate constants and activation energies for the alcoholysis of hydroxymethylacetamide in *isopropanol*.

t°	Concentrations mole/l						$K = \frac{c_M}{c_A c_F}$		$10^3 \times k_1 \text{ sec}^{-1}$		$E_{0^\circ-40^\circ}$ kcal
	initial			at equilibrium			exptl.	calc.**	exptl.	calc.*	
	c_{RO^-}	c_M	c_A	c_M	c_A	c_R					
0	0.0023	0.0180	0.100	0.0114	0.1066	0.0066	16.1	25.9	0.165	0.120	22.1
	0.0092	0.0089	0.0015	0.0015	0.0089	0.0074	23.4	31.3	0.577	0.535	22.8
	0.0100	0.0180	0.0030	0.0046	0.0164	0.0134	21.2	28.4	0.456	0.422	23.0
	0.0393	0.0090	0.0015	0.0016	0.0089	0.0074	23.9	26.5	0.920	0.975	23.2
	0.0394	0.0164	0.0027	0.0044	0.0150	0.0120	24.4	27.1	0.850	0.960	23.1
	0.0393	0.0360	0.0060	0.0153	0.0267	0.0207	27.7	30.7	0.682	0.810	23.6
	0.0735	0.0180	0.100	0.0133	0.1047	0.0047	27.4	29.2	1.315		
	0.0895	0.0180	0.0030	0.0053	0.0157	0.0127	26.7	28.1	0.950	1.07	23.7
	∞						mean	28.4		1.16	23.2
	20	0.0023	0.0180	0.100	0.0094	0.1086	0.0086	10.1	15.3	2.66	1.97
0.0092		0.0089	0.0015	0.0009	0.0094	0.0080	12.5	16.0	10.4	9.85	
0.0100		0.0180	0.0030	0.0029	0.0181	0.0150	10.8	13.7	8.25	8.10	
0.0195		0.0180	0.0030	0.0035	0.0175	0.0145	13.8	16.0	12.7	12.7	
0.0393		0.0090	0.0015	0.0009	0.0095	0.0080	12.3	13.5	17.4	18.0	
0.0394		0.0164	0.0027	0.0031	0.0160	0.0133	14.1	15.4	15.7	17.4	
0.0393		0.0360	0.0060	0.0111	0.0309	0.0249	14.4	15.7	13.1	15.8	
0.0895		0.0180	0.0030	0.0038	0.0172	0.0142	15.5	16.1	18.5	19.8	
0.120		0.0180	0.103				15.0	15.5	20.2	20.3	
∞							mean	15.2		21.5	

* Calculated using eqns. (7) and (8) with $K_1 = 0.006$ at 0° and 20° .

** Calculated using eqn. (9) with $K_2 = 0.0103$ and 0.0111 at 0° and 20° , respectively.

implies that $K_1 \neq K_2$. By making the simplifying assumption, $c_{RO^-} \gg c_M^-$ and c_F^- , which was previously found to be a good approximation, the equation

$$K_2 = K_{\text{tot}} \frac{K_3 + c_{RO^-}}{K_1 + c_{RO^-}} \quad (9)$$

used previously¹ is obtained. K_2 is the equilibrium constant for reaction (2) and K_{tot} the equilibrium constant for the same reaction when total concentrations of hydroxymethylacetamide and formaldehyde are substituted in eqn. (6). K_2 and K_3 both can be determined, as K_1 is previously known from kinetic experiments, from the slope and intercept of the straight line plotting $K_{\text{tot}} / (K_1 + c_{RO^-})$ versus $K_{\text{tot}} c_{RO^-} / (K_1 + c_{RO^-})$. The values of K_{tot} and K_2 are given in Tables 2, 3 and 4. The constancy of calculated K_2 values illustrate the validity of the approximations made in the calculations.

RESULTS AND DISCUSSION

The values of the rate and equilibrium constants of reaction (2) and the equilibrium constants of the proton transfer reactions (1) and (3) calculated from the kinetic experiments by the methods described are summarized in Tables 5 and 6. For comparison, also values obtained previously¹ are included. Because of the poor reproducibility of the experiments made in *tert.*-butanol due to the high rate of the reaction and to the great sensitivity of the alcoholate

Table 5. Rate constants (k_1 and k_2), equilibrium constant (K), heats of reaction (ΔH) and the Arrhenius parameters (E and A) for reaction (2) in water, methanol, ethanol, isopropanol and *tert.*-butanol.

Solvent	$10^3 \times k_1 \text{ sec}^{-1}$			$10^3 \times k_2 = k_1 K$	$K = \frac{c_{M^-}}{c_A c_{F^-}}$			E_1 kcal	E_2 kcal	ΔH kcal	log A_1	log A_2
	0°	20°	40°		0°	20°	40°					
H ₂ O	0.264	3.72	44.1	80	41.4	21.4	14.8	21.8	17.5	-4.3	13.8	12.0
MeOH	0.5	6	70	6	1.42*	1.05*	0.72*	21.1	18.0	-3.1	13.5	11.2
EtOH	0.27	5.3	53	18	4.67	3.43	2.76	22.3	19.8	-2.1	14.3	13.0
<i>i</i> -PrOH		21.5		327	28.4	15.2		23.2	18.3	-4.9	15.7	13.2
<i>t</i> -BuOH		~200		~20.000		~100						

* measured with $c_{RO^-} = 0.975 \text{ M}$.

solution to traces of water, only approximate values were obtained; these are included in Table 5 to illustrate the order of magnitude.

The values obtained for the proton transfer constants K_1 and K_3 given in Table 6 show that the acidities of the hydroxylic solvents decrease in the order methanol, water, ethanol, isopropanol. Similar results were obtained by Koivisto⁴, Caldin⁵, and Hine⁶. Formaldehyde is known to exist practically entirely in the hydrated form HOCH₂OH in dilute aqueous solutions and thus contains two hydroxyl groups (for references see Ref.¹) whereas the monoformal ROCH₂OH present in alcohol solutions contains only one hydroxyl. In order to get comparable values, the value of K_3 obtained in water should be multiplied by two; for example at 20° $K_3 = 2 \times 0.11 = 0.22$. After this correction, the formaldehyde-solvent addition product is found to be an about 1.5 times stronger acid than hydroxymethylacetamide in all the solvents studied. Compared with the solvents, hydroxymethylacetamide and formaldehyde monoformals at first seem to be of the same order of strength as acids, but according to the reaction $FH + RO^- = F^- + ROH$, the concentrations of the solvent molecules should be included in eqns. (7). Thus the hyd-

Table 6. Equilibrium constants and heats of the proton transfer equilibria between hydroxymethylacetamide (K_1) and formaldehyde hydrate and monoformal (K_3) and the solvent anions (HO⁻, MeO⁻, EtO⁻, *iso*PrO⁻) in the respective solvents.

Solvent	$K_1 = \frac{c_{MH} \cdot c_{RO^-}}{c_{M^-}}$			$K_3 = \frac{c_{FH} \cdot c_{RO^-}}{c_{F^-}}$			ΔH_1 kcal	ΔH_3 kcal
	0°	20°	40°	0°	20°	40°		
H ₂ O	0.14	0.16	0.19	0.09	0.11	0.13	1.3	1.4
MeOH	7.8	3.2	1.7				-6.5	
EtOH	0.10	0.07	0.05	0.13	0.10	0.08	-2.1	-1.8
<i>i</i> -PrOH	0.006	0.006		0.010	0.011		0	0.5

roxymethylacetamide and formaldehyde monoformals are much stronger acids than the alcohols used as solvents.

Great differences were found in the heats of proton transfer reactions (1) and (3) in the solvents studied. Although the values obtained by extrapolation in methanol are not very accurate, the values of ΔH of proton transfer equilibria in methanol and water were found to differ by about 7.8 kcal. It is of the same order of magnitude as found by other methods. Koivisto⁴ found calorimetrically when neutralizing phenol or acetic acid with sodium alcoholate in methanol and sodium hydroxide in water, a difference $\Delta H_w - \Delta H_m = 7.2$ kcal. In ethanol and *isopropanol* the values of ΔH are 3.4 and 1.3 kcal. greater than the value of ΔH in water for the proton transfer reaction (1), whereas the calorimetric values obtained by Koivisto using carboxylic acids and phenol gave a difference of about 6 and 4 kcal in ΔH in the corresponding solvents.

At low alcoholate concentrations the experimental rate constant k'_1 is approximately proportional to the alcoholate concentration. When $c_{RO^-} \gg c_M^-$ and $c_{MH} \gg c_M^-$, $k' = k_1 c_{RO^-} / K_1$ (eqns. (7) and (8)).

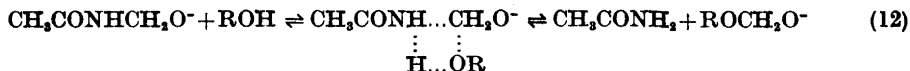
The experimental activation energy should approach the value $E' = E - \Delta H_1$ at low alcoholate concentrations. From the last column in Tables 2, 3 and 4 it will be seen that the change in the calculated activation energy is of the same order of magnitude as ΔH_1 in Table 6, which gives further evidence that the method of extrapolation used gives correct values.

When comparing the rate constants of reaction 2 (Table 5), it must be remembered that as the group R in the reactant is altered, also the solvent is changed. Thus both the solvent and substituent effects are superimposed in the change in the reaction rate. The rates of solvolysis of hydroxymethylacetamide anion in water, methanol and ethanol are approximately equal. It seems that the solvent effects are of minor importance as the rate is not much altered in spite of a considerable change in the nature of the solvent. The observed difference in the reaction rates in *isopropanol* and *tert.*-butanol is evidently mainly due to substituent effects. For the two reactions:

		Values of ΔH (kcal) when R is				
		H	CH_3	CH_3CH_2	$(\text{CH}_3)_2\text{C}$	
$\text{ROH} + \text{CH}_3\text{CONHCH}_2\text{O}^- \rightarrow \text{RO}^- + \text{CH}_3\text{CONHCH}_2\text{OH}$	(10)	-1.3	6.5	2.1	0	
$\text{ROH} + \text{CH}_3\text{CONHCH}_2\text{O}^- \rightarrow \text{ROCH}_2\text{O}^- + \text{CH}_3\text{CONH}_2$	(11)	-4.3	-3.1	-2.1	-4.9	

the heats of the proton transfer and solvolysis reactions change in the same direction when R is altered. The equilibria of both reactions (10) and (11) are shifted towards the left in the series $\text{R} = \text{CH}_3, \text{CH}_3\text{CH}_2, (\text{CH}_3)_2\text{CH}$, the equilibrium values found in water ($\text{R} = \text{H}$) being exceptional in that they are intermediate between those in methanol and ethanol for reaction (10) and between those in ethanol and *isopropanol* for reaction (11). Both reactions involve a proton transfer. A proton is donated by ROH to an oxygen atom in reaction (10) and to a nitrogen atom of the amide in reaction (11). In the latter reaction there occurs in addition a breaking-up of the formaldehyde-amide bond and the formation of the formaldehyde-alcohol bond. These latter changes are the reason for the smaller changes observed in the heats and rates

of reaction as compared with those of the proton exchange. In accordance with the above discussion, the following mechanism is proposed for reaction (2):



The hydrogen of ROH can become bonded ("hydrogen bond") to the nitrogen of hydroxymethylacetamide before the molecule reaches the energy level necessary for reaction and only a part of the energy of proton transfer is included in the activation energy. The formation of two bonds and the breaking of two other bonds in the transition complex probably occurs in one step simply by a simultaneous shift of the electron pairs forming the four reacting bonds.

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