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The Alkaline Hydrolysis of Alkoxymethyl Ureas

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Alkoxy methyl ureas, surprisingly enough, were found to be quite readily hydrolysed in moderately alkaline solution at room temperature, giving urea, formaldehyde and an alcohol as end products. The decomposition of different alkoxymethyl ureas was investigated kinetically. The hydrolysis was found to be proportional to the OH^- ion concentration. Based on kinetic investigations in strongly alkaline solution a choice is made between two possible reaction paths for the reaction. It may be concluded that the reaction involves the breaking of an ether bond, *i.e.* that methylol urea and alcohol are the first decomposition products.

The reaction is specific for ethers of methylol urea, ethers of methylol compounds of carboxylic acid amides being comparatively very stable in alkaline solution.

The reaction mechanism is discussed.

Ethers of methylol urea are usually prepared in acid solution from methylol urea and alcohol.

$$NH_2CONHCH_2OH + ROH \rightleftharpoons NH_2CONHCH_2OR + H_2O$$
$$HOCH_2NHCONHCH_2OH + 2ROH \rightleftharpoons ROCH_2NHCONHCH_2OR$$

As indicated in the above equations these reactions are reversible. The ethers are readily decomposed under the catalytic influence of acids, probably giving the methylol compound and the alcohol as the first decomposition products. The details of this decomposition in acid solution are not yet known.

Contrary to some observations in the literature, it can be shown that such ethers are also hydrolysed in alkaline solutions. The experimental evidence for a hydrolysis of this type of ethers in alkaline aqueous solution is the appearance of free formaldehyde.

This result could be due to the decomposition of the urea part of the ether molecules. The breaking of a C—N bond at one of the places indicated by the dotted lines in equation (a) would result in a total break-down of the ether molecule:

$$NH_2\vdots CO\vdots NHCH_2OCH_3 + 2H_2O \rightarrow 2NH_3 + CO_2 + CH_2O + CH_3OH \qquad (a)$$

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From what is known of the stability of urea in alkaline solution it is not very probable that such a reaction occurs in the present instance. The conditions under which the alkaline hydrolysis of the ethers appears to occur are so mild that the urea molecule may safely be regarded as stable.

It was possible to confirm this experimentally.

The compound $NH_2CONHCH_2OCH_3$ was hydrolysed practically completely after being dissolved in 0.3 N NaOH for 24 hours at room temperature (95 % free CH_2O). Urea could then be precipitated from the solution as its addition compound with xanthydrol with a yield of 90 % (More details of these experiments are to be found in the experimental part of this chapter).

It is therefore more probable that the ether will break initially at one of the points indicated by a dotted line in $NH_2CONH\vdots CH_2\vdots OR$. In both cases the final products will be urea and formaldehyde, in accord with experimental evidence. Should the C-N bond between the urea fragment and the methylene group be broken initially the decomposition would proceed as follows:

$$\left.\begin{array}{ll} 1. & NH_2CONHCH_2OR \rightarrow NH_2CONH_2 + HOCH_2OR \\ 2. & HOCH_2OR \rightarrow CH_2O + ROH \end{array}\right\} \quad (b)$$

The hemiacetal primarily formed is known to be very unstable in alkaline solution and will quickly decompose into formaldehyde and the alcohol.

If the C-O bond is broken initially the following reaction occurs:

$$\left.\begin{array}{ll} 1. & NH_2CONHCH_2OR \rightarrow NH_2CONHCH_2OH + ROH \\ 2. & NH_2CONHCH_2OH \rightarrow NH_2CONH_2 + CH_2O \end{array}\right\} \quad (c)$$

Under the catalytic influence of hydroxyl ions, the ether is decomposed into the alcohol ROH and methylol urea, this involving the rupture of an ether bridge —$CH_2\vdots OR$. The methylol compound is broken down further in a subsequent reaction into urea and formaldehyde, a reaction which is known to occur in alkaline solution [1].

The two latter reaction paths (b) and (c) are very similar and both involve a series of two subsequent reactions with an unstable intermediate. It is very difficult to show by any chemical method which of these two reactions paths (b) or (c) does in fact predominate since the possible intermediates are both highly unstable compared to the parent compound. Later in this paper arguments will be given that monomethylol urea is the initial product in the ether decomposition (scheme (c)). The evidene for this has been derived from kinetic measurements. The kinectic investigation of the decomposition also gave an insight into the mechanism of the reaction.

KINETIC INVESTIGATIONS

A. General outline of the kinetic measurements

1. The rate of hydrolysis of various alkyl ethers of methylol urea was measured in alkaline solution at 25°C.

$$NH_2CONHCH_2OR \rightarrow NH_2CONH_2 + CH_2O + ROH$$

Formaldehyde was considered to be the component most suitable for determination. It was possible to obtain satisfactory results with "the KCN method"[2]. In alkaline solution formaldehyde reacts very rapidly and completely with KCN by the familiar equation:

$$CH_2O + CN^- + H_2O \rightarrow CH_2(OH)CN + OH^-$$

The excess KCN is titrated with $Hg(NO_3)_2$ after reducing the pH of the sample to about 5.

2. As already indicated the decomposition of the ether may be formulated as a sequence of two reactions:

$$1.\ E \rightarrow I + \ldots \qquad 2.\ I \rightarrow F + \ldots,$$

in which E is the ether, I the intermediate (hemiacetal or methylol urea) and F formaldehyde.

If it is required to use rate of formation of free formaldehyde in ascertaining the rate of decomposition, it should be noted that reaction 2 does not go to completion but reaches an equilibrium. This inconvenience can be overcome by arranging for the measured amount of KCN to be present from the very start of a kinetic run. (To keep the pH constant during the run the experiments were carried out in strong phosphate-buffer. More details of the experimental procedure are found in the experimental part).

Under these conditions reaction 2 will be irreversible because in the alkaline solution any free formaldehyde will be completely removed by KCN by an instantaneous reaction. Nothing is known regarding the reversibility of reacttion 1. From what is known of similar organic chemical reactions it is to be expected that a possible equilibrium will be far over to the right. In any case under the present experimental conditions, reaction 1 may be considered as going to completion because the concentration of the intermediate will always be very low compared to the concentration of the undecomposed ether.

The system is therefore considered as being a sequence of two irreversible reactions 1 and 2 (scheme b or c). Later in this chapter it will be shown experimentally that the ether decomposition is a first order reaction. The concentration of the compounds in the system can be derived from the following equations:

$$-\frac{d[E]}{dt} = k_1[E] \tag{1}$$

$$\frac{d[I]}{dt} = k_1[E] - k_2[I] \tag{2}$$

in which E is the ether, I is the initially formed intermediate, (hemiacetal or methylol urea) k_1 and k_2 are the rate constants for reaction 1 and 2. This gives:

$$[E] = [E_0]e^{-k_1t} \tag{3}$$

$$[I] = \frac{[E_0]k_1}{k_2 - k_1}(e^{-k_1t} - e^{-k_2t}) \tag{4}$$

Accordingly, for the ratio α of the amount of formaldehyde liberated to the amount of ether decomposed is obtained the expression:

$$\alpha = \frac{[F]}{[E_0]-[E]} = 1 - \frac{k_1}{k_2-k_1}\,\frac{e^{-k_1t}-e^{-k_2t}}{1-e^{-k_1t}} \tag{5}$$

The required rate constant for the ether decomposition in reaction 1 is given by:

$$k_1 = \frac{1}{t}\ln\frac{[E_0]}{[E_0]-([E_0]-[E])} \tag{6}$$

We define an "experimental rate constant" by:

$$k_1' = \frac{1}{t}\ln\frac{[E_0]}{[E_0]-[F]} \tag{7}$$

which is obtained by substituting for the amount of ether decomposed $[E_0]-[E]$ the measured concentration of formaldehyde liberated $[F]$.

From eqn. (5) it will be seen that the ratio $\alpha = \frac{[F]}{[E_0]-[E]}$ is less than 1 and approaches 1 as the time increases which from eqns. (6) and (7) means that the "experimental rate constant" k_1' will approach the true constant k_1 as the degree of decomposition increases. From eqn. (5) it also follows that the value of α will approach 1 the more rapidly the higher the ratio k_2/k_1 is. The same applies therefore to the way in which k_1' will approach k_1 with increasing reaction time. When k_2 is much larger than k_1 the ratio α will be practically equal to 1 already at low degrees of decomposition and accordingly we shall find that the "experimental rate constant" k_1' is constant and equal to the required rate constant k_1 after a low degree of decomposition. This appeared to be the case for all experiments at moderate pH values. Table 1 shows an example of a run.

Table 1. The decomposition of methoxymethyl urea.
E_0 = 0.02 moles/l. Temp. = 25°C
pH = 11.27–11.30. $k_2 = 16.5\ 10^{-5}$
$k_2/k_1 = 142$.

Time (hours)	$Hg(NO_3)_2$ 0.1073 N	% F	$k_1' \times 10^7$ (sec.$^{-1}$)
0	6.60		
14	6.30	5.4	11.0
24	6.08	9.3	11.1
48	5.64	17.2	10.9
96	4.72	33.6	11.8
168	3.80	50.1	11.5
264	2.84	67.2	11.7

The second column of Table 1 gives the amount of $Hg(NO_3)_2$ required for the titration of excess KCN. The third column gives the % of formaldehyde liberated and in the fourth column are given the values of the rate constant k_1' as calculated from eqn. (7). The value of k_1' is within experimental error constant already at low degrees of decomposition and may be taken as equal to the required rate constant k_1. With all ethers of methylol urea decomposed at pH 11—12 and 25°C the "experimental rate constant" k_1' was constant at low degrees of decomposition.

As explained above this result means that the second step in the decomposition reaction, the splitting of hemiacetal (scheme b) or the splitting of methylol urea (scheme c), is very fast compared to the ether decomposition. However, the results do not give any indication as to what scheme is the right one, because both possible intermediates decompose very fast compared to the ether decomposition under the given conditions. The hemiacetal may be expected to split practically spontaneously under the conditions cited in Table 1 [3]. The decomposition of methylol urea was measured separately under the same condition. The value for the rate constant is given in the top of Table 1 (k_2) and has indeed also a much higher value than the rate constant of the ether hydrolysis ($k_2/k_1 = 142$). Therefore both schemes b and c are in agreement with the constant value experimentally observed for the "experimental rate constant". The question is further discussed in part D of this chapter.

B. The order of the decomposition reaction

The hydrolysis of methoxymethyl urea is a first order reaction. This follows from the fact that in each separate run we find a constant value for the rate constant as calculated from the equation for a first order reaction (Table 1).

Furthermore the reaction is shown to be first order by decomposition measurements with different initial concentrations of the ether: The degree of decomposition after a certain time is independent of the initial concentration of the ether (Table 2).

Table 2. The decomposition of methoxymethyl urea is a first order reaction. Temp. = 25°C pH = 11.27—11.30.

Time (hours)	24	48	96	168	
% F liberated	9.3	18.3	32.7	49.0	$[E_0] = 0.01$ mole/l
	9.3	17.2	33.6	50.1	$[E_0] = 0.02$ mole/l
	9.0	18.0	32.1	49.8	$[E_0] = 0.03$ mole/l

C. The influence of pH on the rate of decomposition

Table 3 gives the value of the rate constant k_1 for the decomposition of methoxymethyl urea at three different pH values at 25°C. It is evident that the rate is directly proportional to the concentration of hydroxyl ions.

Table 3. The first order rate constant for the decomposition of methoxymethyl urea at different pH values.

pH	11.27—11.30	11.61—11.63	11.97—12.0
$10^7 k_1$(sec^{-1})	11.6	24.8	58.6

D. Evidence that monomethylol urea is initially formed as an intermediate in the decomposition of the ethers

In the introduction it was pointed out that the appearance of free formaldehyde from, *e.g.*, methoxymethyl urea may be described by two different reaction schemes both involving a series of two subsequent reactions. The molecule $NH_2CONH\underset{x}{\vdots}CH_2\underset{y}{\vdots}OCH_3$ may break at x giving the hemiacetal as intermediate product (scheme b) or at y with methylol urea as intermediate (scheme c). As explained above the measurements hitherto described do not give any indication as to which of these two possibilities does in fact occur.

Let us now tentatively assume that methylol urea (UF) is the intermediate, *i.e.* that the reaction course given in scheme c is correct.

$$1. \quad \mathrm{E} \xrightarrow{k_1} \mathrm{UF}$$

$$2. \quad \mathrm{UF} \xrightarrow{k_2} \mathrm{U+F}$$

and let us try to find conditions under which the rate of decomposition of methylol urea k_2 (which can be measured separately) is much closer to the value of k_1 than it was under the conditions given in Table 1 ($k_2/k_1 = 142$).

From the discussion of the rate expressions (5) (6) and (7) it will be evident that in this case we shall (if our assumption is right) expect to find that the "experimental rate constant" increases with time and only reaches a constant value after a considerably degree of decomposition.

Ether decomposition experiments at slightly different pH values from 11—12 will not change the ratio of the rates of the two subsequent reactions, because both are proportional to $[OH^-]$. However, the authors have shown in the investigation of the kinetics of formaldehyde — amide reactions [4] that the velocity of the decomposition of monomethylol urea at very high alkalinities (0.1 N NaOH and higher) is not longer proportional to the OH^- concentration but approaches an upper limit where a further increase in $[OH^-]$ no longer affects the rate. Fortunately the hydrolysis of the ether was now found to be still proportional to $[OH^-]$ even in these strongly alkaline solutions. The result is a smaller value of the ratio k_2/k_1 as is required.

The decomposition of methoxymethyl urea was measured in 0.4 and 1 N NaOH at 0° C. The amount of formaldehyde formed was determined with the KCN-method as described. (At such high OH^- concentrations as used here, the increase in $[OH^-]$ due to the reaction of KCN with formaldehyde, is negligible compared to the $[OH^-]$ already present. Therefore no buffers are necessary under these conditions. More details are found in the experimental part.)

The results are shown in Table 4. It can be seen that the rate constant for the hydrolysis of the ether k_1 ($=k_1'$ at high conversions) is indeed still proportional to the OH^- concentration. The independently measured values for the rate constant of the decomposition of monomethylol urea (k_2) are given at the top of the tables. As will be seen the value of k_2 at such high alkalinities is no longer proportional to $[OH^-]$. The result is that the ratio k_2/k_1 is less than its value at pH 11—12, where k_2/k_1 was about 140. This effect is most obvious at the highest alkalinity.

With this more favourable ratio of k_2/k_1 the predicted increase in the value of k_1' on increasing the reaction time is now clearly observed.

In the tables are also given the values of the ratio $\alpha = [F]/([E_0]-[E])$ at the different time intervals, calculated from eqn. (5), using the value of $k_1' = k_1$ for high conversions and the measured value of k_2. With the aid of the values of α and eqn. (6), the rate constant k_1 can now be calculated for low conversions from the [F]-values measured. The values are given in the table as k_1 calc.

Table 4. The decomposition of methoxymethyl urea in 0.4 N and 1 N NaOH at 0°C.

a) $[Na^+] = 0.40$; $k_2 = 2.45 \times 10^{-4}$; $k_2/k_1 = 44.5$

Time in min.	% F	$k_1' \times 10^6$ (sec^{-1})	$\frac{[F]}{[E_0]-[E]}$	k_1 calc. $\times 10^6$
215	4.60	3.66	0.702	5.27
360	9.40	4.57	0.819	5.66
986	26.8	5.28	0.938	5.69
2520	56.0	5.43	0.983	
4200	74.1	5.49		

b) $[Na^+] = 1.00$; $k_2 = 3.44 \times 10^{-4}$; $k_2/k_1 = 24.6$

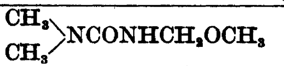
60	2.18	6.1	0.424	14.4
120	6.10	8.7	0.638	13.9
180	10.5	10.4	0.750	13.9
240	14.6	11.0	0.813	13.8
300	19.5	12.1	0.852	14.4
370	23.9	12.3	0.872	14.3
946	53.7	13.6	0.965	
1251	64.1	13.7		
1675	74.8	13.7		
1749	76.3	13.7		

It will be seen that these calculated values for k_1 at low conversions are constant, allowance being made for the experimental error, and have practically the same value as $k_1' = k_1$ found at high conversions. This result is a very strong indication that methylol urea is indeed the initial intermediate compound in the splitting of ether since we used the directly measured value of the rate constant for the decomposition of methylol urea (k_2) to obtain this result. It is extremely unlikely that the rate constant for the hydrolysis of the hemi-acetal $HOCH_2OCH_3$ has the same value under these conditions. In fact, the hydrolysis of a hemiacetal should be expected to be spontaneous at such high alkalinities, which means that not even qualitatively an increase in k_1' could have been observed.

E. Influence of the alkyl group on the rate of decomposition

To establish the influence of the alkyl group R on the rate of hydrolysis of the ethers $NH_2CONHCH_2OR$ investigations were made on the methyl, ethyl, propyl and *iso*propyl ethers. These ethers have been prepared by a procedure described by Kadowaki [5]. The propyl and *iso*propyl ethers are new compounds. The results of the decomposition experiments are given in Table 5. As will be seen the rate constant is roughly doubled in going from the *iso*propyl ether to the propyl ether, is nearly unchanged in going from the propyl ether to the ethyl ether and is again doubled in going from the ethyl ether to the methyl ether.

Table 5. The rate of decomposition of various alkyl ethers of methylol urea. Temp. = 25°C; pH = 11.98.

	$k_1 \times 10^6$ (sec^{-1})
$NH_2CONHCH_2OCH_3$	5.87
$NH_2CONHCH_2OC_2H_5$	2.87
$NH_2CONHCH_2OCH_2CH_2CH_3$	2.96
 $NH_2CONHCH_2OCH{<}\begin{smallmatrix}CH_3\\CH_3\end{smallmatrix}$	1.67
 $\begin{smallmatrix}CH_3\\CH_3\end{smallmatrix}{>}NCONHCH_2OCH_3$	27

F. Hydrolysis of di-alkyl ethers of dimethylol urea

A few experiments have been performed with some of the ethers of dimethylol urea $ROCH_2NHCONHCH_2OR$. These compounds were likewise found to hydrolyse readily in alkaline solution, at a higher rate even than the monoethers. It has been observed that practically the theoretical amount of formaldehyde can be obtained from such a di-alkyl ether after a prolonged reaction time which means that both ether bonds can be hydrolysed. The overall reaction is rather complicated. The complexity of the reaction makes it difficult to derive any accurate value for the rate constant in this case.

In the kinetic investigations the hydrolysis of a di-ether was followed up to a degree of conversion, where about 5—10 % of the theoretical amount of formaldehyde had been set free. The hydrolysis of the second ether group then may probably be neglected and the rate of liberation of formaldehyde will be determined by the following two reactions.

$$1.\quad ROCH_2NHCONHCH_2OR \xrightarrow{k_1} ROCH_2NHCONHCH_2OH + ROH$$

$$2.\quad ROCH_2NHCONHCH_2OH \xrightarrow{k_2} ROCH_2NHCONH_2 + CH_2O$$

The rate constant k_2 is unknown and cannot be readily determined, because methylol alkoxymethyl ureas are unknown compounds and will be difficult to prepare. However, the experimental rate constant for the appearance of formaldehyde, as calculated from a first order reaction equation, appears to be nearly constant after 10 % conversion, and as explained in connexion with the mono ethers we may therefore assume that in this manner we are measuring the rate of decomposition of the first ether group in the di-ether.

The rate constants at 35°C and pH 11.9 found in this way, for three di-alkyl ethers, are collected in Table 6. As will be seen the rates of decomposition with different alkyl groups vary in the same manner as was observed for the monoethers, *viz.* $CH_3 > C_2H_5 \sim CH_3CH_2CH_2$. The ratios of the rate constants are about the same as those found for the mono ethers.

Table 6. Rate constants for the hydrolysis of some di-alkyl ethers of dimethylol urea. Temp. = = 35°C; pH = 11.90.

	$k_1 \times 10^5$(sec.$^{-1}$)
$CH_3OCH_2NHCONHCH_2OCH_3$	6.4
$CH_3CH_2OCH_2NHCONHCH_2OCH_2CH_3$	3.3
$CH_3CH_2CH_2OCH_2NHCONHCH_2OCH_2CH_2CH_3$	3.6

The fact that a di-ether like $CH_3OCH_2NHCONHCH_2OCH_3$ decomposes in alkaline solution proves that for the decomposition it is not necessary for the molecule to have a free amino group H_2N. An even better proof is provided by the observed decomposition of the methyl ether of N-dimethyl N'-methylol urea $(CH_3)_2NCONHCH_2OCH_3$. The rate constant for the decomposition of this ether is about 5 times higher than for $NH_2CONHCH_2OCH_3$. (The value has been given in Table 5).

G. Hydrolysis of ethers of methylolamides

Urea may be looked upon as a special type of amide, and it might have been expected that ethers of methylol compounds of amides of carboxylic acids would also be hydrolysed in alkaline solution at a rate of the same order of magnitude as the rate of hydrolysis of ethers of methylol urea.

This did not appear to be the case. The methyl ether of methylol benzamide did not liberate any detectable amount of formaldehyde after long intervals under conditions, which had led to a ready break-down of the ethers of methylol urea (pH 11—12, temp. 25°C).

To find any measurable hydrolysis in a reasonable time it was necessary to use a much higher alkalinity. Table 7 gives the result of the hydrolysis of the methyl ether in 1 N NaOH at 25°C.

Table 7. The rate of decomposition for the methyl ether of methylol benzamide. Temp. 25°C; [OH$^-$] = 1.0 N.

Time (hours)	% F	$k_1 \times 10^7$
24	12.3	15.2
43.5	20.8	14.9
120	50.1	16.0
168	61.3	15.7

However, the experimental conditions in the above hydrolysis are so severe, that the formation of formaldehyde may quite well be due to another reaction, *e.g.* to an amide hydrolysis:

$$C_6H_5CO\vdots NHCH_2OCH_3 \rightarrow C_6H_5COOH + NH_3 + CH_2O + CH_3OH$$

Ogato and Okano [6] give $k = 2.14 \times 10^{-4}$ sec^{-1} for the first order rate constant for the hydrolysis of benzamide in 1 N NaOH at 70°C; at 25° the value will be about 5×10^{-6} sec^{-1} at a very rough estimate. The apparent rate constant for the hydrolysis of the ether is calculated from the present measurements to be 1.5×10^{-6} sec^{-1} in 1 N NaOH at 25°C. These values are of the same order of magnitude.

Alkyl ethers of other methylol amides also are known to be fairly stable towards alkali. Haworth, Peacock and Smith [7] observed that ethers of some other methylol amides liberate formaldehyde on treatment with strong alkali. The rate constant for the decomposition, which can be calculated from their experimental data, is of about the same magnitude as the rate constant for the decomposition of N-methoxymethyl benzamide.

REACTION MECHANISM

The decomposition of alkoxymethyl ureas in alkaline solution is shown to be a first order reaction with a rate proportional to the hydroxyl ion concentration. The decomposition probably involves the rupture of an ether bridge:

$$NH_2CONHCH_2OR + H_2O \rightarrow NH_2CONHCH_2OH + HOR$$

While ordinary dialkyl ethers such as CH_3—OR are known to be very stable towards alkali, it is well known that hemiacetals like $HOCH_2$—OR are readily split in alkaline solution. The mutarotation of glucose, which also involves the splitting of an ether bridge in a hemiacetal structure, is known to be catalysed by bases [8].

It is assumed in the literature that the instability of the ether bond in these cases is due to the active hydrogen in the β position to the oxygen atom of the ether group. This is in harmony with the fact that diacetals like RO—CH_2—OR are stable towards alkali. The ethers of methylol urea $NH_2CONHCH_2$—OR also have an active hydrogen in β position, in this case at an N atom. It seems reasonable to assume that with these ethers also the instability is primarily due to this fact. In accordance with the reaction scheme proposed in the literature for the mutarotation of glucose we may assume that the hydrolysis of the ethers of methylol urea in alkaline solution will take place in a sequence of steps as indicated below.

$$a.\quad NH_2CONHCH_2OR + OH^- \rightleftharpoons NH_2CO\bar{N}CH_2OR + H_2O$$

$$b.\quad NH_2CO\bar{N}CH_2OR \rightleftharpoons NH_2CON{=}CH_2 + OR^-$$

$$c.\quad RO^- + H_2O \rightleftharpoons ROH + OH^-$$

$$d.\quad NH_2CON{=}CH_2 + H_2O \rightleftharpoons NH_2CONHCH_2OH$$

In step *a* a proton is removed from the N atom, and this step is followed by the elimination of the alkoxy group in step *b* with the formation of an unstable Schiff's base. In step *c* the base is formed back by neutralisation of the alkoxy group and in step *d* the Schiff's base reacts with water with formation of the methylol compound. As in the mutarotation of glucose, steps *b* and *c* may be assumed to take place simultaneously in one single step.

Step *c* or *d* cannot be rate determining in this reaction scheme because such an assumption does not lead to the right expression for the rate. Moreover from a chemical point of view these reactions may be expected to be rapid. In principle either reaction *a* or reaction *b* can be the rate-determining step to explain the first order, base-catalysed, decomposition reaction. Most probably step *b*, the elimination of the alkoxy group, will be rate-determining. With this assumption the rate constant for the decomposition will be given by

$$k = k_b \cdot K_a[\mathrm{OH^-}] = k_b \cdot K_\mathrm{N}[\mathrm{OH^-}]/K_w \qquad (8)$$

where k_b = the rate constant for step *b*.
K_a = the equilibrium constant of step *a*.
K_N = the acid dissociation constant of the ether.
K_w = the ionisation product of water.

The rate of hydrolysis will therefore be determined by two factors: the acidity of the hydrogen at the N atom in β position to the ether group (K_N) and the rate of step *b* (k_b).

It is known that an increased branching of an alkyl group increases the polarisibility of the group while an increase in chain length has hardly any effect in this respect. Thus, when an electron-attracting group *x* is bound to the alkyl group, the electron density at the group *x* will increase in the following order:

$$\mathrm{CH_3}x < \mathrm{CH_3CH_2}x \sim \mathrm{CH_3CH_2CH_2}x < \mathrm{(CH_3)_2CH}x$$

The nature of the alkyl group R will hardly influence the value of the acidity constant K_N of the urea methylol ether because the distance between the N atom and the alkyl group is too great. It may, however, be expected to influence the value of k_b appreciably. An increased branching of the alkyl group R in $\mathrm{NH_2CONHCH_2OR}$ increases the electron density at the O atom and will counteract the introduction of a negative charge into the O atom as is involved in the transition state of step *b*:

$$\mathrm{NH_2CO\overset{-\delta}{N}{=}CH_2{\cdots}\overset{-\delta}{O}R}$$

The value of k_b will therefore be lowered. This explains the experimental observation that the rate of splitting of the urea methylol ethers decreases in the order: methyl>ethyl>*iso*propyl ether.

It is difficult to explain this effect if reaction step *a* is taken as rate determining. Also from a chemical point of view step *a* would be expected to establish equilibrium rapidly since this step involves a proton transfer at an N atom.

On comparing the ether of methylol benzamide and the ether of methylol urea it seems probable that the benzamide compound will have a higher value of K_N which from eqn. (8) should in fact favour the reaction. The surprisingly slow rate of decomposition of the benzamide compound compared with the urea compound as found experimentally must therefore be explained by a low value of k_b. If we formulate the formation of the transition state of step *b* as follows:

$$\mathrm{R'CO\bar{N}CH_2OR \rightleftharpoons R'CO\overset{-\delta}{N}{=}CH_2{\cdots}\overset{-\delta}{O}R}$$

it will be seen that the formation of the transition state involves an electron displacement from left to right. This displacement may be expected to be largely influenced by the nature of the group R'; thus it will be hampered by the electron attracting $\mathrm{C_6H_5}$ group and facilitated by the electron releasing

NH_2 group. Therefore we may expect that k_b for the benzamide ether will indeed be lower than for te urea ether and apparently this effect more than outweighs the higher value of K_N for the benzamide ether.

The suggestion that a decreased acidity of the amide favours the rate of decomposition of the ether is further supported by the comparison of the ethers $(CH_3)_2NCONHCH_2OCH_3$ and $NH_2CONHCH_2OCH_3$. The former may be expected to be the less acidic and the rate of decomposition of this ether has been found to be about 5 times higher than that for the ether from urea (Table 5).

EXPERIMENTAL PART

Materials

Monomethylol urea methyl ether (m.p. 91°C), monomethylol urea ethyl ether (m.p 111°C), dimethylol urea dimethyl ether (m.p. 101°C), dimethylol urea diethyl ether (m.p. 124°C) and dimethylol urea di-*n*-propyl ether (m.p. 95°C) were prepared by Kadowaki's method [5] by treating the appropriate methylol compound with the appropriate alcohol in the presence of small amounts of HCl.

Other ethers were prepared for the first time: Methylol urea appeared to be only slightly soluble in propyl or *iso*propyl alcohol. It was therefore found preferable in the preparation of the *n*-propyl and *i*-propyl ether of monomethylol urea to dissolve monomethylol urea in a small amount of water before the addition of the alcohol and the catalysing acid. .This appreciably reduces the reaction time and thus reduces the danger of condensation reactions (resinifying) which is otherwise appreciable. The procedure for the preparation of the two new propyl ethers is the same. The preparation of the *n*-propyl ether is given below in detail: 10 g methylol urea were dissolved in 15 ml H_2O at *ca*. 40°C. Thereupon 100 ml propyl alcohol were added, followed by 0.5 ml of 2 N HCl. The temperature was maintained at 40°C for *ca.* 5 minutes. The reaction mixture was then neutralised by shaking with Ag_2O, filtered and evaporated *in vacuo.* The residue was crystallised from propyl alcohol-diethyl ether (1:1) giving *monomethylol urea* n-*propyl ether* in colourless needles, m.p. 86.5—87.5°C.

Monomethylol urea iso*propyl ether* was crystallised from *iso*propyl alcohol-diethyl ether (1:1) giving colourless plates, m.p. 103°C.

	H	N	C
Calculated for $C_5H_{12}O_2N_2$	9.15	21.18	45.43
Found for *n*-propylether	9.08	21.12	45.52
Found for *i*-propylether	9.11	21.33	45.41

N,N-dimethyl-N'-methylol urea methyl ether (m.p. 66°C) was prepared from N,N-dimethyl-N'-methylol urea by a similar procedure as was used for monomethylol urea methylether.

N-methylol benzamide methyl ether has hitherto not been reported in the literature. It was prepared as follows: 5 g N-methylol benzamide were dissolved in 10 ml methyl alcohol at room temperature and 5 drops of conc. HCl were added. After standing for 10 min. at room temperature the solution was neutralised with an excess of Ag_2O, and after filtration the solution was cooled to 0°C. Long, prismatic, colourless crystals separated out and were recrystallised from ether. M.p. 73—74°C. (Found: C 65.47; H 6.68; N 8.57. Calc. for $C_9H_{11}O_2N$: C 65.45; H 6.67; N 8.48).

Isolation of urea after hydrolysis of the ether

208 mg of the methyl ether of monomethylol urea were dissolved in 40 ml of an alkaline KCN solution (0.24 N NaOH, 0.1 N KCN) and the solution was left to stand at room temperature for 24 hours. Then 12 ml of concentrated acetic acid and 12 ml of a 10 % solu-

tion of xanthydrol in ethyl alcohol were added. After 4 h the white finely crystalline precipitate was filtered off, washed 3 times with alcohol and dried at 60°. Yield: 762 mg. Calculated for $C_{27}H_{20}O_3N_2$: 840 mg. In a separate experiment, with the same time of hydrolysis for the ether, a titration was made with $Hg(NO_3)_2$ and 97.1 % of the theoretical amount of formaldehyde was found.

The decomposition of an ether at pH 11-12 and 25°C

The reaction medium was made up of 100 ml Na_2HPO_4 solution (1 M) 50 ml KCN (0.1 N) and a certain volume of NaOH solution (2 N). It was diluted to 200.0 ml with water (the amount of NaOH was variable depending upon the pH value of the solution required). This mixture was transferred into a well stoppered erlenmeyer flask which was placed in a thermostat at 25°C. A weighed amount of the finely powdered ether was added to the solution and dissolved by vigorous shaking. The time when the ether was added was taken as zero time for the kinetic run. A sample of this solution was taken and the pH carefully measured.

In order to follow the decomposition of the ether, samples of 30 ml were drawn out of the solution after suitable time intervals. 5 drops of diphenyl carbazone solution were added and the solution was then acidified with 2 N HNO_3 to the appearance of a faint orange-yellow colour (pH 5—4). The solution was then at once titrated with 0.1 N $Hg(NO_3)_2$ from a micro burette. The time when HNO_3 was added was taken as the time of sampling.

The decomposition of an ether in NaOH solution at 0°C

Solutions were made up consisting of 2 N NaOH, 10 ml 0.1 N KCN and diluted to 50.0 ml with water. The mixture was brought into an erlenmeyer flask which was placed in ice-water. When the temperature of the mixture had reached 0°C, 52 mg of finely powdered methoxymethyl urea were added and dissolved immediately on shaking the mixture.

After a certain time the reaction was stopped by neutralising the mixture with a solution containing as much HNO_3 as is equivalent to the NaOH in the sample and 20 ml of a phosphate buffer (0.5 M KH_2PO_4 + 0.5 M Na_2HPO_4). The excess KCN was determined with $Hg(NO_3)_2$ as described earlier.

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