Kinetics & Mechanism of Reactions of Amides with Formaldehyde

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Kinetics of the reactions of substituted ureas like methylurea, phenylurea, acetamide and benzamide with formaldehyde have been studied, using a TLC method developed for the purpose. The increased reactivity of methylurea towards formaldehyde, as compared to urea, is due to the electron-releasing nature of the methyl group. The reduced reactivity of phenylurea is due to the electron-withdrawing nature of the phenyl group. The reduced reactivity observed in the case of acetamide and benzamide is also explained.

The kinetics of reactions leading to the formation of methylolurea and methyleneureas in urea-formaldehyde reaction have been recently investigated using a quantitative TLC method. Similar studies have now been carried out on the reactions of substituted ureas, like methylurea, phenylurea, acetamide and benzamide with formaldehyde, with a view to elucidating the effect of substituents on the course of the reaction.

Formalin (38% BDH, AR), containing less than 2% methanol was used. Methylurea (MeU) (BDH, AR) was recrystallised from water, m.p. 102. Mono-methylolmethylurea (MMMeU) was prepared as follows:

A mixture of methylurea (7.4 g) and formaldehyde (8 ml) was stirred along with potassium carbonate to bring the pH to 9. The reaction mixture was kept at room temperature for 2 hr and for 48 hr at O°. The crystals of MMMeU formed were decanted from the viscous liquid and recrystallised from ethanol twice, m.p. 122-25°.

Phenylurea (PhU) (BDH, AR) was recrystallised from ethanol, m.p. 147°. Methylenebisphenylurea (MeBPhU) was prepared as follows:

A solution of phenylurea (13.6 g) in 1, 4-dioxane (100 ml) was stirred with formaldehyde (4 ml) and hydrochloric acid (0.5 ml). After 30 min, MeBPhU separated out as a white solid which was filtered, washed with water and recrystallised from 1, 4-dioxane, m.p. 81°.

Acetamide (A) (BDH, AR) was recrystallised from water, m.p. 81°. Monomethylolacetamide (MMA), m.p. 51°, and methylenebisacetamide (MeBA), m.p. 199-201° were prepared as reported earlier.

Benzamide (B) (BDH, AR) was recrystallised from ethanol, m.p. 130°. Monomethylolbenzamide (MMB), m.p. 108-109, and methylenebisbenzamide (MeBB), m.p. 222-242° were also prepared by the method as reported earlier. The structures of the compounds, viz. MMMeU, MeBPhU, MMA, MeBA, MMB and MeBB were compatible with their IR and PMR spectra.

Kinetics of all reactions, except acetamide-formaldehyde reaction were followed by estimating the unreacted formaldehyde alone by the sulphite method and sum of the free formaldehyde and methylols by the iodimetric method. In the reaction of acetamide with formaldehyde, the free formaldehyde was estimated by the hydroxylamine hydrochloride method since in the sulphite method large amount of sodium hydroxide, liberated when free formaldehyde reacted with sodium sulphite solution, hydrolysed the acetamide and its compounds to acetic acid. Due to the poor solubility of benzamide, methylenebisbenzamide, phenylurea and methylenebisphenylurea in water, a mixture of water and 1, 4-dioxane was used as the solvent.

Quantitative analysis of the reaction products of acetamide and benzamide with formaldehyde was carried out using quantitative TLC. In the case of methylurea and phenylurea the reaction products were estimated as follows: The reaction was arrested and the unreacted formaldehyde destroyed with aq. sodium bisulphite as reported earlier. A portion (20 μl) of the resulting reaction mixture was spotted on a silica gel G plate, dried at room temperature and developed in suitable solvents. Methylurea and monomethylolmethylurea were separated using 1-butanol and phenylurea, monomethylolphenylurea and methylenebisphenylurea were separated using ethyl acetate as eluting solvent. The plates were dried for 15 min at room temperature and spots developed by spraying with phenylhydrazine sulphate-ferric chloride. The spots were removed and estimated colorimetrically by the diacetylmonoxime method using a Systronics 103 spectrophotometer. The accuracy of the method was ±2%.

The main reaction steps involved in the present investigation are given by Eqs (1) and (2)

\[ R - \text{NH}_2 \text{CONH}_2 + \text{CH}_2\text{O} \rightarrow \text{RNHCONHCH}_2\text{OH} \]

\[ 1 + \text{RNHCONH}_2 \rightarrow \text{RNHCONHCH}_2\text{NHCONHR} \]

... (1)
Table 1—Second Order Rate Constants \((k)\), Activation Energy \((E)\) and Relative Reactivity Ratios for Various Amide-Formaldehyde Reactions at Various \(pH\) Values

<table>
<thead>
<tr>
<th>Amide</th>
<th>(pH)</th>
<th>(k \times 10^4) dm(^3)rnol(^{-1})s(^{-1}) at</th>
<th></th>
<th>(E_a) kJmol(^{-1})</th>
<th>Relative Reactivity Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>20</td>
<td>30</td>
<td>40</td>
<td>50</td>
<td>60</td>
</tr>
<tr>
<td>U(^2)</td>
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<td></td>
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<td></td>
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<td>U(^2)</td>
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<td></td>
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<td></td>
<td>0.93</td>
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<td></td>
<td>1.13</td>
<td></td>
</tr>
<tr>
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<td></td>
<td>15.95</td>
<td></td>
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<tr>
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<td></td>
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<td></td>
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<tr>
<td>PhU(^*)</td>
<td>3.7</td>
<td></td>
<td></td>
<td>0.14</td>
<td></td>
</tr>
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</table>

*First order rate constants \((s^{-1})\).†Reactivity of one primary amine nitrogen in urea is taken as unity.

\[ \text{CH}_2\text{O} + \text{RCONH}_2 \rightleftharpoons \text{RCONHCH}_2\text{OH} \]

II

\[ \text{II} + \text{RCONH}_2 \rightarrow \text{RCONHCH}_2\text{NHCOR} \ldots (2) \]

\((R = -\text{CH}_3 \text{ or } -\text{C}_6\text{H}_5)\)

The rate constants and activation energy values are summarised in Table 1. The methyl substituent in urea increases the rate of reaction with formaldehyde ten times at \(pH 7\) and four times at \(pH 2.5\) at 30°C. But under alkaline condition \((pH = 9)\) at 30°C, the increase is nearly 26 times. The increased reactivity of methylurea towards formaldehyde, as compared to urea, can be attributed to the electron-releasing nature of the methyl group. The lower rate under acid \(pH\) in comparison to alkaline \(pH\) may be due to the fact that (i) the free base concentration is reduced by protonation in acid \(pH\) (Eq. 3)

\[ \text{CH}_3\text{NHCONHz} + \text{H}^+ \rightarrow \text{H}_3\text{NHCONH}_2 \ldots (3) \]

and (ii) in alkaline \(pH\) the electron-releasing \(\text{CH}_3\) group facilitates the formation of the anion (Eq. 4)

\[ \text{CH}_3\text{NHCONHz} + \text{OH}^- \rightarrow \text{CH}_3\text{NHCONH}_2^- + \text{H}_2\text{O} \ldots (4) \]

and hence the rate of addition of formaldehyde is increased.

Since the reaction of phenylurea with formaldehyde directly results in the formation of \(\text{MeBPhU}\), a direct comparison of the rate constants with those of urea or methylurea cannot be made. But first order rate constants calculated for the disappearance of formaldehyde show that reactivity of phenylurea towards formaldehyde is only approximately 0.3 times that of urea. This reduced reactivity of phenylurea is due to the electron-withdrawing nature of the phenyl group.

When one of the amino groups in urea is replaced by \(-\text{CH}_3\) group (as in acetamide) and by \(-\text{C}_6\text{H}_5\) group (as in benzamide) the rate of reaction of the respective amide is reduced considerably. For acetamide the rate decreases to 1/400th of that of urea at \(pH 3.5\) and 60°C. But for the benzamide the rate decreases to 1/8th of that of urea under the same conditions.

IR and PMR spectra of the amides indicate that the amides are resonance hybrids and the \(\text{C} \rightarrow \text{N}\) bond has a partial double bond character. These are feebly basic and combine with acids (protons) to form salts. PMR studies show that the salt of acetamide is protonated on the oxygen atom. This would be in agreement with the fact that amides are resonance hybrids, the oxygen carrying a negative charge and the nitrogen a positive charge. In acetamide the amino group is deactivated since nitrogen is positively charged and oxygen negatively charged. In addition, in acid medium the oxygen of acetamide is protonated.
and nitrogen is permanently becoming positive even though $-\text{CH}_3$ group is slightly electron-donating. Hence the attack by the methylol carbonium ion at the amino group is inhibited and the rate of the reaction is much reduced. In benzamide the amino group is deactivated to a lesser extent as compared to acetamide, since the strongly electron-attracting carbonyl group which is in conjugation with the benzene ring causes electron displacement away from the nucleus and towards the carbonyl group ($-\text{R effect}$). In acid medium the negatively charged oxygen will be protonated and amino group will be free for reaction. Therefore, the rate of its reaction with formaldehyde is not much reduced as compared to urea-formaldehyde reaction. Small decrease in rate may also be explained as due to mild inductive effect of benzene ring.

References