Kinetics & Mechanism of Acid Hydrolysis of Formamide, Acetamide, Propanamide & Butanamide over an Extended Concentration Range: Kinetic Evidence for Fast Protonation Pre-equilibrium

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Received 3 July 1981; revised 24 October 1981; accepted 18 November 1981

The rates of HCl catalysed hydrolysis of formamide, acetamide, propanamide and butanamide under pseudo-first order conditions obey Michaelis-Menton type rate law,

\[
- \frac{d[H^+]}{dt} = kK[H^+][\text{Amide}] \quad \text{at } 1 + k[\text{Amide}]
\]

which is in conformity with the accepted mechanism depicted below:

\[\begin{align*}
K & \quad \text{RCONH}_2 + H^+ \Leftrightarrow [\text{RCONH}_2]^+ \quad \text{(rapid)} \\
\quad & \quad \text{[Amide.H]^+} \Leftrightarrow \text{products, (slow)} \quad \text{(2)}
\end{align*}\]

The protonation pre-equilibrium (1) is evident from the fact that a maximum rate is obtained at some high concentration of the acid in the hydrolysis of several aliphatic and aromatic amides\(^1-3\), the maximum corresponding to the complete protonation of the amide present in the system.

Under the condition, [Amide] \(\gg [H^+]\), the mechanistic paths (1) and (2) would lead to the rate law (3) which is of familiar Michaelis-Menton type\(^6\). In the studies so far made\(^5-13\) amide concentration was varied over a limited range and rate law (3) was not obeyed but rate law (4) was found to hold good.

\[
- \frac{d[H^+]}{dt} = kK[H^+][\text{Amide}] \\
\text{rate} = k_2[\text{Amide}][H^+] 
\]

Previously, several groups of workers have studied the acid hydrolysis of formamide\(^8-12\), acetamide\(^2,9,10,12-17\), propanamide\(^9,11,12,15\) and butanamide\(^12\) under second order conditions and wherever the results of the present study overlap with those of previous workers, the agreement is found to be excellent.

Materials and Methods

Formamide (BDH, LR) was distilled before use. Acetamide (BDH, LR), propanamide and butanamide (Fluka) were used as such. All the amides were standardised by hydrolysing their known amounts and determining the ammonia content by Sorenson's formol titration method\(^18\).

The stock solutions of the amides were prepared in conductivity water and checked for the presence of ammonium ions which might be present as an impurity. Wherever necessary a blank correction was made, particularly at higher concentrations of amides.

The reactions were carried out in stoppered conical flasks. The reactions were initiated by mixing temperature pre-equilibrated solutions of amides and HCl and the kinetics were followed by taking samples at definite time intervals and analysing them for ammonia\(^19\). The results were reproducible within \(\pm 5\%\).

Results and Discussion

Formamide — In all kinetic runs [HCONH\(_2\)] was at least 10 times that of [HCl]. Since formamide is miscible with water in all proportions, a variation in its concentration over the range (1-20\(M\)) at fixed 0.1M HCl was possible. From first order plots the values of pseudo first order constants, \(k_{obs}\), were
obtained and a plot of these values versus corresponding [HCONH₂] is given in Fig. 1. It is seen that on increasing [HCONH₂], the rate of hydrolysis initially increases attaining a maximal value \( \approx 16M \) and thereafter decreases with further increase in [HCONH₂].

From a double reciprocal plot of \( k_{\text{obs}} \) and [HCONH₂], which was linear (Fig. 2), the values of \( k \) and \( K \) were found to be \( 5 \pm 0.5 \times 10^{-3} \) litre mol⁻¹ sec⁻¹ and \( 5.5 \pm 0.5 \times 10^{-2} \) litre mol⁻¹ respectively at 30°.

**Acetamide, propanamide and butanamide** — Under pseudo-order conditions with excess [amide] the kinetics were first order. At a fixed 0.1M HCl, and appropriate temperature, the [amide] was varied between 1-6M the maximum concentration for each amide being limited by its solubility in water. The plots of \( 1/k_{\text{obs}} \) and \( 1/[\text{Amide}] \) were linear (Figs 3 and 4) from which the values of \( k \) and \( K \) were obtained (Table 1).

The kinetic results obtained in the present investigation with regard to the variation of [amide] under pseudo-first order conditions conform to the rate law (3) which is of familiar Michaelis-Menton type and therefore support the accepted mechanism as given by Eqs (1) and (2). The pre-equilibrium (1) was proposed on the basis of ester hydrolysis14.

The present work provides a direct kinetic evidence for it. The present work also affords a kinetic method for the evaluation of \( K \) and \( k \).

The results of varying [formamide] over the range 1-20M are unusual and interesting because the plot of \( k_{\text{obs}} \) versus [HCONH₂] passes through a maximum. Since for other three amides such a large variation in [amide] is not possible one cannot say whether similar results would be obtained in other cases too. The results obtained for varying [formamide] are similar to those obtained earlier13,11 based on varying [acid] except that the maximum in the case of formamide occurs at a much larger [formamide] \( \approx 16M \) as compared to maximum at [acid] = 6M (see ref. 11). This difference can probably be ascribed to considerable hydration of hydrogen ions in concentrated acid solutions which decreases the water activity significantly and the
Kinetics of Acid Hydrolysis of Amides

The variation in [amide], in principle, affects equilibrium (1) up to the maximum in Fig. 1. The decrease in rate after the maximum can be ascribed to the decrease in the water activity since a 20 M solution of HCONH₂ consists of nearly 80% formamide. This explanation is rather too simple, since the variation of [formamide] in the higher concentration range is accompanied by drastic changes in the medium.

A perusal of the data in Table 2 clearly shows that the values of K as determined kinetically and as determined by other methods are in agreement for all the amides. In the case of acetamide the K values obtained at three temperatures are in good agreement with those values obtained at these temperatures by other methods (Table 2). For propanamide and butanamide despite a large difference in temperatures the K-values from kinetic and spectrophotometric methods are not much different. For benzamide, the K values are found to be same by the two methods at 25 and 50°. The equilibrium (1) thus appears to be thermoneutral i.e. ΔH = 0. This fact is in agreement with the reported observation that the temperature effects on the protonation equilibria in the hydrolysis of amides and their derivatives are very small. In view of this, temperature dependence of K for propanamide and butanamide has not been studied. In the rate law (3) under second order conditions, so it reduces to (5).

\[
\text{Rate} = kK [\text{H}^+] [\text{Amide}].
\]

A comparison of Eqs (5) and (4) shows that

\[
k_s = kK
\]

A comparison of k_s and kK values (Table 1) shows this to be true.

As the acid hydrolysis of amides is a two step process [(1) and (2)], changing alkyl group from H in HCONH₂ to n-C₃H₇ in butanamide would affect the magnitude of both k and K and hence it is the net effect which would be observed. However the polar influences for the acid catalysed hydrolysis of acid derivatives have been found to be small because an A-2 reaction is controlled by two factors which respond differently to polarity. The introduction of a more electron releasing group would accelerate the conversion of amide substrate to its conjugate acid and the magnitude of K is increased. On the other hand the substitution of such a group would slow down the step (2) because the coordination of nucleophile water with RCONH₂ would be more difficult. Hence k is expected to decrease from HCONH₂ to n-C₃H₇CONH₂. As predicted there is a sudden increase in the value of K in going from HCONH₂ to C₆H₅CONH₂. Thereafter the values of K do not change much. A similar trend is found in the dissociation constants of parent acids of these amides. On the other hand as expected the value of k continuously decreases along the series.

### Table 1: Rate Parameters and Entropies of Activation for the Acid Hydrolysis of Amides

<table>
<thead>
<tr>
<th>Amide</th>
<th>10^4k (eq. 3)</th>
<th>K(eq. 3)</th>
<th>10^4kK</th>
<th>10^4k_s (eq. 4)</th>
<th>ΔS^‡_K</th>
<th>ΔS^‡_s</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>litre mol⁻¹ sec⁻¹</td>
<td>litre mol⁻¹</td>
<td>litre mol⁻¹ sec⁻¹</td>
<td>cal mol⁻¹ deg⁻¹</td>
<td>cal mol⁻¹ deg⁻¹</td>
<td></td>
</tr>
<tr>
<td>Formamide</td>
<td>30 ± 5 (30°)</td>
<td>0.055 ± 0.005 (30°)</td>
<td>2.75</td>
<td>2.7</td>
<td>-5.9</td>
<td>-2.1</td>
</tr>
<tr>
<td></td>
<td>74 (60°)²</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acetamide</td>
<td>11 ± 0.5(60°)³</td>
<td>0.33 ± 0.02(60°)³</td>
<td>6.66</td>
<td>6.3³</td>
<td>-2.2³</td>
<td>-1.8³</td>
</tr>
<tr>
<td>Propanamide</td>
<td>1.3 ± 0.05(40°)³</td>
<td>0.41 ± 0.04(40°)³</td>
<td>0.53</td>
<td>0.45³</td>
<td>-1.8³</td>
<td>-20.3³</td>
</tr>
<tr>
<td>Butanamide</td>
<td>7.1 ± 0.5 (60°)³</td>
<td>0.35 ± 0.01(60°)³</td>
<td>2.5</td>
<td>2.80³</td>
<td>-2.1³</td>
<td>-19.5³</td>
</tr>
</tbody>
</table>

(a) calculated; (b) reference (14); (c) reference (13); (d) reference (12); (e) determined at [Butanamide] – [HCl] = 0.5M;
(1) calculated assuming ΔH = 0 for step (1); (g) reference (17).
TABLE 2 — VALUES OF PROTONATION CONSTANTS FOR THE EQUILIBRIUM: RCONH₂ + H⁺ ⇌ [RCONH₃]⁺

<table>
<thead>
<tr>
<th>Method</th>
<th>Temp. °C</th>
<th>K · 10⁻¹⁰ litre mol⁻¹</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FORMAMIDE</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kinetic</td>
<td>30</td>
<td>5.0 · 10⁻⁴</td>
<td>This work</td>
</tr>
<tr>
<td>NMR</td>
<td>33.5</td>
<td>1.0 · 10⁻⁴</td>
<td>(21)</td>
</tr>
<tr>
<td><strong>ACETAMIDE</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kinetic</td>
<td>55</td>
<td>0.30</td>
<td>(14)</td>
</tr>
<tr>
<td>Do</td>
<td>60</td>
<td>0.33</td>
<td>(14)</td>
</tr>
<tr>
<td>Do</td>
<td>65</td>
<td>0.36</td>
<td>(14)</td>
</tr>
<tr>
<td>Do</td>
<td>60</td>
<td>0.33</td>
<td>(5)</td>
</tr>
<tr>
<td>Spectrophotometric</td>
<td>25</td>
<td>0.42</td>
<td>(22)</td>
</tr>
<tr>
<td>Do</td>
<td>25</td>
<td>0.37</td>
<td>(23)</td>
</tr>
<tr>
<td>Potentiometric</td>
<td>25</td>
<td>0.31</td>
<td>(24)</td>
</tr>
<tr>
<td><strong>PROPANAMIDE</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kinetic</td>
<td>40</td>
<td>0.41</td>
<td>This work</td>
</tr>
<tr>
<td>Spectrophotometric</td>
<td>25</td>
<td>0.31</td>
<td>(23)</td>
</tr>
<tr>
<td><strong>BUTANAMIDE</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kinetic</td>
<td>60</td>
<td>0.35</td>
<td>This work</td>
</tr>
<tr>
<td>Spectrophotometric</td>
<td>25</td>
<td>0.27</td>
<td>(23)</td>
</tr>
</tbody>
</table>

It has been argued that for A-2 mechanism\textsuperscript{26,27}, e.g. the acid hydrolysis of amides, the entropy of activation, \(\Delta S^‡\), for the equilibrium step (1) should have a low value and that the overall entropy of activation, \(\Delta S^‡_K\), is largely due to second step. This is clearly borne out by the data given in Table 1. Except for HCONH₂⁺, the value of \(\Delta S^‡\) is about -2 cal mol deg⁻¹ for all other amides. The more negative \(\Delta S^‡_K\) (-6 cal mol deg⁻¹) for formamide may be due to solvation effects\textsuperscript{27}.

References