Kinetics and Mechanism of the Pyrrolidinolysis of N-Substituted Phthalimides in Non-Aqueous Solvents

Yoke-Leng Sim*, Wan Hamdah Wan Ahmad and M. Niyaz Khan
Department of Chemistry, Faculty of Science, University of Malaya, 50603 Kuala Lumpur, Malaysia.

Abstract:

Pseudo-first-order rate constants (k_{obs}) for the reactions between pyrrolidine and N-(2-methoxyphenyl)phthalimide (2) as well as N-(4-nitrophenyl)phthalimide (3) in the absence and presence of DABCO in CH$_2$CN and THF, showed upward curvature with the increase in [pyrrolidine]. These observations indicate that pyrrolidine is acting as a nucleophile as well as a general base catalyst in the cleavage of these imides. The k_{obs} values for the pyrrolidinolysis of 2, in the presence of CH$_2$CN, are larger than that in THF under comparable reaction conditions. Similar observations were obtained for 3 with pyrrolidine. The values of k_{obs} decreased slightly with the addition of DABCO into the reaction mixture for both 2 and 3 in CH$_2$CN. Spectrophotometric product characterization coupled with HPLC studies showed the formation of N,N-disubstituted diamide as the final product from the pyrrolidinolysis of imides.

Objectives:

1. Develop the analytical method(s) for the determination of rate law for amine-catalyzed reactions with imides in non-aqueous solvents.
2. Investigate the kinetics and mechanism of amine-catalyzed reactions with imides in non-aqueous solvents.
3. Determine the types of molecular interactions and possible catalysis occurring in the aminolysis of imides in non-aqueous solvents.

Results:

Pseudo-first-order rate constants, k_{obs}, obtained within a range of [Ami], for 2 and 3 were fitted into Eqs (3) and (4), where [Ami]$_0$ represents total pyrrolidine concentration, k$_r$ and k$_o$ represent respective second-order rate constant and third-order constant for amine assisted cleavage of imide.

\[
k_{obs} = \frac{k_r \cdot [Ami]_0 + k_o \cdot [Ami]^2}{[Ami]_0}
\]

(3)

(4)

Table 1. Values of Rate Constants, k$_r$ and k$_o$, Calculated from Equation 3 for the Cleavege of N-Substituted Phthalimides in Non-Aqueous Solvents.

<table>
<thead>
<tr>
<th>Substrate</th>
<th>[Pyrro]$_0$ range M</th>
<th>[DABCO] M</th>
<th>10$^9$ k$_r$</th>
<th>10$^9$ k$_o$</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>0.20 – 1.00</td>
<td>0.10</td>
<td>4.30 ± 0.9</td>
<td>3.74 ± 1.03</td>
</tr>
<tr>
<td>3</td>
<td>0.20 – 1.00</td>
<td>0.05 – 0.75</td>
<td>4.46 ± 0.41</td>
<td>1.43 ± 0.51</td>
</tr>
<tr>
<td>3</td>
<td>0.20 – 1.00</td>
<td>0.10</td>
<td>59.3 ± 17.0</td>
<td>517 ± 27</td>
</tr>
<tr>
<td>3</td>
<td>0.20 – 1.00</td>
<td>0.05 – 0.75</td>
<td>30.0 ± 18.3</td>
<td>578 ± 22</td>
</tr>
<tr>
<td>3</td>
<td>0.20 – 1.00</td>
<td>0.05 – 0.75</td>
<td>152 ± 7</td>
<td>106 ± 13</td>
</tr>
<tr>
<td>3</td>
<td>0.20 – 1.00</td>
<td>0.05 – 0.75</td>
<td>170 ± 7</td>
<td>70.0 ± 17.3</td>
</tr>
</tbody>
</table>

Discussion:

2 + pyrrolidine

% k$_r$, contribution at [Ami]$_0$ = 0.50M:

CH$_2$CN = 70%  
CH$_2$CN + DABCO = 89%  
THF = 92%

- Pyrrolidine acts as a main nucleophile in the reaction.
- Methoxy group creates steric hindrance to the reactive site of 2.
- Electron-withdrawing property of 2-OCH$_3$ by resonance destabilizes the partial negative charges developed in the TS.
- Pyrrolidine acts as a nucleophile to carbonyl carbon of 3 as well as a general base catalyzing the reaction.
- Electron-withdrawing property of 4-NO$_2$ by inductive and resonance effects destabilized the TS, helped to facilitate the proton transfer at TS to form product.
- Increasing the k$_o$ to > 13 fold as compared to 2.
- Another pyrrolidine acts as a general base catalyst, encourage charge transfer to occur as shown in TS1, hence weakening the C-N bond.
- Increasing the k$_r$ to > 30 fold as compared to 2.

3 + Pyrrolidine

% k$_r$, contribution at [Ami]$_0$ = 0.50M:

CH$_2$CN = 19%  
CH$_2$CN + DABCO = 0%

- Pyrrolidine behaves as a stronger base in THF compared to CH$_2$CN → slight increase in nucleophilicity of pyrrolidine nitrogen in THF: observed slight decrease of k$_o$ in THF by nearly 4 fold.

Inhibition shown by DABCO is only due to the steric hindrance created by DABCO at the reactive sites (C=O) of 2 and 3.

Kinetic Measurements:

The reaction rates were studied spectrophotometrically by monitoring the appearance of cleavage product of 2 at 290nm and the disappearance of 3 at 320nm as a function of time. Kinetic parameters, k_{obs}, δ$_{Ami}$, A$_0$ or A$_n$, were calculated from Eqs (1) and (2), for appearance of product of 2 and disappearance of 3, respectively. In Eqs (1) and (2), A$_n$ is observed absorbance of the reaction mixture at any reaction t, δ$_{Ami}$ is apparent molar extinction coefficient of the reaction mixture, [Ami] = initial concentration of 2 or 3, A$_0$ = A$_n$ at t = 0 and A$_n$ = A$_{Ami}$ at t = ∞. The reactions were generally carried out for reaction period of 7 halflives.

\[
A_{Ami} = \frac{\delta_{Ami} \cdot [R]_0 \cdot [1 - \exp(-k_{obs} \cdot t)] + A_0}{\exp(-k_{obs} \cdot t) + A_0}
\]

(1)

\[
A_{Ami} = \frac{\delta_{Ami} \cdot [R]_0 \cdot [1 - \exp(-k_{obs} \cdot t)] + A_0}{\exp(-k_{obs} \cdot t) + A_0}
\]

(2)

Figure 1. The plots showing the dependence of k_{obs} versus [Ami], for the cleavage of 2 and 3 where Ami represents pyrrolidine, in the presence of MeCN (○), THF (■) and DABCO in MeCN (▲) for 2 as well as MeCN (●), THF (▲) and DABCO in MeCN (△) for 3, respectively. The solid lines are drawn through the calculated data points using Eq (3) as described in the text.

Scheme 1

Concerted mechanism: pyrrolidine acts as a nucleophile attacking the carbonyl carbon of 2 and 3 forming of a stable product, N,N-disubstituted phthalalimide.

* facilitated by electron-withdrawing group

● partial negative charge developed at the reaction site in the TS → TS is more polar than reactant state

Conclusion:

- Remarkable 13 – 130 fold larger k$_r$ and k$_o$ increasing for pyrrolidinolysis of 3 compared to that of 2.
- Significant polar effect exhibited by 4-NO$_2$ as well as active participation of 4-NO$_2$ substituent in the TS in 3.
- 4-NO$_2$ of 3 is acting as intramolecular general base catalyst and a second pyrrolidine acting as intermolecular general base catalyst in the pyrrolidinolysis of 3.


Acknowledgement: University of Malaya Research Grant UMBRG (Grant No. RG-091/10AFR).