KINETICS AND MECHANISM OF AMINOLYSIS OF
*p*-NITROPHENYL ACETATE IN MIXED WATER-
ACETONITRILE SOLVENTS

NOR SALMI BINTI ABDULLAH

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ABSTRACT

First chapter deals with the literature review of amino alcohols and their derivatives, as well as kinetics and mechanism of aminolysis of esters. The uses of these compounds in biological, pharmacological, synthesis, industries and applied chemistry were discussed briefly. The literature search on some available methods for the synthesis of amine derivatives and esters such as \(N,N\)-(diethylaminomethyl)benzyl alcohol (35) and \(p\)-nitrophenyl acetate (26) is described.

Chapter two reports the experimental details on the syntheses and characterization of \(N,N\)-(diethylaminomethyl)benzyl alcohol (35), \(N,N\)-diethylphthalamic acid (34), 2-((diethylamino)methyl)benzyl acetate (42), \(N\)-benzylacetamide (44) and \(N,N\)-diethylacetamide (45).

Chapter three provides a brief introduction of chemical kinetics and common methods of carrying out the kinetic studies. General procedures in determining suitable wavelength (\(\lambda\)) for kinetic studies have been discussed. Some experimental details of product characterization using Reverse-phase High Performance Liquid Chromatography have been also described. The results have been divided into four parts according to the types of amines.

Final chapter contains the results of aminolysis of 26. These results are classified into four major parts, 1) primary amines, 2) secondary amines, 3) tertiary amines and 4) amino alcohols (tertiary amines). The aminolysis of 26 with primary and secondary amines gave an amide and \(p\)-nitrophenolate ion (48), while the hydrolysis of 26 with tertiary amines and amino alcohol gave acetic acid and 48. The aminolysis of 26 with a series of amines (methylamine, \(N,N\)-dimethylamine, \(N,N\)-diethylamine, benzyamine, \(N,N\)-methylbenzylamine, \(N,N\)-ethylbenzylamine, \(N,N\)-
dimethylbenzylamine and \(N,N\)-(diethylaminomethyl)benzyl alcohol) have been studied in mixed aqueous solvent containing 50 \% v/v acetonitrile. The kinetics of aminolysis of 26 in the presence of amine buffers at 0.3 M or 0.4 M ionic strength have been discussed in terms of the following reaction scheme 1:

\[
\begin{align*}
C + E & \xrightleftharpoons[k_0][k_1] B \\
& \xrightarrow{k_1[A]} C + D
\end{align*}
\]

Scheme 1

where A = free amine base, B = 26, C = 48, D = amide, E = acetic acid. In case of tertiary amine and amino alcohol, the final product gave 48 and acetic acid. In most cases, the plot of \(k_{obs}\) versus total amine buffer concentration gave straight line with ~ zero intercepts. The aminolysis of 26 under buffers of primary and secondary amines revealed a bronsted plot of \(\beta_{nac} = 0.91 \pm 0.20\).
ABSTRAK

Bab pertama, mengumpulkan maklumat-maklumat daripada rujukan berkenaan dengan sebatian amino alkohol, ester dan terbitannya, disamping kinetik dan mekanisma aminolisis ester. Turut membincangkan berkenaan kegunaan sebatian ini dalam bidang biologi, farmakologi, sintesis, industry dan kimia gunaan. Beberapa kaedah sintesis sebatian N-tertukar ganti amino alkohol dan ester seperti N,N- (dietilaminometil)benzil alkohol dan p-nitrophenil acetat dan N-tertukar ganti acetat turut dibincangkan.

Bab kedua menjelaskan secara terperinci langkah-langkah eksperimen untuk mensintesis sebatian dan pengenalpastian spektroskopi sebatian berikut: N,N- (dietilaminometil)benzil alkohol (35), N,N-dietilfthlamic asid (34), 2-((dietilamino)metal)benzil acetat (42), N-benzilacetamida (44) dan N,N-dietilacetamida (45).


Bab terakhir mengadungi keputusan hasil daripada aminolisis 26. Keputusan dibahagikan kepada tiga bahagian iaitu 1) amina primer, 2) amina sekunder, 3) amina tertiari dan 4) amino alkohol. Aminolisis 26 dengan amina primer dan sekunder memberikan amida dan 48 sebagai hasil akhir, manakala hidrolisis 26 dengan amina ketiga dan amino alkohol memberikan asid asetik dan 48. Aminolisis 26 dengan
beberapa siri amina seperti (metilamina, \(N,N\)-dimetilamina, \(N,N\)-dietilamina, benzilamina, \(N,N\)-metilbenzilamina, \(N,N\)-etilbenzilamina, \(N,N\)-dimetilbenzilamina dan \(N,N\)-(dietilaminometil)benzil alkohol) dijalankan didalam campuran pelarut akues yang mengandungi 50 \% v/v acetonitril. Kinetik bagi aminolisis 26 dengan kehadiran amina pada kepekatan 0.3 M atau 0.4 M dibincangkan dalam terma seperti skema 1:

\[
\begin{align*}
\text{C} + \text{E} & \quad \xrightarrow{k_0[\text{HO}^-]} \quad \text{B} \\
& \quad \xrightarrow{k_1[\text{A}]} \quad \text{C} + \text{D}
\end{align*}
\]

Skema 1

dimana A = amina, B = 26, C = 48, D = amida dan E = asid asetik. Dalam kebanyakan kes, plot \(k_{\text{obs}}\) melawan kepekatan amina memberikan graf garis lurus dengan pintasan menghampiri kosong. Tindak balas aminolisis 26 dalam kehadiran amina primer dan sekunder memberikan plot Bronsted dengan kecerunan \(\beta_{\text{nuc}} = 0.91 \pm 0.20\).
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The work presented in this these would not have been possible the help of a great number of people. Most of all, I want to express my gratitude to my supervisors, Associate Prof. Dr. Azhar Bin Ariffin and Prof. Mohammad Niyaz Khan for their help, encouragement, support and advice over the whole duration of this research. They always available when needed and willing to review my research work and schedule from time to time. I gratefully acknowledgement my indebtedness to my supervisors for many valuable and inspiring ideas as well as comments of the original manuscript of this thesis. A millions thanks to Dr. Azhar, for his kindness, the opportunities and trust he gave to me. Only Allah can pay for their helps.

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Thank you so much
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**Figure 4-6:** Plot of pH versus ln [NaOH] for determination of [OH$^-$] at 50 % CH$_3$CN : 50 % H$_2$O v/v, µ = 0.4 M and T = 30° C. The solid line is drawn using
empirical Eq. (4-7).

Figure 4-7: Plots of $k_b/f_b$ versus $[\text{OH}^-]$ for aminolysis of 26 in the presence of primary amines: 49 ($\blacktriangle$), 43 ($\triangle$) and 43 ($\bigodot$) respectively. The solid line are drawn through the calculated data points using Eq. (4-5) as described in text. $^a \mu = 0.4 \text{ M}$, $^b \mu = 0.3 \text{ M}$.

Figure 4-8: Plots of pseudo-first order rate constant $k_{obs}$ versus $[\text{Am}]_T$ at different pH for aminolysis of 26 with $[\text{Am}]_T = [50]_T$ is $= 0.4$ at pH 10.05 (■), 10.20 ($\blacktriangle$), 10.29 ($\bigodot$), 10.32 (□) and 10.66 ($\Delta$) respectively. The solid line are drawn through the calculated data points using Eq. (3-15) as described in the text.

Figure 4-9: Plots of pseudo-first order rate constant $k_{obs}$ versus $[\text{Am}]_T$ at different pH for aminolysis of 26 with $[\text{Am}]_T = [37]_T$ is $= 0.4$ at pH 10.34 (■), 10.44 ($\blacktriangle$), 10.77 (□) and 11.10 ($\bigodot$) respectively. The solid line are drawn through the calculated data points using Eq. (3-15) as described in the text.

Figure 4-10: Plots of pseudo-first order rate constant $k_{obs}$ versus $[\text{Am}]_T$ at different pH for aminolysis of 26 with $[\text{Am}]_T = [51]_T$ is $= 0.4$ at pH 8.64 (■), 8.79 ($\blacktriangle$), 9.00 ($\bigodot$), 9.22 (□) and 9.63 ($\Delta$) respectively. The solid line are drawn through the calculated data points using Eq. (3-15) as described in the text.

Figure 4-11: Plots of pseudo-first order rate constant $k_{obs}$ versus $[\text{Am}]_T$ at different pH for aminolysis of 26 with $[\text{Am}]_T = [52]_T$ is $= 0.4$ at pH 8.72 ($\blacktriangle$), 8.81 ($\bigodot$), 9.11 (□), 9.31 ($\bigodot$) and 9.71 ($\Delta$) respectively. The solid line are drawn through the calculated data points using Eq. (3-15) as described in the text.

Figure 4-12: Plots of pseudo-first order rate constant $k_{obs}$ versus $[\text{Am}]_T$ at different pH for aminolysis of 26 with $[\text{Am}]_T = [51]_T$ is $= 0.3$ at pH 8.60 (■), 8.71 ($\blacktriangle$), 8.97 ($\bigodot$), 9.16 (□) and 9.60 ($\Delta$) respectively. The solid line are...
drawn through the calculated data points using Eq. (3-15) as described in the text.

**Figure 4-13:** Plots of pseudo-first order rate constant $k_{\text{obs}}$ versus $[\text{Am}]_{\text{T}}$ at different pH for aminolysis of 26 with $[\text{Am}]_{\text{T}} = [52]_{\text{T}}$ is= 0.3 at pH 8.65 (■), 8.77 (▲), 8.97 (●), 9.21 (□) and 9.61 (△) respectively. The solid line are drawn through the calculated data points using Eq. (3-15) as described in the text.

**Figure 4-14:** Plots of $k_b/f_b$ (A1) versus $[\text{OH}^-]$ for aminolysis of 26 in the presence of secondary amines: (50 (▲)°), 51 (○)°, 52 (□)°, 51 (●)°, and 52 (■)° respectively. The solid line are drawn through the calculated data points using Eq. (4-5) as described in text. $^a = \mu = 0.4$ M, $^b = \mu = 0.3$ M.

**Figure 4-15:** Plots of pseudo-first order rate constant $k_{\text{obs}}$ versus $[\text{Am}]_{\text{T}}$ at different pH for aminolysis of 26 with $[\text{Am}]_{\text{T}} = [53]_{\text{T}}$ at pH 8.07 (♦), 8.20 (△), 8.16 (○), 8.34 (▲), 8.35 (●), 8.45 (×), 8.76 (●) and 8.65 (◇) respectively. The solid line are drawn through the calculated data points using Eq. (3-15) as described in the text. $\mu = 0.4$ M.

**Figure 4-16:** Plots of pseudo-first order rate constant $k_{\text{obs}}$ versus $[\text{Am}]_{\text{T}}$ at different pH for aminolysis of 26 with $[\text{Am}]_{\text{T}} = [35]_{\text{T}}$ at pH 7.91 (▲), 7.99 (◇), 8.21 (△), 8.22 (●), 8.27 (○), 8.56 (□), 8.68 (●) and 8.93 (+), and 8.85 (★) respectively. The solid line are drawn through the calculated data points using Eq. (3-15) as described in the text. $\mu = 0.4$ M.

**Figure 4-17:** The dependence of the nucleophilic second-order rate constant ($k_a$) for the reaction of 26 with amines nucleophiles on the $pK_a$ of the conjugate acid of the amines at 30°C. The solid line is drawn through the least-squares calculated points using Bronsted equation with slope ($\beta_{\text{nuc}}$) of 0.91 ± 0.20 and intercept (C) -9.12 ± 1.8 M$^{-1}$s$^{-1}$. In the Bronsted plot : Methylamine (○)°, N-benzylamine (Δ), N-benzylamine (▲)°, $N,N'$-dimethylamine (●)°, $N,N'$-diethylamine (★)°, $N$-methylbenzylamine (◇)°,
N-methylbenzylamine (♦), N-ethylbenzylamine (□), N-ethylbenzylamine (■), N,N-dimethylbenzylamine (×) and N,N-(diethylaminomethyl)benzyl alcohol (+). a µ = 0.4 M, b µ = 0.3

Figure 4-17: The dependence of the third-order rate constant (k$_{OH}$) for the reaction of 26 with amines nucleophiles on the pK$_a$ of the conjugate acid of the amines at 30°C. The solid line is drawn through the least-squares calculated points using Bronsted equation with slope ($\beta_{nuc}$) of 0.88 ± 0.20 and intercept (C) -5.40 ± 1.9 M$^{-1}$s$^{-1}$. In the Bronsted plot:

Methylamine (○), N-benzylamine (□), N-benzylamine (Δ), N,N-dimethylamine (★), N,N-methylbenzylamine (●), N,N-methylbenzylamine (◊), N,N-ethylbenzylamine (▲) a µ = 0.4 M, b µ = 0.3
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mp. melting point
m minute
(m) multiplet
Mw molecular weight
NMR nuclear magnetic resonance
NaOH sodium hydroxide
NaBr sodium bromide
(q) quartet
ref. reference
Rf retention rime
rt room temperature
s second
(s) singlet
t time
(t) triplet
T temperature
THF tetrahydrofuran
TLC thin layer chromatography
UV ultraviolet
vis visible
v/v volume per volume
λ wavelength
β nuc Bronsted slope
μ ionic strength
% percentage
[ ] concentration
[Am] T total amine buffer concentration
[Buf] T total buffer concentration
LIST OF COMPOUNDS

1. \( R_1 R_2 \text{C}_\text{OH} \)
   \( R_3 \text{R}_4 \)

2. \( R_2 R_1 \text{N}_\text{OH} \)

3. \( R_3 R_1 \text{N}_\text{OH} \)

4. \( R_4 \text{R}_4 \)

5. \( \text{C}_\text{OH} \)
   \( R \)

6. \( \text{C}_\text{OH} \)
   \( \text{NH}_2 \)

7. \( \text{C}_\text{OH} \)
   \( \text{NH}_2 \)

8. \( \text{C}_\text{OH} \)
   \( \text{NH}_2 \)

9. \( \text{C}_\text{OH} \)
   \( \text{NH}_{\text{BOC}} \)

10. \( \text{C}_\text{OH} \)
    \( \text{O} \text{O} \)

11. \( \text{C}_\text{OH} \)
    \( \text{O} \text{O} \)

12. \( \text{C}_\text{OH} \)
    \( \text{O} \text{O} \)

13. \( \text{C}_\text{OH} \)
    \( \text{O} \text{O} \)

14. \( \text{C}_\text{OH} \)
    \( \text{O} \text{O} \)

15. \( \text{C}_\text{OH} \)
    \( \text{O} \text{O} \)

16. \( \text{C}_\text{OH} \)
    \( \text{O} \text{O} \)

17. \( \text{C}_\text{OH} \)
    \( \text{O} \text{O} \)

18. \( \text{C}_\text{OH} \)
    \( \text{O} \text{O} \)

R = \( -\text{CH}_2\text{CH}_2\text{OH}, -(\text{CH}_2)_2\text{OH}, -(\text{CH}_2)_4\text{OH} \)