

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

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**SUBMISSION OF DISSERTATION FOR THE
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**CHEMISTRY DEPARTMENT
FACULTY OF SCIENCE
UNIVERSITY OF MALAYA
KUALA LUMPUR**

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ABSTRACT

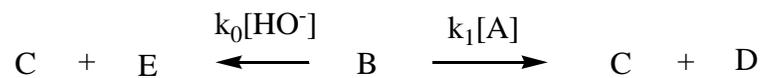
First chapter deals with the literature review of amino alcohols and their derivatives, as well as kinetics and mechanism of aminolysis of esters. The uses of these compounds in biological, pharmacological, synthesis, industries and applied chemistry were discussed briefly. The literature search on some 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 (λ) 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, benzylamine, *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:



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 $\beta_{\text{nuc}} = 0.91 \pm 0.20$.

ABSTRAK

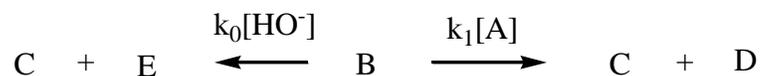
Bab pertama, mengumpulkan maklumat-maklumat daripada rujukan berkenaan dengan sebatian amino alkohol, ester dan terbitannya, disamping kinetik dan mekanisma aminolisis ester. Turut membincangkan berkenaan kegunaan sebatian ini dalam bidang biologi, farmakologi, sintesis, industry dan kimia gunaan. Beberapa 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*-dietilftlamic asid (**34**), 2-((dietilamino)metal)benzil acetat (**42**), *N*-benzilacetamida (**44**) dan *N,N*-dietilacetamida (**45**).

Bab ketiga mengandungi pengenalan ringkas berkenaan kimia kinetik dan kaedah-kaedah biasa yang digunakan semasa menjalankan kajian kinetik. Membincangkan secara terperinci kaedah eksperimen untuk penentuan panjang gelombang (λ). Penjelasan berkenaan eksperimen penentuan hasil tindak balas (produk) menggunakan Fasa-Terbalik Kromatografi Cecair Prestasi Tinggi. Keputusan dibahagikan kepada empat bahagian mengikut jenis-jenis amina.

Bab terakhir mengandungi keputusan hasil daripada aminolisis **26**. Keputusan dibahagikan kepada tiga bahagian iaitu 1) amina primer, 2) amina sekunder, 3) amina tertiar 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:



Skema 1

dimana A = amina, B = **26**, C = **48**, D = amida dan E = asid asetik. Dalam kebanyakan kes, plot k_{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 $\beta_{nuc} = 0.91 \pm 0.20$.

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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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Figure 4-9: Plots of pseudo-first order rate constant k_{obs} versus $[\text{Am}]_{\text{T}}$ at different pH for aminolysis of **26** with $[\text{Am}]_{\text{T}} = [\text{37}]_{\text{T}}$ is= 0.4 at pH 10.34 (\blacksquare), 10.44 (\blacktriangle), 10.77 (\square) and 11.10 (\circ) respectively. The solid line are draw through the calculated data points using Eq. (3-15) as described in the text. 82

Figure 4-10: Plotss of pseudo-first order rate constant k_{obs} versus $[\text{Am}]_{\text{T}}$ at different pH for aminolysis of **26** with $[\text{Am}]_{\text{T}} = [\text{51}]_{\text{T}}$ is= 0.4 at pH 8.64 (\blacksquare), 8.79 (\blacktriangle), 9.00 (\circ), 9.22 (\square) and 9.63 (Δ) respectively. The solid line are drawn through the calculated data points using Eq. (3-15) as described in the text. 83

Figure 4-11: Plots of pseudo-first order rate constant k_{obs} versus $[\text{Am}]_{\text{T}}$ at different pH for aminolysis of **26** with $[\text{Am}]_{\text{T}} = [\text{52}]_{\text{T}}$ is= 0.4 at pH 8.72 (\blacksquare), 8.81 (\blacktriangle), 9.11 (\circ), 9.31 (\square) and 9.71 (Δ) respectively. The solid line are drawn through the calculated data points using Eq. (3-15) as described in the text. 84

Figure 4-12: Plots of pseudo-first order rate constant k_{obs} versus $[\text{Am}]_{\text{T}}$ at different pH for aminolysis of **26** with $[\text{Am}]_{\text{T}} = [\text{51}]_{\text{T}}$ is= 0.3 at pH 8.60 (\blacksquare), 8.71 (\blacktriangle), 8.97 (\circ), 9.16 (\square) and 9.60 (Δ) respectively. The solid line are

drawn through the calculated data points using Eq. (3-15) as described in the text. 85

Figure 4-13: Plots of pseudo-first order rate constant k_{obs} versus $[\text{Am}]_{\text{T}}$ at different pH for aminolysis of **26** with $[\text{Am}]_{\text{T}} = [\mathbf{52}]_{\text{T}}$ is= 0.3 at pH 8.65 (\blacksquare), 8.77 (\blacktriangle), 8.97 (\circ), 9.21 (\square) and 9.61 (\triangle) respectively. The solid line are drawn through the calculated data points using Eq. (3-15) as described in the text. 86

Figure 4-14: Plots of $k_{\text{b}}/f_{\text{b}}$ (A1) versus $[\text{OH}^-]$ for aminolysis of **26** in the presence of secondary amines: (**50** (\blacktriangle)^a, **51** (\circ)^a, **52** (\square)^a, **51** (\bullet)^b, and **52** (\blacksquare)^b 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 = $\mu = 0.3 \text{ M}$. 88

Figure 4-15: Plots of pseudo-first order rate constant k_{obs} versus $[\text{Am}]_{\text{T}}$ at different pH for aminolysis of **26** with $[\text{Am}]_{\text{T}} = [\mathbf{53}]_{\text{T}}$ at pH 8.07 (\blacklozenge), 8.20 (\triangle), 8.16 (\circ), 8.34 (\blacktriangle), 8.35 (—), 8.50 (\blacksquare), 8.45 (\times), 8.76 (\bullet) and 8.65 (\diamond) respectively. The solid line are drawn through the calculated data points using Eq. (3-15) as described in the text. $\mu = 0.4 \text{ M}$. 91

Figure 4-16: Plots of pseudo-first order rate constant k_{obs} versus $[\text{Am}]_{\text{T}}$ at different pH for aminolysis of **26** with $[\text{Am}]_{\text{T}} = [\mathbf{35}]_{\text{T}}$ at pH 7.91 (\blacktriangle), 7.99 (\diamond), 8.21 (\triangle), 8.22 (\bullet), 8.27 (\circ), 8.56 (\square), 8.68 (—), 8.93 ($+$), and 8.85 (\blacklozenge) respectively. The solid line are drawn through the calculated data points using Eq. (3-15) as described in the text. $\mu = 0.4 \text{ M}$. 92

Figure 4-17: The dependence of the nucleophilic second-order rate constant (k_{n}) 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 (β_{nuc}) of 0.91 ± 0.20 and intercept (C) $-9.12 \pm 1.8 \text{ M}^{-1}\text{s}^{-1}$. In the Bronsted plot : Methylamine (\circ)^a, *N*-benzylamine (\triangle), *N*-benzylamine (\blacktriangle)^b, *N,N*-dimethylamine (\bullet)^a, *N,N*-diethylamine ($*$)^a, *N*-methylbenzylamine (\diamond)^a,

N-methylbenzylamine (\blacklozenge)^b, *N*-ethylbenzylamine (\square)^a, *N*-ethylbenzylamine (\blacksquare)^b, *N,N*-dimethylbenzylamine (\times)^a and *N,N*-(diethylaminomethyl)benzyl alcohol (+)^a. ^a $\mu = 0.4$ M, ^b $\mu = 0.3$ M **104**

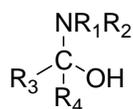
Figure 4-17 : The dependence of the third - order rate constant (k_{OH^-}) for the reaction of **26** with amines nucleophiles on the pK_a of the conjugate acid of the amines at 30°C. The solid line is drawn through the least-squares calculated points using Bronsted equation with slope (β_{nuc}) of 0.88 ± 0.20 and intercept (C) -5.40 ± 1.9 M⁻¹s⁻¹. In the Bronsted plot : Methylamine (\circ)^a, *N*-benzylamine (\square), *N*-benzylamine (Δ)^b, *N,N*-dimethylamine ($*$)^a, *N,N*-methylbenzylamine (\bullet)^a, *N,N*-methylbenzylamine (\diamond)^b, *N,N*-ethylbenzylamine (\blacktriangle)^a, *N,N*-ethylbenzylamine (\blacksquare)^a. $\mu = 0.4$ M, ^b $\mu = 0.3$ M **107**

LIST OF SYMBOLS AND ABBREVIATIONS

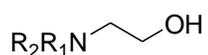
Abs	absorbance
Ar	aromatic
A_{cald}	calculated absorbance
A_{obs}	observed absorbance
$[\text{Am}]_{\text{T}}$	total amine buffer concentrations
A1	$k_{\text{b}}/f_{\text{b}}$
b.p.	boiling point
CDCl_3	deuterated chloroform
CH_3CN	acetonitrile
CH_3NH_2	methylamine
$\text{C}_6\text{H}_5\text{CH}_2\text{NH}_2$	benzylamine
(d)	doublet
Eq.	equation
f_{b}	free base
HPLC	high performance liquid chromatography
HCl	hydrochloric acid
H_2O	water
IGA	intramolecular general acid
IGB	intramolecular general acid
IR	infrared
J	coupling constant
K_{a}	ionization constant
k_{n}	second – order rate constant for nucleophilic
k_{OH^-}	third – order rate constant for specific base – catalyzed
k_{b}	second – order rate constant
k_{o}	uncatalyzed catalysis
M	mole per liter

mp.	melting point
m	minute
(m)	multiplet
M _w	molecular weight
NMR	nuclear magnetic resonance
NaOH	sodium hydroxide
NaBr	sodium bromide
(q)	quartet
ref.	reference
R _f	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

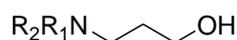
LIST OF COMPOUNDS



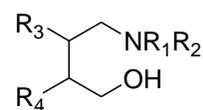
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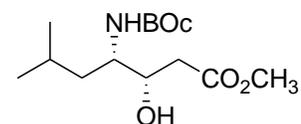
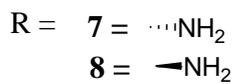
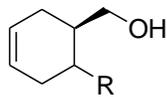
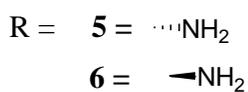
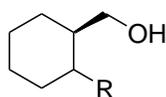
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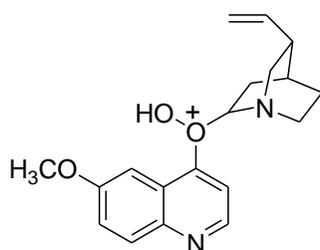
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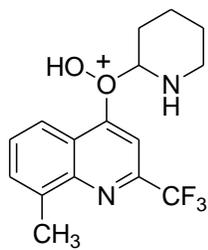
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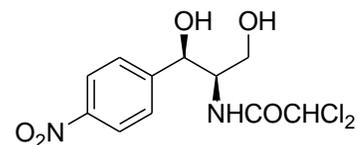
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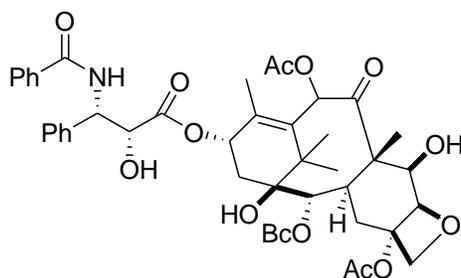
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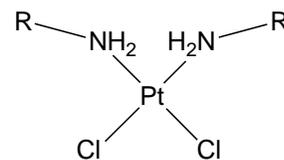
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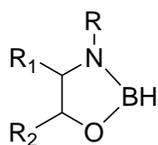
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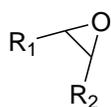
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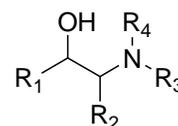
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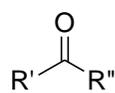
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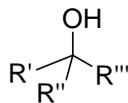
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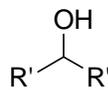
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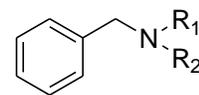
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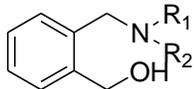
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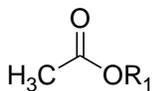
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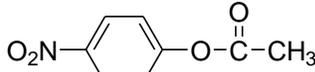
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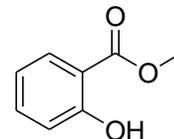
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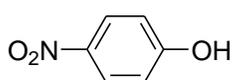
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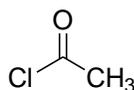
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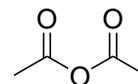
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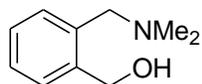
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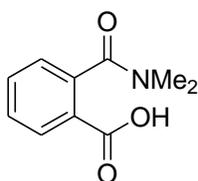
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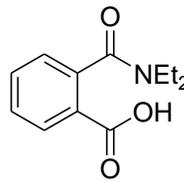
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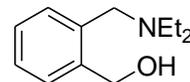
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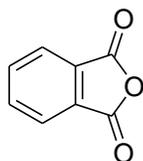
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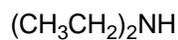
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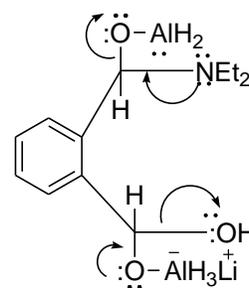
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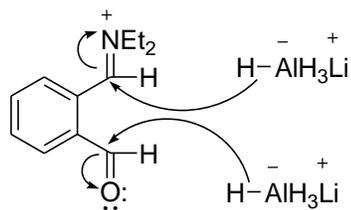
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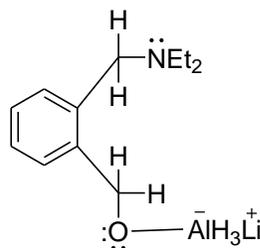
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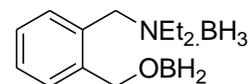
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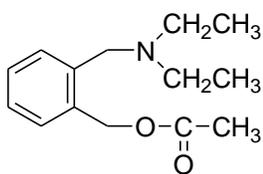
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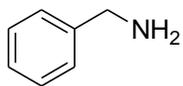
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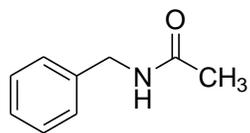
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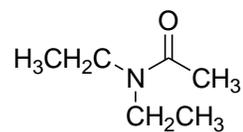
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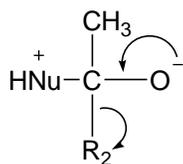
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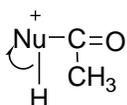
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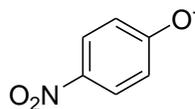
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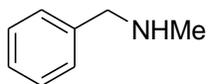
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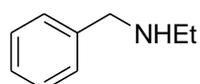
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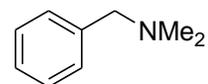
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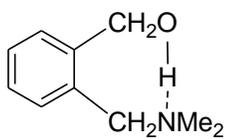
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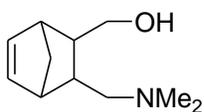
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