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Kinetics and Mechanism of Acylation of Amines with 2-Naphthoyl Azide

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KINETICS AND MECHANISM OF ACYLATION OF AMINES WITH 2-NAPHTHOYL AZIDE

by

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A Dissertation
Submitted to the
Faculty of The Graduate College
in partial fulfillment of the
Requirements for the
Degree of Doctor of Philosophy
Department of Chemistry

Western Michigan University
Kalamazoo, Michigan
April, 1983

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Abraham L. Faburada, Ph. D.

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The reaction of 2-naphthoyl azide with primary and secondary amines in protic and aprotic solvents follows second-order kinetics. The effect of increasing solvent polarity is shown to increase the rate of reaction. For amines of similar basicity, the rate of reaction decreases with increasing steric hindrance on the amine. The changes in free energy and entropy of activation for n-butylamine and cyclohexylamine are in accord with steric requirements of amines. For amines of similar steric hindrance, the rate of reaction increases with increasing amine basicity. The mechanism of addition-elimination involving the formation of a tetrahedral intermediate is consistent with the data obtained. The rate-determining step in this reaction is postulated on the basis of amine and azide ion basicities, and the possibility of anchimeric-type assistance by the azide group in the expulsion of the amine from the tetrahedral intermediate. The absence of general base catalysis in this reaction is explained in terms of a fast proton transfer from the protonated amide intermediate to a solvent or an amine molecule which occurs after the rate-determining step. Qualitative evaluation

of the total steric and electronic effects on the rate of this reaction indicates that the former factor is predominant. The combination of high basicity and small steric hindrance on the amine results in a dramatic enhancement in rate of reaction as demonstrated by pyrrolidine.

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Western Michigan University PH.D. 1983

ACKNOWLEDGEMENTS

I wish to take this opportunity to express my sincere thanks of gratitude to Dr. Donald C. Berndt, my research advisor, for his guidance, understanding, and constructive criticisms in the course of this research project; to the members of my dissertation committee, Dr. Stephen Friedman, Dr. Robert Harmon, Dr. Robert Nagler, and Dr. Jochanan Stenesh, for their kind attention and careful evaluation of the work accomplished; to the Department of Chemistry and The Graduate College for the much needed monetary support in the form of assistantship and fellowship awards which both have provided me through the years; to all the people who, in one way or another, have extended me their help unselfishly to make this undertaking possible; and to my dear wife, Yolanda, for her unyielding patience, encouragement, and understanding in bearing with me through.

Abraham L. Faburada

To

Kerwin and Kathleen

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INTRODUCTION

The reaction of acyl azides with amines was first introduced by Curtius in 1902.[1] Since then, the reaction has been utilized in the synthesis of peptides.[2, 3]

$$R\text{-}\overset{O}{\overset{\|}{C}}\text{-}N_3 + R''R'NH \longrightarrow R\text{-}\overset{O}{\overset{\|}{C}}NR'R'' + HN_3$$

In peptide systhesis a common problem often encountered is the tendency of reactants to undergo racemization during the process. Although such racemization has been observed in the azide method of peptide synthesis, the extent is in general lower than those in other established methods.[4] This constitutes a significant advantage of the azide method and the reason for its routine application in these syntheses.

For several years after its discovery, the coupling of acyl azides with amines has been largely employed in the synthesis of low molecular weight polypeptides. It was not until the 1960's that the method was successfully employed in the synthesis of long-chain polypeptides with molecular weights greater than 100,000.[5, 6, 7, 8, 9] This success demonstrates further the significance of this reaction in this area of synthesis.

One disadvantage encountered in this reaction however, is the tendency of the acyl azide to undergo the so-called Curtius rearrangement to the corresponding isocyanate which,

$$R\text{-}\overset{O}{\overset{\|}{C}}\text{-}N_3 \longrightarrow R\text{-}N{=}C{=}O + N_2$$

in the presence of amines, reacts to form urea derivatives.[10] Nevertheless, the occurrence of such rearrangement has been observed only at elevated temperatures. Thus, in peptide preparations by the azide method, reactions are normally carried out at or below 0 ^{o}C. Excellent yields of products have been obtained under such conditions.

The little activity, if any, of acyl azides toward water, alcohols, and acids[7] provides further advantage in using the azide method in peptide synthesis.

Although extensive investigations have been conducted on this reaction in peptide syntheses, little is reported of its kinetics and mechanism in the literature. In this study, a survey was undertaken on the behaviour of 2-naphthoyl azide towards various primary and secondary amines in both protic and aprotic solvents. The kinetics of this reaction were examined and subsequently utilized in an attempt to establish a mechanistic pathway for this reaction.

CHAPTER II

REVIEW OF LITERATURE

The reaction of amines with acyl azides to form the corresponding amides is known to involve the nucleophilic displacement of the azide group from the carbonyl carbon of the acyl azide by the amino group. This particular reaction is analogous to the well-established aminolysis (with amines) or ammonolysis (with ammonia) of carboxylic acid esters in which the alcohol portion of the ester is displaced from the carbonyl carbon.

$$R'''R''NH + R\text{-}\overset{O}{\overset{\|}{C}}\text{-}OR' \longrightarrow R'''R''N\text{-}\overset{O}{\overset{\|}{C}}\text{-}R + R'OH$$

Although both reactions appear to involve a bimolecular process, the kinetics and mechanism of the latter reaction were found, at least in some of the previous work reported, to be more complex than perhaps anticipated. Since very little is known from a review of the literature in the case of the reaction of acyl azides with amines, a review of past work on ester aminolysis should provide some insights into the present study.

In the past, investigators were puzzled by the fact that the reaction of esters with amines under second-order conditions proceeded with a continuous change in the rate constants during the course of reaction.[11] These obser-

vations led investigators to believe that perhaps these reactions are not purely second-order processes. Consequently, reactions were carried out under first-order conditions in order to eliminate some of the uncertainties encountered in previous studies. Thus, in reactions of esters with amines, a large excess of the latter was used.

The first of such studies reported involved the reaction of thiolesters with n-butylamine in aqueous solution.[12] This reaction was shown to follow the rate expression given by equation (1). Here the k_{obs} corresponds to the pseudo first-order rate constant. Since

$$k_{obs} = k_1 \left[RNH_2\right]^{3/2} + k_2 \left[RNH_2\right]^{1/2} \qquad (1)$$

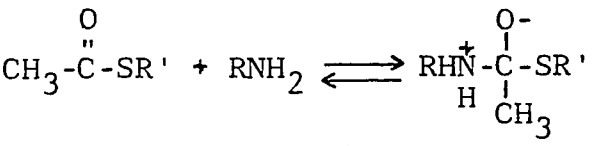
in aqueous solution the following equilibrium exists, the

$$RNH_2 + H_2O \underset{}{\overset{K_b}{\rightleftharpoons}} R\overset{+}{N}H_3 + \bar{O}H$$

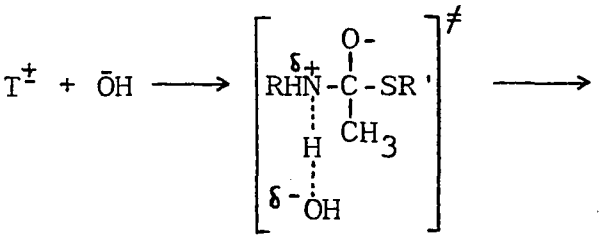
first term in equation (1), was interpreted as a hydroxide ion-catalyzed aminolysis and the second term for hydrolysis. Thus, equation (2) is written.

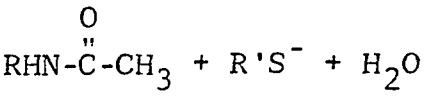
$$k_{obs} = k_3 \left[RNH_2\right] \left[\bar{O}H\right] + k_4 \left[\bar{O}H\right] \qquad (2)$$

A mechanism was then proposed which involves reversible addition of the amine to the ester to form a zwitterionic tetrahedral intermediate followed by a rate-determining abstraction of a proton from the intermediate by the hydroxide ion to give the products.

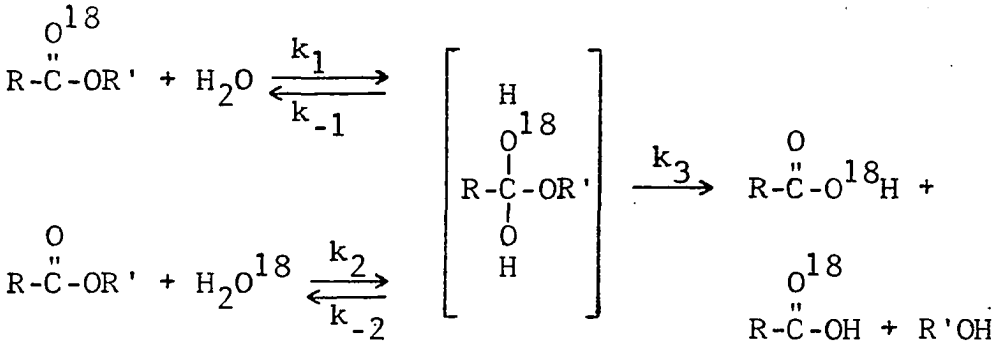


$T^{\pm}$

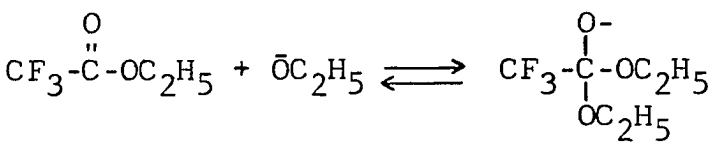


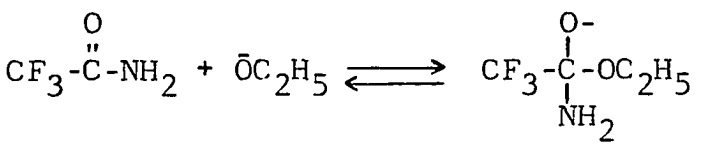


Evidence has been presented for the existence of tetrahedral intermediates in reactions of carbonyl compounds with nucleophiles.[13] For example, isotope exchange studies involving the hydrolysis of an ester labeled with O^{18} at the carbonyl oxygen have shown the concurrent isotopic oxygen exchange and hydrolysis of the esters during the course of the reaction.[14]



Infrared studies of the following equilibria have shown that the reactions favored the formation of the addition compounds.[15]

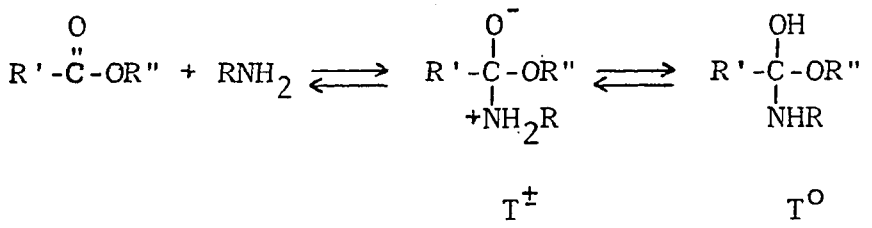


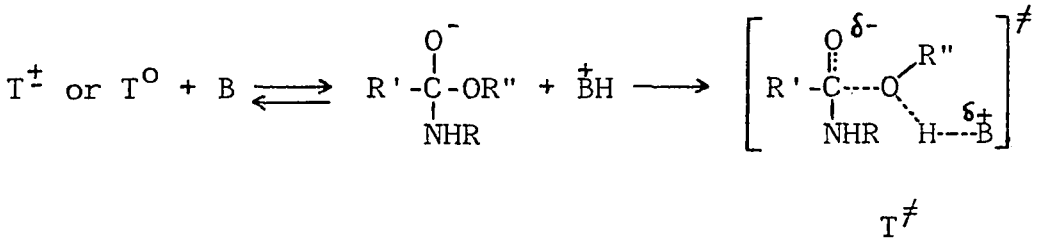


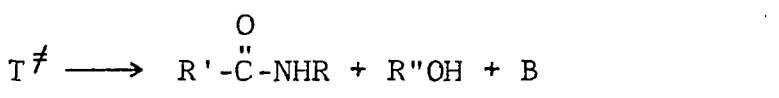
Although the proposed mechanism for the thiolester aminolysis is consistent with the fact that the reaction is base-catalyzed, it was criticized by others for the reason that solvent molecules could accept protons frequently enough for the uncatalyzed reaction to be detectable. Thus, in the reaction of ethyl formate with n-butylamine in aqueous solution which was shown to follow the rate expression of equation (3), a mechanism was

$$k_{obs} = k_1 \left[RNH_2\right]^{3/2} + k_2 \left[RNH_2\right]^2 \qquad (3)$$

proposed which involves a series of pre-equilibria followed by a rate-determining breakdown of a tetrahedral intermediate.[16] Here, the removal of the alkoxy group







is said to be catalyzed by the conjugate acid of the base. It has been shown that a general base-catalyzed reaction involving general acid-catalysis in the slow step is legitimate.[16]

The occurrence of basic and acidic catalyses was further shown in the reaction of phenyl acetate with various amines in aqueous solution.[17, 18] For example, the rate of reaction of the ester with dimethylamine and n-butylamine

showed a greater than first-order dependence on amine concentration as well as an increase in rate with increasing pH of solution. These obervations demonstrate that these systems are subject to both general and specific base catalysis.

On the other hand, the reaction of the ester with glycine was observed to involve general base catalysis only, while that with piperidine and morpholine showed specific ion catalysis only with hydroxide ion. The reaction of the weak base, methoxyamine in a relatively acidic solution in the presence methoxyammonium salt was shown to follow the rate expression of equation (4). Thus, general acid catalysis is involved in this system.

$$k_{obs} = k_1 \left[RNH_2\right] + k_2 \left[RNH_2\right] \left[R\overset{+}{N}H_3\right] \qquad (4)$$

In the reaction of hydrazine with acetate esters in buffered aqueous solutions, the data obtained were shown to fit the rate equation (5).[19] A mechanism consistent

$$k_{obs} - k_o\, a_{\bar{O}H} = k_1 \left[N_2H_4\right] + k_2 \left[N_2H_4\right]^2 + k_3 \left[N_2H_4\right] a_{\bar{O}H} + k_4 \left[N_2H_4\right] \left[N_2\overset{+}{H}_5\right] + k_5 \left[N_2H_4\right] \left[Buffer\right] \qquad (5)$$

with the preceding equation was proposed which involves the formation of a tetrahedral intermediate, $T^{\pm}$. For alkyl

$$RNH_2 + R''\text{-}\overset{O}{\overset{\|}{C}}\text{-}OR' \rightleftharpoons RH\overset{+}{N}\text{-}\underset{H}{\overset{O^-}{\overset{|}{C}}}\text{-}\underset{R''}{OR'}$$

$T^{\pm}$

and moderately reactive phenyl acetates, the formation of the intermediate is said to be rapid and reversible. In the case with phenyl acetates, the uncatalyzed breakdown of the intermediate is considered to be rate-determining expulsion of the phenoxide ion. With poorer leaving groups, as in alkyl acetates, the $T^{\pm}$ intermediate undergoes a rate-determining transformation into a neutral intermediate, T^{o}, which is perhaps thermodynamically favored, by a proton switch mechanism involving two molecules of water. The intermediate, T^{o}, may then proceed to form the products in a fast step.

$$T^{\pm} \underset{k_{-s}}{\overset{k_s}{\rightleftharpoons}} RN\text{-}\underset{H}{\overset{OH}{\overset{|}{C}}}\text{-}\underset{CH_3}{OR'} \xrightarrow{\text{fast}} RN\text{-}\underset{H}{\overset{O}{\overset{\|}{C}}}\text{-}CH_3 + R'OH$$

T^{o}

The $T^{\pm}$ intermediate of both alkyl and phenyl esters may also undergo a rate-determining general base-catalyzed reaction by removal of a proton to trap the unstable intermediate. With alkyl esters, the reaction may undergo a

$$T^{\pm} \underset{k_{-b}[HB+]}{\overset{k_b[B]}{\rightleftharpoons}} RN\text{-}\underset{H}{\overset{O^-}{\overset{|}{C}}}\text{-}\underset{R''}{OR'}$$

T^{-}

change to a rate-determining breakdown of the T^- intermediate to products with decreasing pH of solution. At still lower pH, the T^- intermediate may undergo a rate-determining pH-independent and buffer-catalyzed decomposition to products.

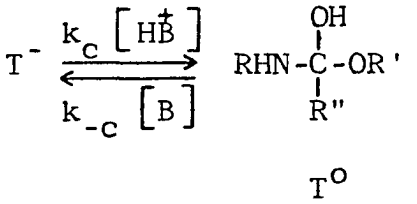
For both phenyl and alkyl acetates also, the $T^{\pm}$ intermediate may proceed to react by proton transfer from a general acid catalyst forming a T^+ intermediate.

$$T^{\pm} \underset{k_{-a}[A^-]}{\overset{k_a[HA]}{\rightleftharpoons}} \underset{T^+}{RH\overset{+}{N}-\underset{H}{\overset{OH}{\underset{|}{\overset{|}{C}}}}-\underset{CH_3}{\overset{OR'}{\underset{|}{\overset{|}{C}}}}}$$

The latter may then undergo transformation to products through the T^o intermediate.

$$T^+ \underset{k_{-e}[HA]}{\overset{k_e[A^-]}{\rightleftharpoons}} \underset{T^o}{RN-\underset{CH_3}{\overset{OH}{\underset{|}{\overset{|}{C}}}}-OR'} \longrightarrow RHN-\overset{O}{\overset{\|}{C}}-CH_3 + R'OH$$

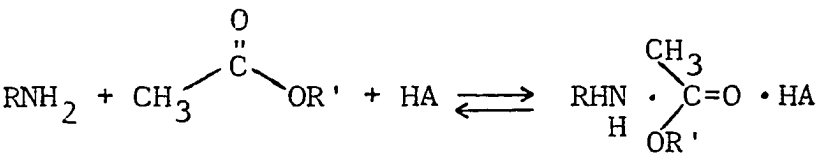
The T^- intermediate may also undergo a proton transfer from a general acid catalyst to form the T^o intermediate, although from pK_a considerations it appears as if the reaction is thermodynamically unfavorable. In this reaction of esters and hydrazine, the amine attack becomes rate-



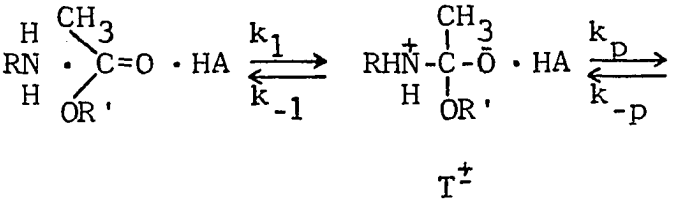
T^{o}

determining in the presence of good leaving groups on the esters.

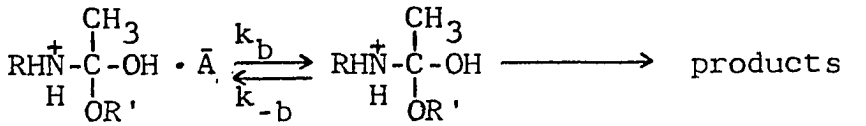
More recently, the methoxyaminolysis of phenylacetate in aqueous solution has been shown to be subject to general acid catalysis through a preassociation mechanism.[20, 21]



In the presence of strong acids, the acid catalysis is enforced and proton transfer to the intermediate is very fast. Under this condition, amine attack on the ester becomes rate-determining. With weaker acids, the intermediate, $T^{\pm}$, undergoes a rate-determining proton transfer



$T^{\pm}$



$T^{+} \cdot A^{-}$ T^{+}

from the general acid catalyst to give the encounter pair, $T^+ \cdot A^-$. With weak acids, the separation of the encounter pair becomes rate-determining. A Bronsted plot for these systems showed a convex curvature which represented three different regions corresponding to k_1, k_p, and k_b for strong, weaker and weak acid catalysts respectively.

The reactions of esters with amines in aprotic solvents have been investigated also, and studies have shown that various rate expressions are involved in different systems. For example, the reaction of phenyl dichloroacetate with n-butylamine in anhydrous dioxane was observed to follow the rate expression given in equation (6).[22] Whereas in

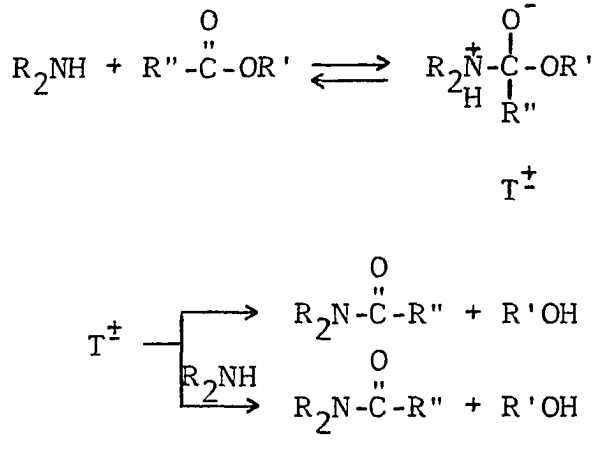
$$k_{obs} = k_1 \left[\text{Amine}\right] + k_2 \left[\text{Amine}\right]^2 \qquad (6)$$

cyclohexane, the reaction involves only the second-order term in amine. The reaction of phenyl dichloroacetate with secondary amines in anhydrous dioxane showed second-order kinetics only, equation (7).

$$k_{obs} = k \left[\text{Amine}\right] \qquad (7)$$

In diethyl ether, the aminolysis of phenyl acetate and benzoate esters with various primary and secondary amines showed both second- and third-order kinetics as in equation (6). In acetonitrile however, only first-order

dependence on amine concentration was observed with para-nitrophenyl acetate and para-nitrobenzoate esters.[23] In another study, the reaction of the preceding esters with pyrrolidine in acetonitrile was also shown to follow second-order kinetics.[24] Esters with lesser electron-withdrawing substituents showed first- and second-order dependence on amine concentration. In these systems, a mechanism was proposed which involves the formation of a tetrahedral intermediate also, followed by a general base-catalyzed or uncatalyzed collapse of the intermediate to products.



CHAPTER III

RESULTS AND OBSERVATIONS

Certain acyl azides have been known to be dangerously explosive. This is particularly so when the acyl group is attached to an aliphatic carbon or when the azide nitrogen content exceeds 25% of the azide molecule. Aromatic acyl azides on the other hand, are known to be more stable, and even more so when the azide nitrogen content is less than 25% of the acyl azide molecule.[25] On this basis therefore, 2-naphthoyl azide was chosen.

The very low or absence of reactivity of alcohols toward acyl azides[7] and the polarity of the former based on dielectric constants formed the basis in choosing ethanol and 2-methyl-2-butanol as protic solvents. Acetonitrile on the other hand, was chosen to serve as an aprotic solvent for its polar and unreactive nature in systems involving amines.[26] n-Heptane was chosen to serve as diluent for ethanol and 2-methyl-2-butanol for its non-polar nature and its moderate volatility.

The various primary and secondary amines were chosen according to established values of pK_a of ammonium salts in aqueous solutions, and their molecular structure. Table 1 lists the amines employed in this study with the respective pK_a values of their conjugate acids.

The reaction of 2-naphthoyl azide with the amines in

Table 1

pK_a of Ammonium Ions of Amines in Aqueous Solution[27]

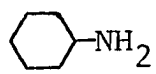
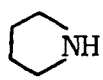
Amine	pK_a
n-$C_4H_9NH_2$	10.61
$C_6H_5CH_2CH_2CH_2NH_2$	10.16
$C_6H_5CH_2CH_2NH_2$	9.83
	10.68
t-$C_4H_9NH_2$	10.68
$(C_2H_5)_2NH$	10.98
(n-$C_3H_7)_2NH$	11.00
(n-$C_4H_9)_2NH$	11.25
$CH_3CH_2CH(CH_3)CH_2NH_2$	10.56
$CH_3OCH_2CH_2NH_2$	9.45
	11.27

Table 1 was observed to proceed well at room temperature in ethanol, 2-methyl-2-butanol, and acetonitrile. The yields of the corresponding amide products were excellent except with t-butylamine in ethanol as shown in Table 2.

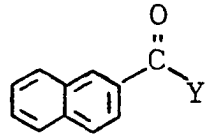
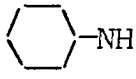
Analysis by NMR spectroscopy of crude reaction mixtures of diethyl-, di-n-propyl-, and di-n-butylamines in ethanol indicated the presence of a second product, most likely ethyl 2-naphthoate.

The absorption maxima in the ultraviolet regions of the spectra for reactants and products were determined using the Cary 14 spectrophotometer. The results showed maximum absorptions at 255 nm by 2-naphthoyl azide, between 230 and 236 nm by amide products of primary amines and that of pyrrolidine, and at 215 nm by amide products of the secondary amines, diethyl-, di-n-propyl-, and di-n-butylamines. A smaller but significant absorption by the azide was also observed at 215 nm.

Reactions for kinetic measurements were carried out under pseudo first-order conditions in acyl aizde concentration by using a large excess of amine over that of the azide. The rate of reaction was monitored spectrophotometrically at 230 to 236 nm with primary amines and pyrrolidine, and at 253 nm for the secondary amines. Absorbance readings of reaction mixtures were taken at equal time intervals until two half-lives were over. This procedure was adapted based on equation (8) es-

Table 2

Per Cent Yield of N-Substituted-2-Naphthamides

Y of 	% Yield		
	in Ethanol[a]	in MB[b]	in Acetonitrile[b]
n-C_4H_9NH	78	95	96
$C_6H_5CH_2CH_2CH_2NH$	89	76[a]	96
$C_6H_5CH_2CH_2NH$	91	79[a]	94
 –NH	87	72[a]	93
t-C_4H_9NH	50	98	95
$(C_2H_5)_2N$		95	90
$(n\text{-}C_3H_7)_2N$		97	97
$(n\text{-}C_4H_9)_2N$		96	92
$CH_3CH_2CH(CH_3)CH_2NH$			98
$CH_3OCH_2CH_2NH$			98
			97

[a]By isolation.

[b]By gas chromatography.

MB is 2-methyl-2-butanol.

tablished by Swinbourne for treating first-order

$$A_t = e^{k_1 T} A_{(t + T)} + (1 - e^{k_1 T}) A_\infty \qquad (8)$$

reactions,[28] where A_t and $A_{(t + T)}$ are absorbance readings at times t and (t + T) respectively. The time constant, T, has a value between one-half and one half-life. The first-order rate constant, k_1, is the observed pseudo first-order rate constant, k_{obs}.

From absorbance-time data and equation (8), values of A_t and $A_{(t + T)}$ at times t and (t + T) respectively were established. Representative data for this are shown in Table 3. For each reaction, a plot of A_t versus $A_{(t + T)}$ was found linear. A representative plot is shown in Figure 1 in which the data in Table 3 are employed. The slope of the line was determined by the method of least squares and the observed pseudo first-order rate constant was calculated using equation (9). The data in

$$k_{obs} = \frac{2.303 \log (\text{slope})}{T} \qquad (9)$$

Table 4 show the calculated observed rate constants for the corresponding concentrations of n-butylamine in acetonitrile. These data are shown as typical of all the data of observed rate constants for all amines in the three solvents employed.

Table 3

Absorbance-Time Data for the Acylation of n-Butylamine in Acetonitrile

$[\text{Acyl Azide}] = 9.00 \times 10^{-6}$ M $[\underline{n}\text{-}C_4H_9NH_2] = 2.446 \times 10^{-4}$ M

t, min	A_t	(t + T), min	$A_{(t+T)}$
0	0.169	320	0.353
40	0.201	360	0.369
80	0.229	400	0.383
120	0.255	440	0.396
160	0.279	480	0.408
200	0.300	520	0.419
240	0.319	560	0.430
280	0.337	600	0.439
320	0.353	640	0.448
360	0.369	680	0.456
400	0.383	720	0.463

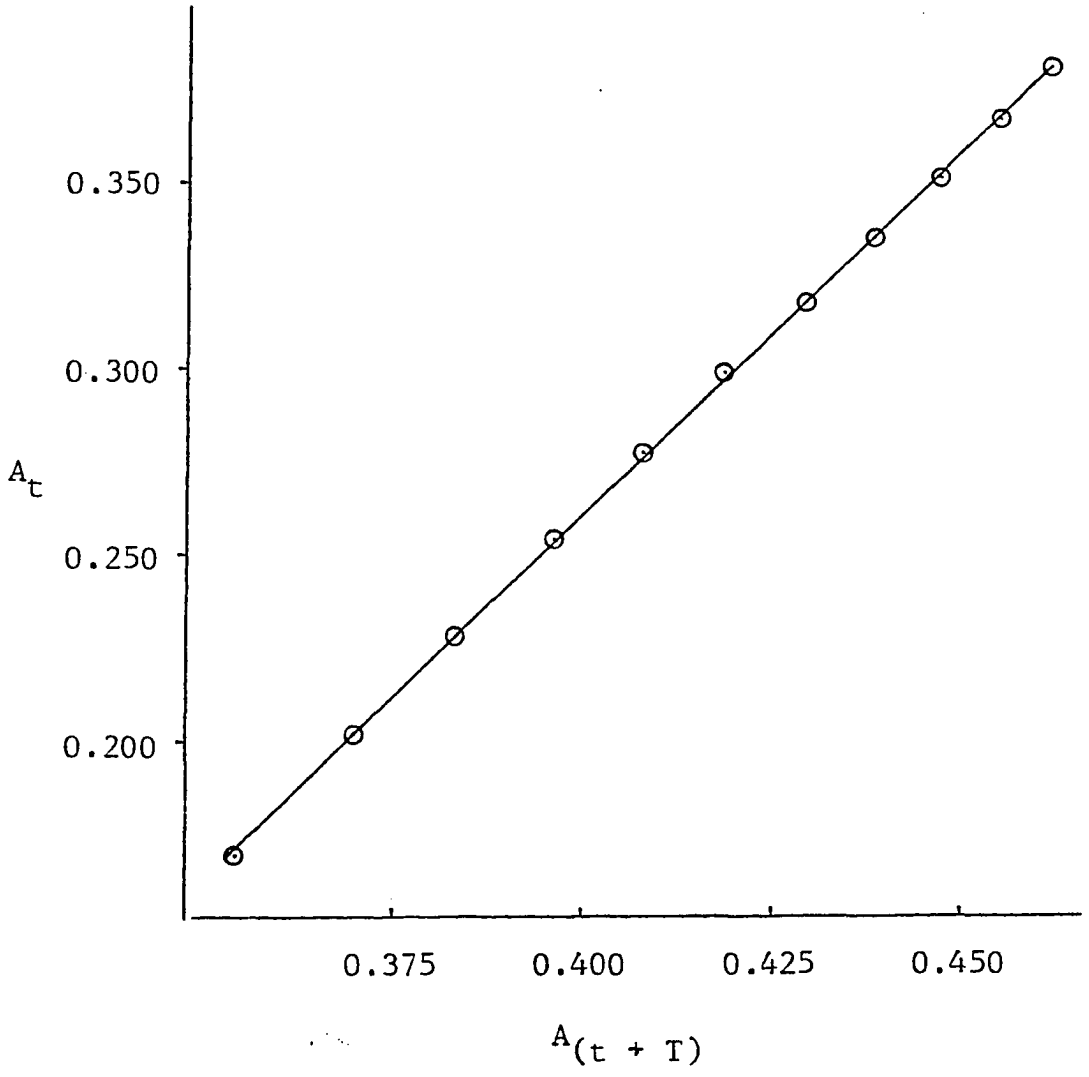


Figure 1. Plot of A_t versus $A_{(t + T)}$

Table 4

Observed Pseudo First-Order Rate Constants for n-Butylamine in Acetonitrile

[Amine] x 10^4, M	k_{obs} x 10^3, min^{-1}
4.83	4.81
9.67	9.03
14.50	13.10
19.34	17.51
29.00	25.67
38.68	35.23
48.35	43.19

Duplicate determinations were made for each amine concentration.

The reaction of 2-naphthoyl azide with t-butylamine in ethanol was excluded from kinetic experiments for the reason that the yield of the corresponding amide was less than 50%. The similar reactions with diethyl-, di-n-propyl-, and di-n-butylamines in the same medium were also excluded from kinetic experiments due to the considerable occurrence of side reactions in these systems, possibly between the acyl azide and the solvent, ethanol. On the other hand, the reactions of these amines with the acyl azide in 2-methyl-2-butanol were observed to be free of complications from side reactions. The rates of reaction in this medium however, were too slow to be of practical importance. In acetonitrile, the rate of reaction of t-butyl- and di-n-butylamines with the acyl azide were observed to be immeasurably slow also.

For all data represented by Table 4, plots of k_{obs} versus amine concentration were found linear with intercepts at zero within experimental accuracy. Such plots are represented by Figure 2. Consequently, equation (10) is written.

$$k_{obs} = k\,[\text{Amine}] \qquad (10)$$

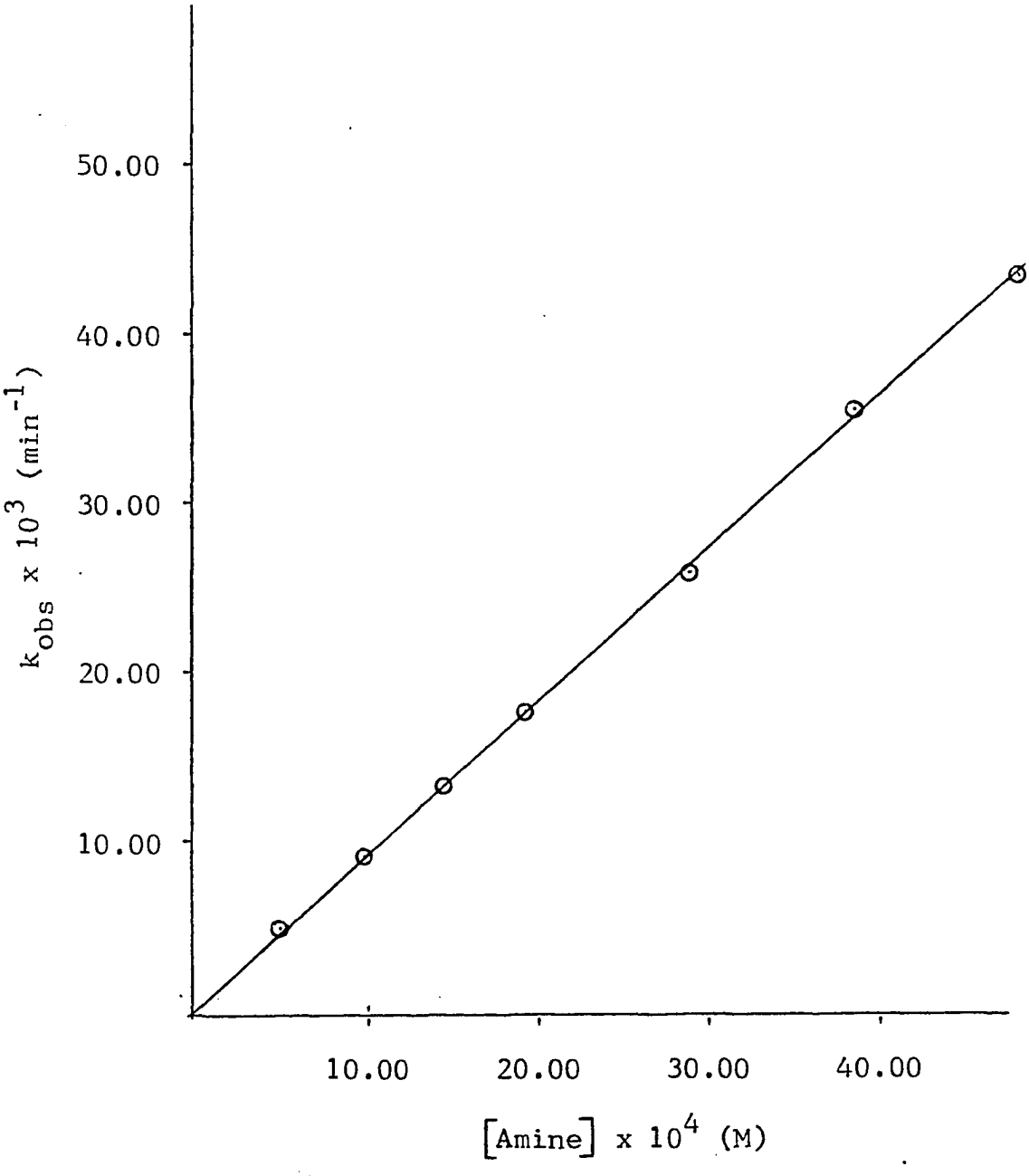


Figure 2. Plot of k_{obs} versus [Amine]

The slopes of plots of k_{obs} versus [Amine] were determined by least squares calculations. These values are also the second-order rate constants for the reaction of 2-naphthoyl azide with amines and are listed in Table 5.

The reaction of 2-naphthoyl azide with n-butylamine was carried out further in the solvent mixtures, 40% n-heptane in ethanol, and 20% 2-methyl-2-butanol in n-heptane. The second-order rate constants for these systems were determined as 6.07 and 0.79 M^{-1} min^{-1} respectively.

The reaction of 2-naphthoyl azide with n-butylamine and cyclohexylamine in ethanol was also carried out at 20 °, 30 °, and 40 °C. The second-order rate constants obtained are listed in Table 6. These values were used to determine enthalpies ($\Delta H^{\neq}$) and entropies ($\Delta S^{\neq}$) of activation for the preceding reaction using equation (11).[29]

$$\ln(k/T) = -(\Delta H^{\neq}/R)(1/T) + \left[\ln(k_B/h) + \Delta S^{\neq}/R\right] \quad (11)$$

Where, k is the second-order rate constant, R is the ideal gas constant (1.987 cal mol^{-1} deg^{-1}), k_B is the Boltzman constant (1.380×10^{-16} erg deg^{-1}), and h is the Planck constant (6.62×10^{-27} erg sec). Plots of ln(k/T) against 1/T were found linear as represented in Figure 3. The slopes and intercepts of the lines were determined by least squares calculations. The enthalpies of activation

Table 5

Second-Order Rate Constants for the Acylation of Amines

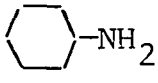
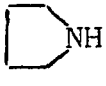
Amine	k, M^{-1} min^{-1} in Ethanol	in MB	in Acetonitrile
n-$C_4H_9NH_2$	7.60	2.75	8.67
$C_6H_5CH_2CH_2CH_2NH_2$	6.53	2.07	5.26
$C_6H_5CH_2CH_2NH_2$	2.94	1.08	1.68
	1.18	0.20	1.25
t-$C_4H_9NH_2$		very slow	very slow
$(C_2H_5)_2NH$		very slow	0.97
(n-$C_3H_7)_2NH$		very slow	0.29
(n-$C_4H_9)_2NH$		very slow	very slow
$CH_3CH_2CH(CH_3)CH_2NH_2$			4.27
$CH_3OCH_2CH_2NH_2$			1.91
			1360

Table 6

Activation Parameters in Ethanol

	n-butylamine			cyclohexylamine		
parameter	20.0 °C	30.0 °C	40.0 °C	20.0 °C	30.0 °C	40.0 °C
k, M^{-1} min^{-1}	5.66	8.04	11.04	0.92	1.23	1.72
$\Delta H^{\neq}$, Kcal mol^{-1}		5.50			5.10	
$\Delta S^{\neq}$, eu		-44.4			-49.4	
$\Delta F^{\neq}$, Kcal mol^{-1}		18.7			19.8	

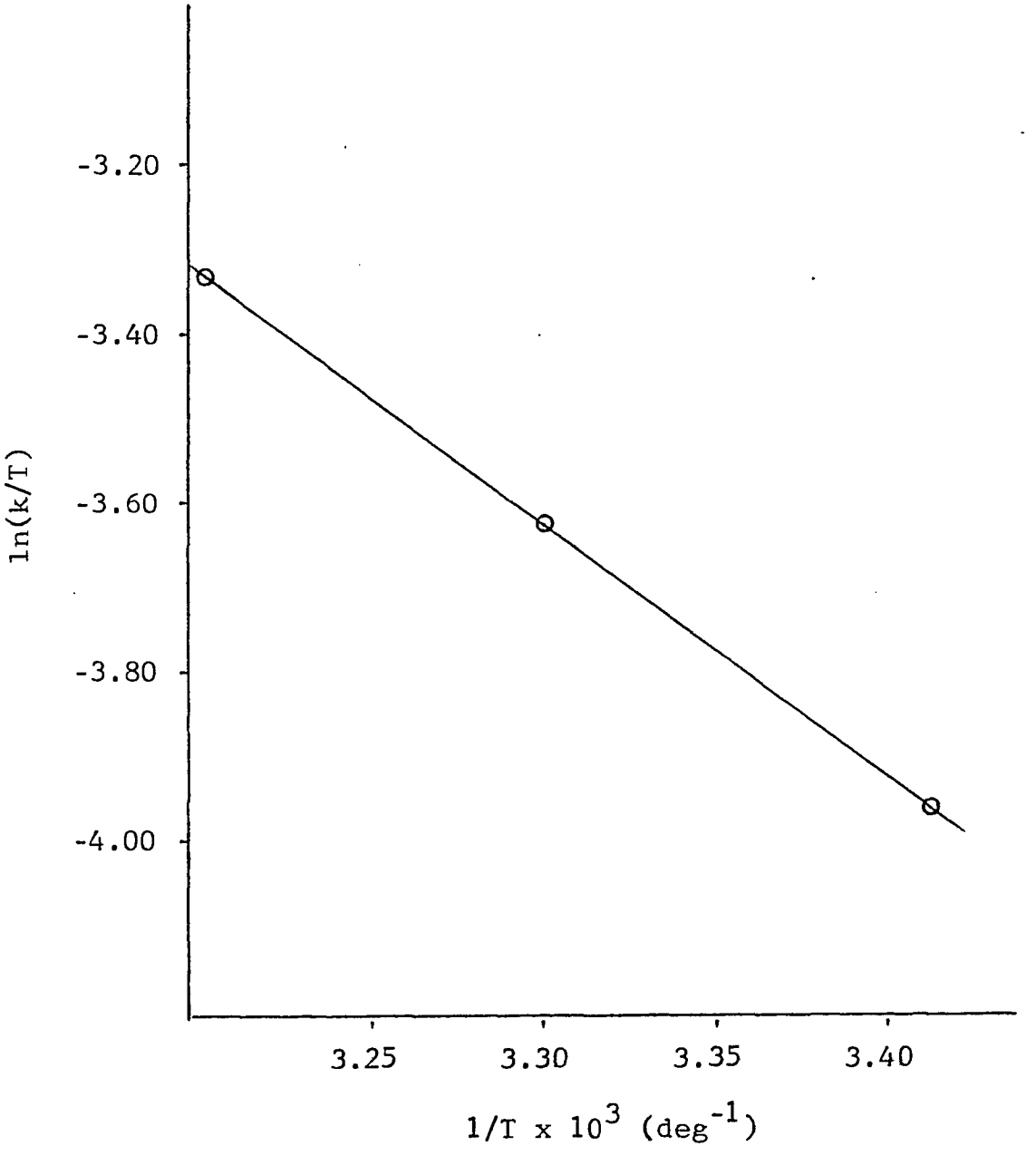


Figure 3. Plot of ln(k/T) versus 1/T

were calculated from the slopes of the lines by equation (12), and the entropies of activation were calculated

$$\Delta H^{\neq} = -R \text{ (slope)} \qquad (12)$$

from the intercepts using equation (13). Values of $\Delta H^{\neq}$

$$\Delta S^{\neq} = R\left[\text{intercept} - \ln(k_B/h)\right] \qquad (13)$$

and $\Delta S^{\neq}$ are also listed in Table 6. From the values of $\Delta H^{\neq}$ and $\Delta S^{\neq}$, the free energy of activation, $\Delta F^{\neq}$, for each amine was calculated by equation (14).

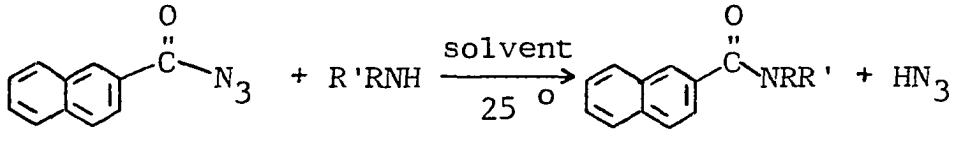
$$\Delta F^{\neq} = \Delta H^{\neq} - T\Delta S^{\neq} \qquad (14)$$

For all kinetic data, correlation coefficients ranged from 0.9917 to 0.9998.

CHAPTER IV

DISCUSSION OF RESULTS

The reaction of 2-naphthoyl azide with amines in this study can be represented by equation (15). Under the



(15)

conditions in which the reaction was carried out in ethanol, 2-methyl-2-butanol, and acetonitrile, the linear plots of A_t versus $A_{(t + T)}$ confirm that the reaction is first-order in azide concentration. Thus, equation (16) is written.

$$-d[\text{Acyl Azide}]/dt = k_{obs}[\text{Acyl Azide}] \qquad (16)$$

Here, k_{obs} is the pseudo first-order rate constant. Furthermore, the linear plots of k_{obs} against amine concentration, with intercepts at zero, also show that the reaction is first-order in the amine. So that k_{obs} is expressed as in equation (10). Consequently, the rate expression for the above reaction is given in equation (17).

$$-d[\text{Acyl Azide}]/dt = k[\text{Acyl Azide}][\text{Amine}] \qquad (17)$$

Here, k is the second-order rate constant.

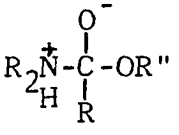
In the preceding rate expression, it is apparent that the reaction of 2-naphthoyl azide with amines does not involve any catalysis of the general base nature which is commonly observed in ester aminolysis.

These results confirm the second-order kinetics observed in the couplings of $PhCH_2OCO$-Gly-Phe N_3 with amino-acid-t-butyl esters in ethyl acetate.[10]

In Table 5, the rate constants for the acylation of the four amines, n-butyl-, γ-phenylpropyl-, β-phenethyl-, and cyclohexylamines in ethanol are shown to be considerably larger than those in 2-methyl-2-butanol. Since the dielectric constant of ethanol is 24.3 and that of 2-methyl-2-butanol is 5.82, the former is obviously the more polar of the two solvents.[30] Furthermore, the rate of reaction of 2-naphthoyl azide with n-butylamine is shown to decrease in the order of the following media, ethanol > 40% n-heptane in ethanol > 2-methyl-2-butanol > 20% 2-methyl-2-butanol in n-heptane. Since the dielectric constant of n-heptane is 1.92,[30] the above solvent systems should follow the same order in dielectric constant, and hence, in solvent polarity. It appears therefore, that increasing the polarity of solvent increases the rate of reaction of 2-naphthoyl azide with amines, although in these systems, solute-solvent interactions through hydrogen bonding may also play an important part.

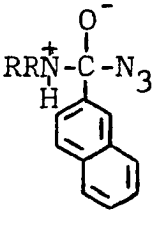
In ester aminolysis, the rate of reaction has also

been observed to increase with increasing polarity of solvent. For example, the reactions of substituted phenyl acetates and benzoates with amines in the more polar acetonitrile were shown to be much faster than in ether or chlorobenzene.[24] Whether ester aminolysis is carried out in protic or aprotic solvents, it has been consistently suggested that the reaction proceeds through an addition-elimination mechanism involving the formation of a tetrahedral intermediate. Such a mechanism is certainly sensitive to variations in the polarity of solvent since the intermediate is more polar than the



initial molecules.

This mechanism would also be consistent with the observation that the reaction of 2-naphthoyl azide with amines appears to increase with increasing polarity of solvent. Thus, a tetrahedral intermediate may also be proposed in this reaction as shown below.



The effect of structure on the rate of reaction of 2-naphthoyl azide with amines may be evaluated on the basis of steric requirements of amines. By addition-elimination mechanism, the intermediate of the preceding reaction should be more crowded than the initial acyl azide since the former is tetrahedral and the latter is trigonal. An increase in steric requirements of an amine should result in a corresponding increase in steric hindrance of the intermediate and hence, in energy barrier or free energy of activation, $\Delta F^{\neq}$, in the formation of the intermediate. Provided that electronic effects are equivalent, the effects of increasing the steric requirements of amines should result in a diminished rate of reaction. Indeed in Table 5, the rate constant for cyclohexylamine in ethanol is considerably smaller than that for n-butylamine. In acetonitrile also, the rate of reaction with t-butylamine was observed to be immeasurably slow compared to that of n-butylamine. In Table 7, it can be seen that both cyclohexylamine and t-butylamine are more sterically hindered than n-butylamine, while in Table 8 the basicities are shown to be similar for cyclohexylamine and n-butylamine in ethanol, and for t-butylamine and n-butylamine in acetonitrile. These results are in accord with those from previous studies on ester aminolysis,[34, 35, 36] and are consistent with addition-elimination mechanism in which a tetra-

Table 7

Steric Substituent Constants, Es, for Aliphatic Substituents in the Series, R'COOR, at 25 °C

Substituent	Es for Acyl Component, R'[31]
n-C_4H_9	-0.39
$C_6H_5CH_2CH_2$	-0.38
$C_6H_5CH_2CH_2CH_2$	-0.45
$CH_3OCH_2CH_2$	-0.77
Cyclo-C_6H_{11}	-0.79
t-C_4H_9	-1.54
$(C_2H_5)_2CH$	-1.98
$(n\text{-}C_3H_7)_2CH$	-2.11

Table 8

pK_a of Ammonium Ions of Amines in Ethanol and Acetonitrile

Amine	pK_a in ethanol[32]	pK_a in acetonitrile[33]
ammonia	8.55	16.46
ethylamine	9.39	18.40
n-propylamine	8.92	18.22
i-propylamine	9.15	–
n-butylamine	9.24	18.26
i-butylamine	–	17.92
t-butylamine	9.82	18.14
cyclohexylamine	9.20	–
benzylamine	8.20	16.76
ethanolamine	8.74	17.53
dimethylamine	–	18.73
diethylamine	9.15	18.75
di-n-propylamine	8.75	–
di-n-butylamine	8.80	18.31
pyrrolidine	9.23	19.58

hedral intermediate is formed.

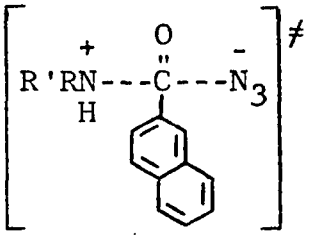
That an increase in steric hindrance of the intermediate would result in a corresponding increase in free energy of activation is consistent with the data shown in Table 6 in which the $\Delta F^{\neq}$ for the reaction of the acyl azide with cyclohexylamine in ethanol is greater than that with n-butylamine. Furthermore, it may be anticipated also that an increase in steric hindrance of the intermediate should result in a decrease in entropy of activation, $\Delta S^{\neq}$. This indeed appears to be the case in which the entropy of activation for the reaction of cyclohexylamine is more negative than that of n-butylamine. These results further support the idea that a tetrahedral intermediate is involved in this reaction.

The effect of structure of an amine on the rate of reaction with the acyl azide may be examined also on the basis of basicity of the amine. Increasing the basicity of the amine should result in an increase in its nucleophilicity towards the acyl azide. Provided that steric effects are approximately equivalent, increasing the basicity of the amine should make the addition of the amine to the carbonyl carbon of the acyl azide proceed faster. By the mechanism of addition-elimination involving the formation of a tetrahedral intermediate, the effects of increasing the basicity of the amine should result in an increase in the rate of intermediate for-

mation, and perhaps in the over-all rate of reaction.

In Table 1, the pK_a values of the following amines in aqueous solution are listed in the order, n-butylamine > γ-phenylpropylamine > β-phenethylamine. Although in the solvents employed, only the pK_a values of n-butylamine in ethanol and acetonitrile are known, the data in Table 8 appear to indicate that the same order in pK_a of the above amines should exist in all three solvents. The basicity of these amines therefore, should be in that order also. Since the steric requirements of these amines should be similar as indicated in Table 7 for the corresponding alkyl side chains, the decreasing order in rate constants for n-butylamine, γ-phenylpropylamine, and β-phenethylamine may be attributed therefore, to differences in amine basicity. Thus, it appears that the rate of reaction of 2-naphthoyl azide with amines in both protic and aprotic solvents increases with increasing basicity of amines. These results are in agreement also with those from previous investigations on ester aminolysis,[34, 35, 36] and consistent with the mechanism of addition-elimination.

Although a direct-displacement mechanism would also



be consistent with the data in Tables 5 and 6, the structural similarity of the acyl azide with esters, and the evidence from previous studies of the existence of tetrahedral intermediates in nucleophilic substitution or addition reactions with esters make addition-elimination the most likely mechanism involved in the reaction of 2-naphthoyl azide with amines in the solvent systems employed.

Although no direct evidence is presented in this study of the existence of a tetrahedral intermediate in this reaction, the agreement of results with proposed mechanism forms the basis in presuming that such an intermediate is involved. To speculate further on the proposed mechanism, the formation of the intermediate should constitute one step in the reaction, and the formation of products as another step. As the intermediate is formed, the azide group may leave the parent structure of the intermediate to form the products, or the protonated amine may depart from it to return to reactants. Nevertheless, the rates of the two processes may appear to depend on the leaving abilities of the amine and the azide ion. Since the ability of a leaving group is known to be inversely related to its basicity,[24, 37, 38] the leaving abilities of the amine and the azide ion may be evaluated on the basis of their respective basicities in the solvents employed.

In Table 9, the pK_a values of hydrazoic acid and

Table 9

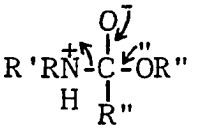
pK_a of Hydrazoic Acid and Substituted Phenols[39, 40]

Compound	pK_a in water	in methanol	in dimethyl sulfoxide	in dimethyl-formamide	in acetonitrile
4-nitrophenol	7.15	11.2	9.9	10.9	20.7
2,4-dinitrophenol	4.10	7.9	5.2	6.0	16.0
hydrazoic acid	4.74	8.9	7.9	8.5	–

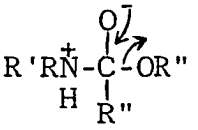
substituted phenols in various protic and polar aprotic solvents are listed. These data appear to suggest that the pK_a values of hydrazoic acid in ethanol and in 2-methyl-2-butanol are in the neighborhood of 9, and that in acetonitrile of approximately 18 to 19. On the other hand, the pK_a values of ammonium ions of various amines in ethanol and in acetonitrile are given in Table 8. It has been reported also that the pK_a values of primary and secondary amines in n-butyl alcohol are slightly higher than those in t-butyl alcohol.[41] These results appear to suggest that the pK_a values of the amines in ethanol are slightly higher than those in 2-methyl-2-butanol. At any rate, it seems as though the pK_a values of hydrazoic acid and those of ammonium ions of the amines employed should be similar. It follows that the basicities and hence, the leaving abilities of the amines and the azide ion must be similar also. On this basis, it may appear that the rate of intermediate breakdown to products may be comparable to that when it returns to reactants.

It has been reported that the leaving ability of a protonated amine in a tetrahedral intermediate is 10^5 times greater than that of an alkoxide group whose conjugate acid has a similar pK_a to that of the protonated amine.[42] These observations have been explained in terms of the leaving ability of each group and the anchimeric-type of assistance provided by the alkoxide group. Thus, in the

following structure of a tetrahedral intermediate, the

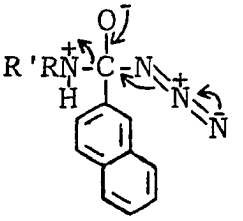


expulsion of the amine is aided by electron donation from the alkoxide group. In the case of the reverse process, the expulsion of the alkoxide ion is not assisted by the protonated amine for lack of electron pair in the latter



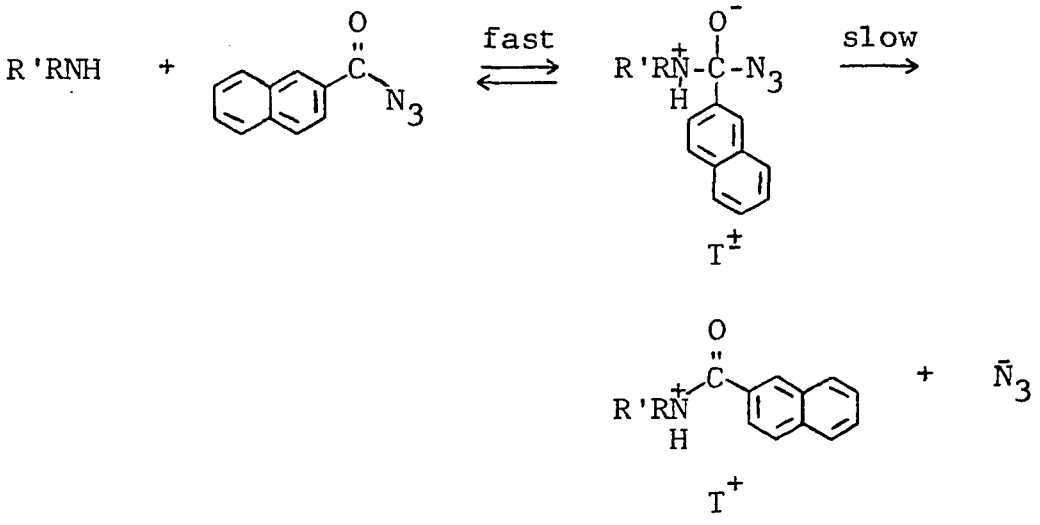
to donate.

In the acyl azide-amine intermediate, such conditions may possibly exist also since the azide group appears to be capable of donating a pair of electrons, whereas the



protonated amine does not have such capability to donate an electron pair. The possibility that the amine may leave the intermediate faster than the azide ion therefore, exists. Although no direct evidence is available in this study to support such possibility, the similarity in the

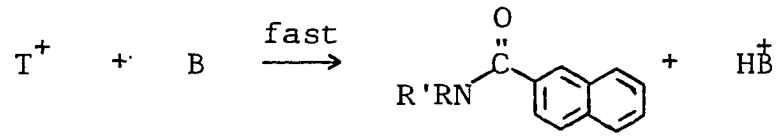
estimated basicities of amines and the azide ion and the possible tendency of the azide group in the tetrahedral intermediate to provide assistance in the expulsion of the protonated amine may be taken as the basis in postulating that the breakdown of the intermediate to expel the azide ion is rate-determining. Thus, the proposed mechanism of addition-elimination for the reaction of 2-naphthoyl azide with amines may be shown to involve a fast equilibrium step in the formation of a tetrahedral intermediate, followed by a slow collapse of the latter to form a protonated amide and an azide ion. In this mechanism,



the partitioning of the $T^{\pm}$ intermediate may be expected to favor the reactants over products since the reverse reaction of the $T^{\pm}$ intermediate dissipates charge. The ions however, may be stabilized through hydrogen bonding or ion-dipole interactions with substrate or solvent molecules.

In the reaction of substituted phenyl acetates and benzoates with pyrrolidine in acetonitrile, the expulsion of the leaving group as phenoxide ion has been confirmed.[24]

The T^+ intermediate may proceed to transfer a proton to a solvent or a second amine molecule and form the amide product. The fact that hydrolysis of amides is subject to hydronium ion catalysis[43, 44] appears to suggest that the removal of the proton from the T^+ intermediate occurs in a rapid manner. In this mechanism, the fast removal of a



proton after the rate-determining step is consistent with the observation that the reaction of 2-naphthoyl azide with amines does not involve general base catalysis.

The sensitivity of the acyl azide-amine reaction to both electronic and steric variations of amines may be considered qualitatively only based on the data in Table 5. These results indicate that β-phenethylamine reacts with 2-naphthoyl azide faster than cyclohexylamine in all three solvents employed. Although the pK_a of β-phenethylamine is not known in any of these solvents, the data in Tables 1 and 8 suggest that cyclohexylamine is the more basic of the two amines, but more hindered sterically than β-phenethylamine as shown by the steric substituent constants for cyclohexyl and β-phenethyl groups re-

spectively in Table 7. Furthermore, the data in Table 5 indicate that n-butylamine reacts with the acyl azide considerably faster than diethylamine in acetonitrile. Again in Table 8, diethylamine is shown to be more basic than n-butylamine in this solvent but, the former is more hindered sterically than the latter amine as indicated also in Table 6. Thus, it appears as if steric effects on the reaction predominates over electronic effects.

On the other hand, the combination of high basicity and small steric hindrance of pyrrolidine is shown to increase the rate of acylation with the acyl azide dramatically.

CHAPTER V

EXPERIMENTAL METHODS AND PROCEDURES

Chemicals and Equipment

Ethanol was received as absolute grade without denaturant and was used without further purification. The solvents, 2-methyl-2-butanol, acetonitrile, and n-heptane, and all the amines employed in this study were also obtained commercially. Purification of these chemicals was accomplished prior to use by established procedures described in the next section. The 2-naphthoyl azide was prepared in the laboratory by a previously described procedure. Authentic samples of amide products were prepared from 2-naphthoyl azide and the corresponding amines as described in the section on the preparation of amide derivatives.

Spectral analyses of amide samples were accomplished with a Varian Associates Model A-60 Nuclear Magnetic Resonance (NMR) and Beckman Acculab 8 Infrared Spectrophotometers. Mass spectra were obtained with a Dupont 21-490 B Mass Spectrometer. Chemical shifts in NMR spectra were expressed as ppm using tetramethylsilane as reference. The multiplicties of signals were recorded as s, d, t, q, m, and b for singlet, doublet, triplet, quartet, multiplet, and broad, respectively. Elemental analyses were performed by Midwest Microlab, Ltd., Indianapolis, Indiana. Absorption

maxima of acyl azide and amide products were determined using the Cary 14 Spectrophotometer. All gas chromatographic analyses were performed on a Varian Aerograph Series 2700 equipped with an SE-30 column. The melting points of solids were determined on a Thomas-Hoover melting point apparatus. Teflon-stoppered quartz cuvettes with one-centimeter path lengths were used to contain reaction mixtures and a Gilford 252 Spectrophotometer was employed to monitor the progress of reactions. The sample compartment of the spectrophotometer was thermostated at 25 ^{o}C using a constant temperature water bath. A glovebag filled with dry nitrogen was used in preparing solutions in acetonitrile.

Purification of Solvents

2-Methyl-2-butanol was purified by first treating with activated carbon several times followed by fractional distillation through an approximately 10-theoretical plate column in an all-glass distillation apparatus. A constant boiling fraction was obtained at 102 ^{o}C.

Acetonitrile[23] was purified by first drying over phosphorus pentoxide twice overnight followed by drying over anhydrous potassium carbonate. Fractional distillation was carried out after each drying process using the all-glass apparatus above. The distillation system was under dry nitrogen and protected from moisture by a

soda lime tower. A constant boiling fraction at 82 °C was recovered and stored in a brown glass bottle which contained 3 Å molecular sieves.

The n-heptane was refluxed over freshly cut pieces of sodium metal for about an hour and distilled through the same fractionating column used above. A constant boiling fraction was recovered at 98 °C.[30]

Purification of Amines[23]

An amine was dried over potassium hydroxide pellets overnight followed by fractional distillation in an all-glass distilling apparatus equipped with a 50-centimeter column under dry nitrogen, and protected from moisture and carbon dioxide by a soda lime tower. A constant boiling middle fraction was collected in a teflon-stoppered glass bottle and stored over potassium hydroxide pellets in a dessicator. Its purity was evaluated on the basis of refractive index, and by gas chromatography. The results are listed in Table 10.

Preparation of 2-Naphthoyl Azide[45]

Into a 250 mL round-bottom flask in a reflux apparatus were placed 34.4 g (0.200 mol) of 2-naphthoic acid, 120 mL (2.0 mol) of ethanol, and 7 mL of concentrated sulfuric acid. The components were mixed thoroughly and allowed to reflux for one hour. The mixture was cooled to room temperature, transferred into a separatory funnel

Table 10

Physical Properties of Purified Amines

Amine	bp, °C[a]	bp, °C[b]	n^{21}[a]	n^{20}[c]	GC, peak
$n\text{-}C_4H_9NH_2$	77.0	77.8	1.4014	1.4015	1
$C_6H_5CH_2CH_2CH_2NH_2$	91.0/2.2 mm	221[c]	1.5258	1.5260	1
$C_6H_5CH_2CH_2NH_2$	89.0/2.3 mm	197-198	1.5334	1.5332	1
$Cyclo\text{-}C_6H_{11}NH_2$	135.0	134.5	1.4593	1.4580	1
$t\text{-}C_4H_9NH_2$	45.5	44.4	1.3788	1.3784[b]	1
$CH_3CH_2CH(CH_3)CH_2NH_2$	97.0	97[c]	1.4113	1.4116	1
$CH_3OCH_2CH_2NH_2$	91.0	95	1.4064	1.4054	1
$(C_2H_5)_2NH$	55.5	56.3	1.3860	1.3864[b]	1
$(n\text{-}C_3H_7)_2NH$	107.0	109	1.4040	1.4050[b]	1
$(n\text{-}C_4H_9)_2NH$	70.0/33 mm	159	1.4180	1.4177[b]	1
 NH	86.0	88	1.4438	1.4431[b]	1

[a]Experimental values.

[b]Weast, R. C. Handbook of Chemistry and Physics (63rd ed.) CRC Press, 1973, p. C-185-C-492.

[c]Aldrich Handbook of Fine Chemicals, Aldrich Chemical Co., Inc., 1980.

containing 125 mL of water, and extracted with 100 mL of ether. The layers were separated, and the ether layer was washed with 60 mL of water followed by washing with 60 mL of 5% sodium bicarbonate solution. (Note: washing with the sodium bicarbonate solution was continued until the organic layer was no longer acidic to litmus.) The ether layer was dried over anhydrous magnesium sulfate and filtered through a sintered glass filter by suction. The ether was removed by distillation over the steam bath and the residual liquid was distilled under reduced pressure of less than 0.5 mm. A 27.15 g sample of ethyl 2-naphthoate was collected at 111-122 ^{o}C at 0.45 mm. (Note: the boiling point of distillate varied with temperature of oil bath.)

Into a 100 mL reound-bottom flask in a reflux apparatus were placed 25.0 g (0.125 mol) of ethyl 2-naphthoate, 8 mL of 95% hydrazine, and 30 mL of absolute ethanol. The components were mixed thoroughly and refluxed for 2.5 hours. The mixture was allowed to cool to room temperature and crystals of crude 2-naphthoyl hydrazide formed. The crude product was then filtered and recrystallized from aqueous ethanol. A 16.86 g sample of purified product was recovered with a melting point of 146-148 ^{o}C.

Into a 250 mL Erlenmeyer flask were placed 3.80 g (0.020 mol) of 2-naphthoyl hydrazide and 30 mL of glacial acetic acid. The solid was dissolved in the acid and

cooled to 0-5 °C. A solution of 3.80 g (0.048 mol) of sodium nitrite in 12 mL of water cooled to 0-5 °C, was added in one portion to the acid solution of the hydrazide. Cooling was continued while the resulting mixture was being stirred. The mixture was then filtered by suction, and the crude solid was washed twice with water. The crude product was purified by recrystallization at freezer temperatures from a 1:1 diethyl ether-petroleum ether mixture. A 3.00 g sample of 2-naphthoyl azide was collected with a melting point of 77.3-78.5 °C.

Preparation of Amide Derivatives

A 0.500 g (2.54×10^{-3} mol) sample of 2-naphthoyl azide was transferred into a 125 mL Erlenmeyer flask, and 20 mL of solvent was added to dissolve it. To this solution was added 5.08×10^{-2} mol of an amine dissolved in 20 mL of the same solvent. The mixture was allowed to stand at room temperature for one hour to overnight. The solvent was removed at reduced pressure in a rotary evaporator which was heated over a hot water bath. The residue was dissolved in a 1:1 methylene chloride-diethyl ether mixture, and transferred into a separatory funnel. The resulting mixture was then washed twice with 5% hydrochloric acid, followed by washing with water, 5% sodium bicarbonate, and finally with water. The organic layer was dried over anhydrous magnesium sulfate, filtered by

suction, and the solvent removed under reduced pressure in the rotary evaporator. Solid products were purified by recrystallization from a 1:1 diethyl ether-petroleum ether mixture, and liquid products by column chromatography using acid washed activated alumina. Determination of the yields of amide products was achieved by isolation and by gas chromatography.

Purification by Column Chromatography

The chromatographic column was prepared in the following manner. A piece of glass wool was fitted at the bottom of a 1.3 x 50 centimeter chromatographic buret. The buret was then filled with petroleum ether 2/3 full. A 30 to 35 g sample of 80 to 140 mesh, acid washed alumina was added through a funnel while constantly tapping the sides of the column. A piece of glass wool was inserted to cover the top of the alumina column, and the level of petroleum ether was brought down to the top of the glass wool.

Column chromatography was accomplished by pipetting one g of crude liquid product dissolved in one mL of methylene chloride into the column. The liquid was allowed to drain to the top of the glass wool and the sides of the buret were rinsed with a little methylene chloride. Again, the liquid was drained slightly, and 20 mL of petroleum ether were added to elute the column first.

This was followed by 40 to 50 mL of a 1:1 methylene chloride-petroleum ether mixture, and finally with pure methylene chloride. The eluate was recovered in approximately 10 mL fractions. The solvent in each fraction was removed by warming over a hot water bath and blowing air on it simultaneously. Purity of the product was evaluated by gas chromatography.

Determination of Yield by Gas Chromatography

The gas chromatograph was first calibrated with a mixture of 1.600×10^{-4} mol of an amide derivative and 1.600×10^{-4} mol of an internal standard, triphenylmethane or phenanthrene, in a 1.00 mL of solution using an SE 30 column. The detector response ratio was determined from the amounts of amide and internal standard used, and the corresponding peaks of the two compounds in the gas chromatogram.

Quantitative analysis of reaction mixtures was accomplished by mixing 0.50 mL of 0.3200 M (1.600×10^{-4} mol) of 2-naphthoyl azide solution with approximately 4×10^{-3} mol of an amine. The mixture was allowed to stand overnight at room temperature, and a 0.50 mL of 0.3200 M (1.600×10^{-4} mol) of an internal standard, triphenylmethane or phenanthrene, was added. Analysis of the mixture was done similarly in the gas chromatograph. Results are listed in Table 2.

Kinetic Measurements

Stock solutions of the acyl azide in the solvents employed were prepared ranging in concentrations from 0.0150 M in acetonitrile to 0.0324 M in 2-methyl-2-butanol. Solutions in acetonitrile were prepared in the glovebag under dry nitrogen atmosphere.

Solutions of amines were prepared as described below. An appropriate amount of an amine was accurately weighed into a volumetric flask in an analytical balance, dissolved in an appropriate solvent, and diluted to the mark to make up the stock solution. A series of dilutions were made on the stock solution to obtain a set of solutions of different amine concentrations. The minimum amine concentration was at least 20 times that of the acyl azide in the final reaction mixture, except in the case with pyrrolidine in which the concentration of the latter was approximately 13 times that of the acyl azide in the mixture. The range in amine concentration was at least 10 fold. Solutions in acetonitrile were prepared in the glovebag under dry nitrogen.

In preparing the reaction mixture, a stock solution of 2-naphthoyl azide, and a 5.00 mL of diluted amine solution in the same solvent were thermostated at 25 ^{o}C in the constant temperature water bath for at least 15 minutes. A 5 μL volume of the acyl azide solution was transferred into the amine solution, and the two were

mixed thoroughly.

Spectrophotometric measurements were carried out on a 3 to 4 mL volume of the reaction mixture above contained in a thermostated quartz cuvette in the sample compartment of the spectrophotometer. Absorbance readings were taken at an appropriate wavelength using the same solvent as reference. Absorbance readings were taken at equal time intervals until at least 2 half-lives of reaction.

Physical Data of Amide Products

N-n-Butyl-2-naphthamide: mp 116-116.5 °C; molecular ion m/e 227 (Calcd 227); nmr ($CDCl_3$) δ 0.7-1.8 (m, 7H, aliphatic CH), 3.46 (d of t, 2H, $NHCH_2CH_2$), 6.9 (b, 1H, NH), 7.3-7.9 (m, 6H, aryl CH), 8.25 (s, 1H, α-aryl CH). Anal. Calcd for $C_{15}H_{17}NO$: C, 79.25; H, 7.55; N, 6.16. Found: C, 79.14; H, 7.41; N, 6.56.

N-(γ-phenylpropyl)-2-naphthamide: mp 99-100 °C; molecular ion m/e 289 (Calcd 289); nmr ($CDCl_3$) δ 2.00 (q, 2CH, $CH_2CH_2CH_2$), 2.70 (t, 2H, CH_2CH_2Ar), 3.50 (q, 2H, $NHCH_2CH_2$), 6.6 (b, 1H, NH), 7.18 (s, 5H, aryl CH), 7.3-7.9 (m, 6H, aryl CH), 8.12 (s, 1H, α-aryl CH). Anal. Calcd for $C_{20}H_{19}NO$: C, 83.00; H, 6.63; N, 4.84. Found: C, 82.39; H, 6.63; N, 5.16.

N-(β-Phenethyl)-2-naphthamide: mp 133-134 °C; molecular ion m/e 275 (Calcd 275); nmr ($CDCl_3$) δ 2.98 (t, 2H, CH_2CH_2Ar), 3.7 (d of t, 2H, $NHCH_2CH_2$), 7.22 (s, 5H, aryl CH), 7.3-8.0 (m, 6H, aryl CH and NH), 8.35 (s, 1H,

aryl CH). Anal. Calcd for $C_{19}H_{17}NO$: C, 82.87; H, 6.24; N, 5.09. Found C, 82.58; H, 6.24; N, 4.94.

N-Cyclohexyl-2-naphthamide: mp 183-184 °C; molecular ion m/e 253 (Calcd 253); nmr ($CDCl_3$) δ 1.1-2.2 (m, 10H, alicyclic CH), 3.95 (b, 1H, alicyclic CH), 7.3-8.0 (m, 7H, aryl CH and NH), 8.35 (s, 1H, α-aryl CH). Anal. Calcd for $C_{17}H_{19}NO$: C, 80.58; H, 7.57: N, 5.53. Found: C, 80.46; H, 7.55; N, 6.21.

N-t-Butyl-2-naphthamide: mp 156.5-157.5 °C; molecular ion m/e 227 (Calcd 227); nmr ($CDCl_3$) δ 1.5 (s, 9H, $C(CH_3)_3$), 6.2 (b, 1H, NH), 7.3-7.9 (m, 6H, aryl CH), 8.18 (s, 1H, α-aryl CH). Anal.Calcd for $C_{15}H_{17}NO$: C, 79.25; H, 7.55; N, 6.16. Found: C, 78.97; H, 7.61; N, 5.84.

N,N-Diethyl-2-naphthamide: thick yellowish oil; molecular ion m/e 227 (Calcd 227); nmr ($CDCl_3$) δ 1.18 (t, 6H, $(CH_2CH_3)_2$), 3.4 (bq, 4H, $N(CH_2CH_3)_2$), 7.3-8.0 (m, 7H, aryl CH). Anal. Calcd for $C_{15}H_{17}NO$: C, 79.25; H, 7.55; N, 6.16. Found: C, 78.73; H, 7.38; N, 6.34.

N,N-(Di-n-propyl)-2-naphthamide: thick, yellowish oil; molecular ion m/e 225 (Calcd 255); nmr ($CDCl_3$) δ 0.6-1.9 (m, 10H, $(CH_2CH_2CH_3)_2$), 3.36 (b, 4H, $N(CH_2CH_2CH_3)_2$), 7.3-8.0 (m, 7H, aryl CH). Anal. Calcd for $C_{17}H_{21}NO$: C, 79.94; H, 8.30; N, 5.49. Found: C, 79.28; H, 8.35; N, 5.27.

N,N-(Di-n-butyl)-2-naphthamide: thick, yellowish oil; molecular ion m/e 283 (Calcd 283); nmr ($CDCl_3$) δ 0.6-

1.9 (bm, 14H, aliphatic CH), 3.4 (b, 4H, $N(CH_2CH_2-)_2$), 7.3-8.0 (m, 7H, aryl CH). Anal. Calcd for $C_{19}H_{25}NO$: C, 80.50; H, 8.91; N, 4.94. Found: C, 80.43; H, 8.78; N, 5.52.

N-(2-Methylbutyl)-2-naphthamide: mp 98-98.5 °C; molecular ion m/e 241 (Calcd 241); nmr ($CDCl_3$) δ 0.8-1.9 (m, 9H, aliphatic CH), 3.38 (t of d, 2H, $NHCH_2CH$), 6.68 (b, 1H, NH), 7.3-80 (m, 6H, aryl CH), 8.22 (s, 1H, α-aryl CH). Anal. Calcd for $C_{16}H_{19}NO$: C, 79.67; H, 7.88; N, 5.81. Found: C, 80.20; H, 8.13; N, 5.92.

N-(2-Methoxyethyl)-2-naphthamide: mp 99-100 °C; molecular ion m/e 229 (Calcd 229); nmr ($CDCl_3$) δ 3.36 (s, 3H, OCH_3), 3.5-3.9 (m, 4H, aliphatic CH), 6.86 (b, 1H, NH), 7.3-8.0 (m, 6H, aryl CH), 8.28 (s, 1H, α-aryl CH). Anal. Calcd for $C_{14}H_{15}NO_2$: C, 73.36; H, 6.55; N, 6.11. Found: C, 73.56; H, 6.76; N, 6.13.

1-(2-Naphthoyl) pyrrolidine: mp 75.5-76.5 °C; molecular ion m/e 225 (Calcd 225); nmr ($CDCl_3$) δ 1.8 (b, 4H, alicyclic CH), 3.2-3.9 (b, 4H, alicyclic CH), 7.3-8.1 (m, 7H, aryl CH). Anal. Calcd for $C_{15}H_{15}NO$: C, 80.00; H, 6.67; N, 6.22. Found: C, 80.73; H, 6.93; N, 6.39.

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