67-17,717

TRATTNER, Richard B., 1938-
THE REACTION OF ACYL HALIDES WITH
2-NAPHTHOXIDE ANION.

The City University of New York, Ph.D., 1967
Chemistry, organic

University Microfilms, Inc., Ann Arbor, Michigan

THE REACTION OF ACYL HALIDES WITH 2-NAPHTHOXIDE ANION

by

RICHARD B. TRATTNER

A dissertation submitted to the
Graduate Faculty in Chemistry in partial
fulfillment of the requirements for the
degree of Doctor of Philosophy,
The City University of New York.

1967

This manuscript has been read and accepted for the University Committee in Chemistry in satisfaction of the dissertation requirement for the degree of Doctor of Philosophy.

July 6, 1967
date

Paul Haberfield
Chairman of Examining Committee

July 10, 1967
date

Richard H Wiley
Executive Officer

Samuel H. Wilen
Aaron Lukton
Paul Haberfield
Supervisory Committee

The City University of New York

ACKNOWLEDGEMENT

To Professor Paul Haberfield, for his encouragement and guidance; and to my wife, for her understanding and patience, many thanks.

The author would also like to thank Professors A.Lukton and S.Wilen for their helpful suggestions during the preparation of this thesis.

TABLE OF CONTENTS

TABLE OF CONTENTS

TABLE OF CONTENTS

LIST OF TABLES

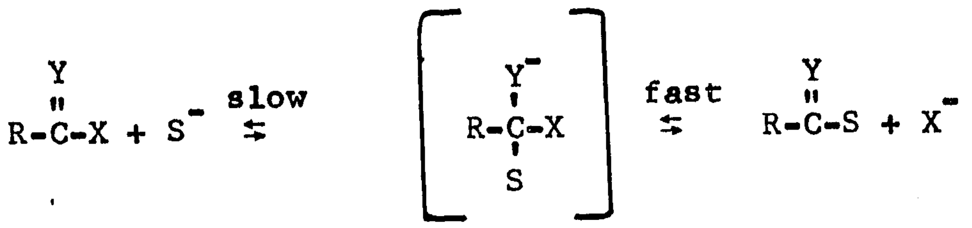
LIST OF TABLES

LIST OF FIGURES

LIST OF FIGURES

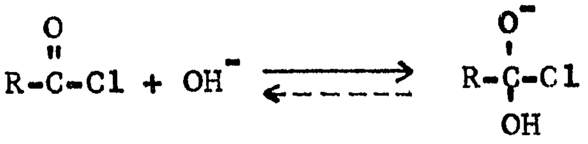
I. INTRODUCTION

If one considers bimolecular nucleophilic displacement reactions in compounds of the general structure R-C(X)=Y (e.g. acyl halides, esters and amides), it is generally assumed that these reactions proceed through a tetrahedral intermediate(i.e. via an addition-elimination mechanism).



$$\text{R-}\overset{\overset{\text{Y}}{\|}}{\text{C}}\text{-X} + \text{S}^- \overset{\text{slow}}{\rightleftarrows} \left[\text{R-}\underset{\underset{\text{S}}{|}}{\overset{\overset{\text{Y}^-}{|}}{\text{C}}}\text{-X} \right] \overset{\text{fast}}{\rightleftarrows} \text{R-}\overset{\overset{\text{Y}}{\|}}{\text{C}}\text{-S} + \text{X}^-$$

However, few examples are available in the literature which provide evidence of such intermediates. The classic examples are found in the specific acid- and base-catalyzed hydrolysis of esters and amides as studied by Bender and coworkers[1]. In these studies it was established that exchange reactions occurred between H_2O^{18} and the ester or amide carbonyl oxygen. No analogous work has been carried out for base-catalyzed nucleophilic attack on an acylating agent(e.g. Y=O, X=halogen) to determine whether, in the case of a bimolecular reaction, the mechanistic pathway involves a tetrahedral intermediate or a synchronous displacement. This is not surprising since the formation of the intermediate



$$\text{R-}\overset{\overset{\text{O}}{\|}}{\text{C}}\text{-Cl} + \text{OH}^- \rightleftarrows \text{R-}\underset{\underset{\text{OH}}{|}}{\overset{\overset{\text{O}^-}{|}}{\text{C}}}\text{-Cl}$$

should not be reversible because Cl^- is a much better leaving group than OH^-. Therefore, exchange between the carbonyl oxygen and H_2O^{18} would not be expected.

The 2-naphthoxide ion is an ambident anion capable of covalency formation at oxygen or at the 1-carbon position (Figure 1).

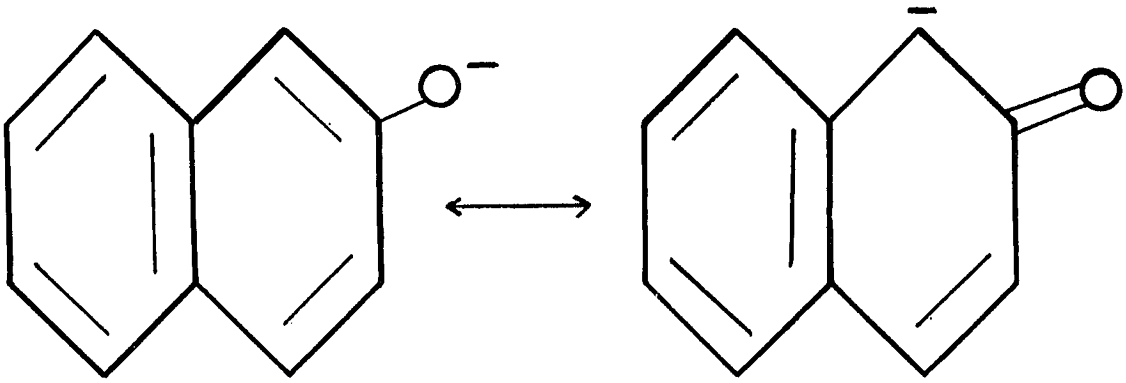


Figure 1

Previous to this report, the literature has reported only the ester as the product when the salts of 2-naphthol are acylated. The discovery that solvation is a factor in the alkylation of ambident phenoxide[2] and naphthoxide ions[3] suggested that an analogous study on the acylation of such ambident anions might allow one to choose between alternative mechanisms for the bimolecular acylation reaction. The need for such a study has recently been pointed out[4].

2-Naphthoxide ion was chosen over phenoxide ion as the ambident anion since it is known that competition between oxygen and carbon for an alkylating agent is more evenly balanced in 2-naphthoxide ion[5]. It is therefore not unreasonable to assume that such conditions would also hold for an acylating agent.

Acylation may take place either on the oxygen to give an ester(Figure 2)

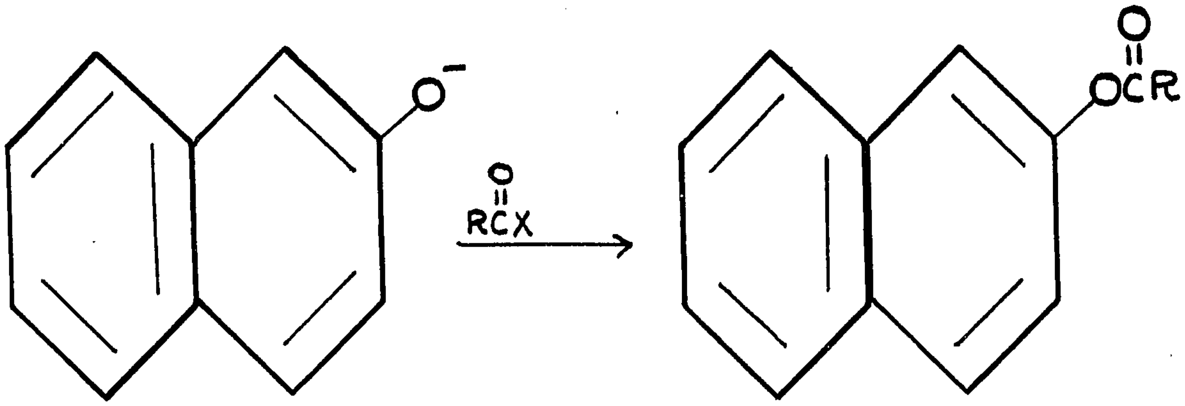


Figure 2

or on the 1-carbon to give a keto-naphthol(Figure 3).

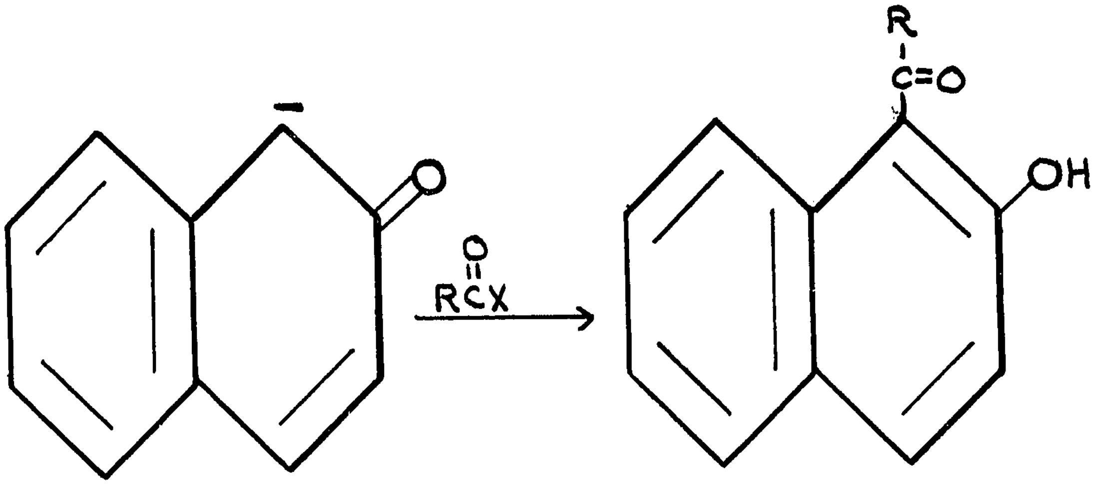


Figure 3

By observing the change in O/C acylation ratio as the reaction conditions are altered(i.e. change in solvent, leaving group, metal cation and the <u>para</u>-substituent of the acyl halide), one may draw inferences as to the nature of the transition state through which this base-catalyzed bimolecular acylation is proceding.

II.HISTORICAL BACKGROUND

Ambident Anions. The usefulness of ambident nucleophiles for studying borderline mechanisms in substitution reactions at saturated carbon has been demonstrated by many investigators.[6,7,8,9,10,11] Kornblum and coworkers first proposed the use of the name "ambident" anion or nucleophile for anions which can undergo covalence formation at either of two available positions.[8] He employed the nitrite ion as an ambident anion in studying the mechanism of the reaction of alkyl halides with silver and alkali metal nitrites in anhydrous diethyl ether. Attention was directed particularly toward the influence of electrical effects on the reaction course. Alkylation may take place on the nitrogen to yield the nitro compound or on the oxygen to yield the nitrite ester. The yield of nitro compound falls progressively as silver nitrite is alkylated with primary,[6,8] secondary and tertiary halides[7]. This reaction of alkyl halides with silver nitrite is proposed to proceed via a transition state which has both S_N1 and S_N2 character in proportions which vary with the structure of the halides(see Tables I II, III, IV and V).

Table I

Reaction of Straight Chain Halides with Silver Nitrite[6,a]

Halide	% Nitroparaffin	% Nitrite Ester
n-Butyl bromide	73	13
n-Butyl iodide	74	12
n-Hexyl chloride	0	0
n-Hexyl bromide	76	10
n-Hexyl iodide	78	13
n-Heptyl bromide	79	11
n-Heptyl iodide	82	10
n-Octyl chloride	0	0
n-Octyl bromide	80	14
n-Octyl iodide	83	11

Table II

Reaction of Branched Chain Primary Halides with Silver Nitrite[6,a]

Isobutyl bromide	17-18	12-16
Isobutyl iodide	55-63	17-22
Isoamyl bromide	72	22
Isoamyl iodide	78	16
Neopentyl iodide	0	0

a. Reactions were initiated at -10 to 0° in diethyl ether and completed at room temperature.

Table III

Reaction of Benzyl Bromides with Silver Nitrite[8,a]

Halide	% Nitroparaffin	% Nitrite Ester
4-Nitrobenzyl	84	16
Benzyl	70	30
4-Methylbenzyl	52	48
4-Methoxybenzyl	39	61

Table IV

Reaction of Secondary Halides with Silver Nitrite[7,a]

2-Chloropropane	0	0
2-Bromopropane	19-26	24-34
2-Iodopropane	15-23	23-35
2-Chlorobutane	0	0
2-Bromobutane	19-24	27-37
2-Iodobutane	10-15	30-35
4-Bromoheptane	7-15	22-29
4-Iodoheptane	9	27
2-Chlorooctane	0	0
2-Bromooctane	17-23	18-25
2-Iodooctane	15-20	17-25
2-Methyl-5-bromooctane	11	34
2-Methyl-5-iodooctane	14	30
1-Phenyl-2-bromopropane	18	33
1-Phenyl-2-iodopropane	15-20	26

a. Reactions were initiated at -10 to 0° in diethyl ether and completed at room temperature.

Table V

Reaction of Tertiary Halides with Silver Nitrite[7,a]

Halide	% Nitroparaffin	% Nitrite Ester
t-Butyl chloride	4-6	63-64
t-Butyl bromide	0	63-64
t-Butyl iodide	0	0
t-Amyl chloride	5-6	57-58
t-Amyl bromide	0	50-60
2-Methyl-2-chlorooctane	0	49
2-Methyl-2-bromooctane	0	33

a. Reactions were initiated at -10 to 0° in diethyl ether and completed at room temperature.

The products of the reaction reflect this variation in character: the greater the carbonium ion-character contribution to the transition state, the greater the yield of nitrite ester and the smaller the yield of nitro compound. The anion NO_2^- shows a preference for covalency formation at the atom of higher electronegativity(oxygen). Electrophilic attack by silver on the halogen of the alkyl halide greatly enhances the carbonium ion contribution to the transition state and this results in a preference for covalency formation to the most electronegative atom of the anion. This prefernce is taken to mean that in a reaction having a relatively large amount of S_N1 character, simple electrostatic forces govern the course of the reaction. The following generalization concerning the alkylation of anions capable of covalency formation at two different atoms(ambident anions), which is fully applicable even if the silver is absent, is presented by Kornblum as an explanation for carbon vs. oxygen alkylation, oxygen vs. nitrogen alkylation etc., in anions derived from acetoacetic ester, thioamides, phenols, nitroparaffins, alpha-pyridone, acid amides etc.: "The greater the S_N1 character of the transition state, the greater is the preference for covalency formation with the atom of higher electronegativity and, conversely, the greater the S_N2 contribution to the transition state, the greater the preference for bond formation to the atom of lower electronegativity."[8]

The silver ion polarizes the carbon-halogen bond of the alkyl halide thereby enhancing the development of carbonium-ion character of the transition state. Silver ions, while very effective for this purpose, are not unique. Changes in the reaction medium and in the structure of the alkylating agent are also able to profoundly effect the nature of the transition state; when this occurs, the nature of the products is also changed.

In a later study of the alkylation of ambident phenoxide ions, it was discovered that a new factor, heterogeneity vs. homogeneity was of paramount importance.[5] Phenoxide ions, being ambident anions, are capable of undergoing alkylation either on carbon or oxygen(see Figure 4).

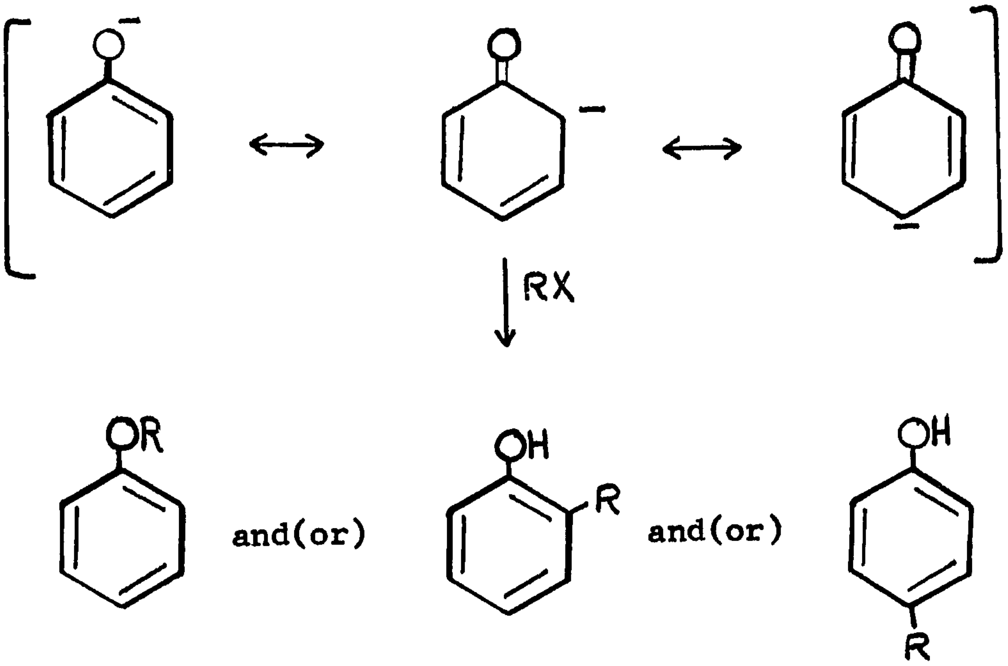
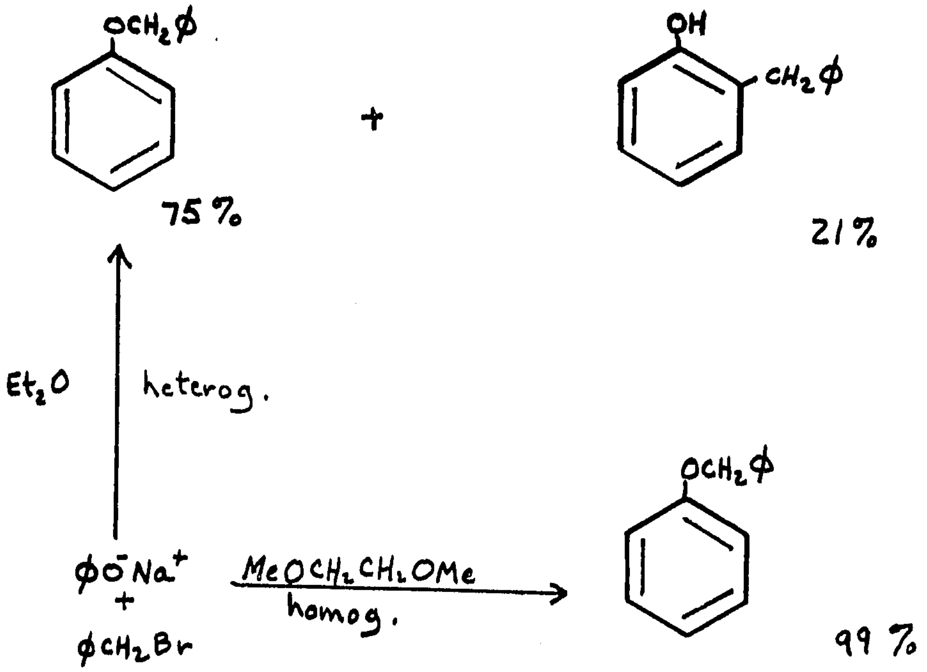


Figure 4

The experiments are summarized in Figure 5.

Part A



Part B

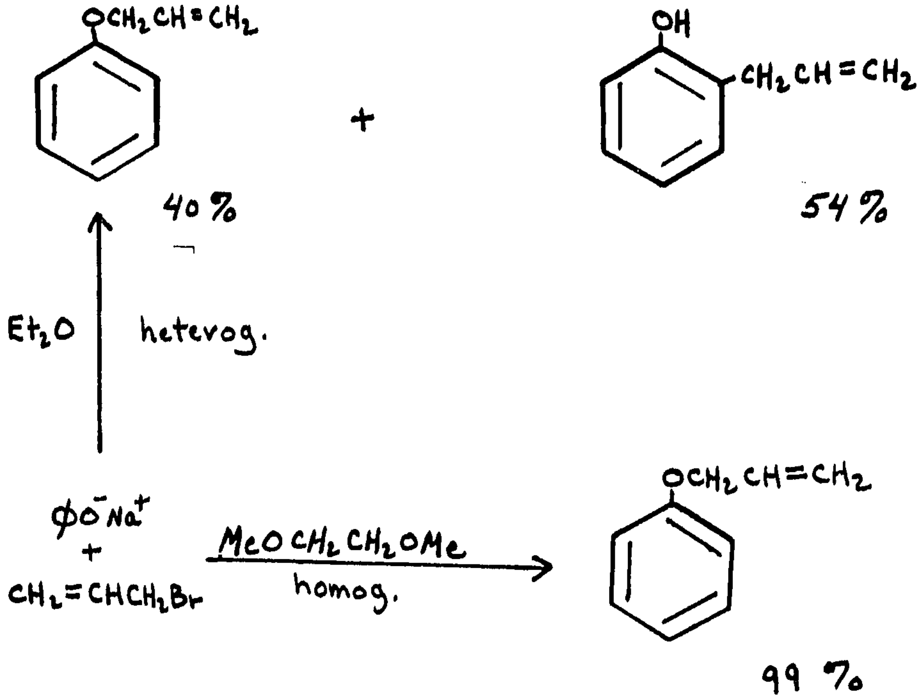
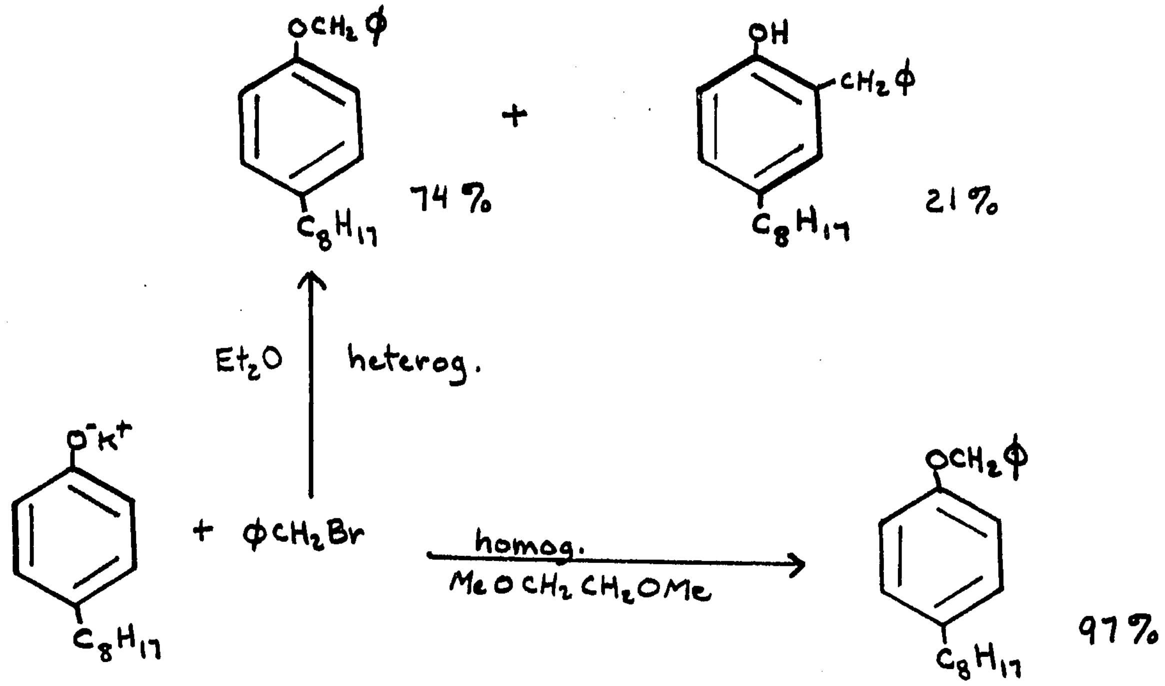


Figure 5

Alkylations in diethyl ether(heterogeneous) were found to give substantial yields of C-alkylation whereas the same alkylations, conducted homogeneously in ethylene glycol dimethyl ether, gave no C-alkylation. Specific solvation was ruled out as a possible cause of this difference by reacting the sodium salt of p-(t-octyl)phenol with benzyl bromide both in ether and ethylene glycol dimethyl ether (both homogeneously). In either case, a 99% yield of the O-alkylated product was obtained. Similar results were obtained with allyl bromide. This rules out specific solvation as a cause of C-alkylation but does not associate C-alkylation with heterogeneity and O-alkylation with homogeneity. In order to associate C-alkylation with heterogeneity and O-alkylation with homogeneity, a set of experiments was carried out, the results of which are shown in Figure 6.[5]

Part A



Part B

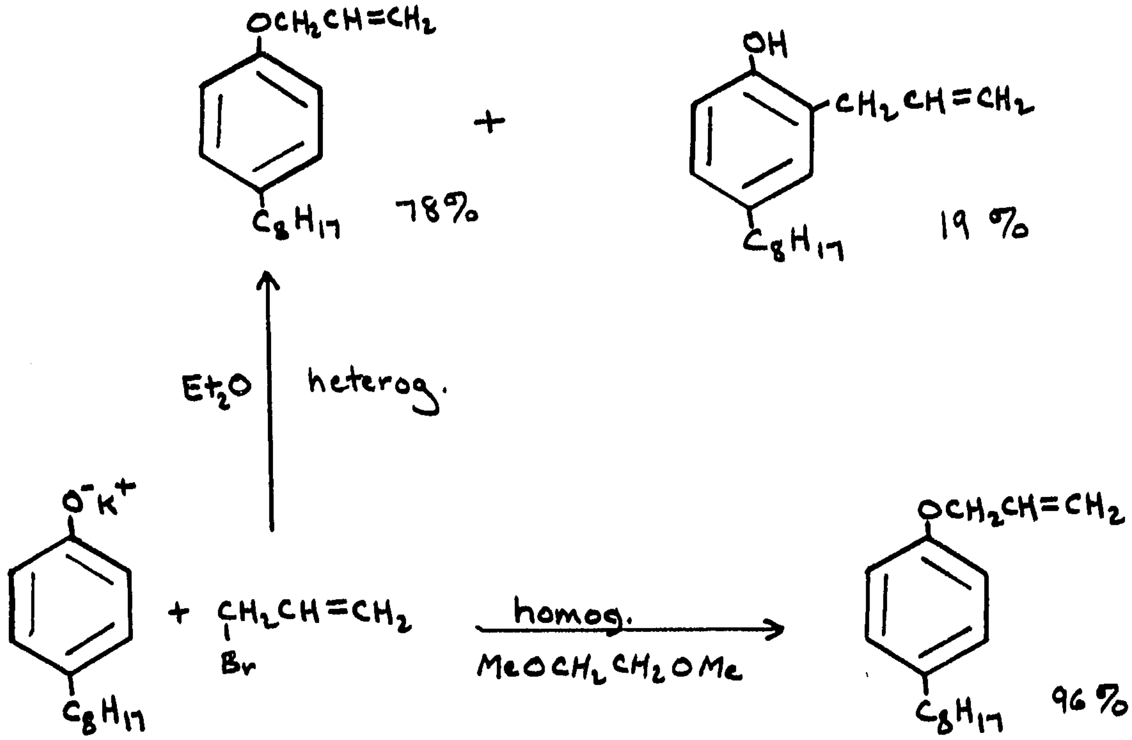


Figure 6

From the data presented in Figure 6 it is clear that the p-t-octyl group is not responsible for the differences noted.[5]

Further support for the correlation between heterogeneity and C-alkylation(benzylation) was obtained by conducting the reaction in a single solvent, toluene. By varying the concentration of the potassium salt of p-t-octyl phenol, the reaction can be converted from heterogeneous (giving 13% C-benzylation) to homogneous(giving 0% C-benzylation). On correcting the heterogeneous results for homogeneity in the latter stages of the reaction, a 100% yield of C-benzylation is obtained. Completely analogous results were obtained on alkylating potassium p-t-octylphenoxide. These results demonstrate that the truly heterogeneous reaction(i.e. the reaction which takes place at the crystal surface) gives exclusively C-alkylation(solely at the ortho position).

Heterogeneous Alkylations. Ether formation is proposed to proceed through the following linear transition state:

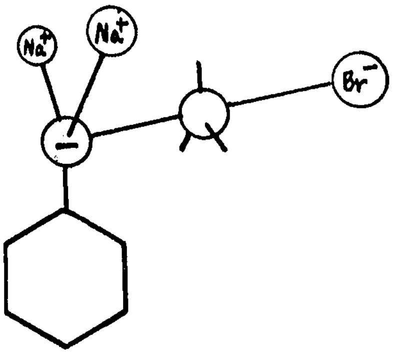


Figure 7

In non-polar solvents, the departing halide is poorly solvated. Also, when the electron density is transferred from the oxygen to the halide, electrostatic repulsion between sodium ions occurs in the crystal lattice and the energy of the system increases sharply. These two factors tend to make such a transition state highly improbable.

C-alkylation proceeds through the following transition state:

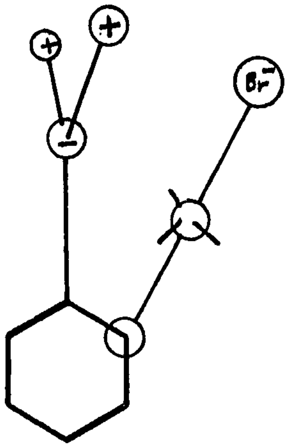


Figure 8

This geometry confers two important advantages. One gets solvation of the departing halide ion through ion-pair formation(sodium ion and halide ion). Also, this ion-pair formation prevents the build-up of coulombic repulsions between sodium ions. It is clear, then, why a phenoxide ion which is part of a crystal lattice manifests such a great preference for o-carbon alkylation over p-carbon alkylation or ether formation.

Homogeneous Alkylations. Since the sodium ions are now free to move in the solvents, electrostatic repulsions are not important in ether formation(in toluene). This is in accord with the idea that the solvation shell of a dissolved ion falls away as that ion loses its charge and forms a co-valence.

Heterogeneity is not the only factor causing carbon alkylation. A number of other factors may operate to produce carbon alkylation even under homogeneous conditions:

(1)Variations in the Relative Nucleophilicity of Oxygen and Carbon----Since the alpha carbon of 2-naphthoxide ion has greater nucleophilicity than any carbon of the phenoxide ion (naphthalene undergoes electrophilic substitution in the alpha position more readily than benzene does and also 2-naphthol can couple with diazonium salts more readily than with phenoxide ion[9]) and since 2-naphthol is a stronger acid than phenol,[12,13,14] it is reasonable to conclude that the oxygen atom in 2-naphthoxide ion has a lower electron density than in the phenoxide ion.

(2)Steric Hindrance----As the steric requirements of 2,6-dialkyl phenoxide ions are increased, ether formation will become increasingly difficult. C-alkylation will also be impeded but less so---especially when the steric requirements of the alkylating agent are large. This steric effect, coupled with the electrical effect of the o-alkyl groups(which serve to increase the electron density of the o-carbon) operates in favor of substitution at an o-carbon.[10,11,15,16]

Steric hindrance can be an overriding factor in determining the alternate reaction paths available to an ambident anion. The reaction of potassium 2,6-t-butylphenoxide in t-butyl alcohol with methyl-, ethyl- and isopropyl iodides provides a particularly clear demonstration of the importance which steric effects may assume in the alkylation of ambident anions.[17] The results of these reactions are shown in Table VI.

Table VI

Reactions of Alkyl Iodides with 2,6-Di-t-butylphenoxide[17],[a]

Alkyl Iodide	% O-Alk.	% C-Alk.
Methyl	88	6
Ethyl	11	66
Isopropyl	0	100

a.All reactions were conducted in t-butanol at 25°.

Coffield and coworkers[18] allowed the sodium salt of 2,6-diisopropyl phenol to react with benzoyl chloride in dioxane at 60 to 80°. The phenol ester, 2,6-diisopropylphenyl benzoate was isolated in 65% yield. Similar treatment of 2,6-di-t-butyl phenol however, gave two products;

4-benzoyl-2,6-di-t-butyl phenol(I) in 24 % yield and the enol benzoate(II). I and II were obtained in separate runs although I is undoubtedly the precursor of II. II was obtained when the reaction mixture at 70° was added to cold water and then worked up. I was obtained when the reaction mixture was permitted to cool to 25° before adding it to cold water. The probable path of the reaction is shown in Figure 9.

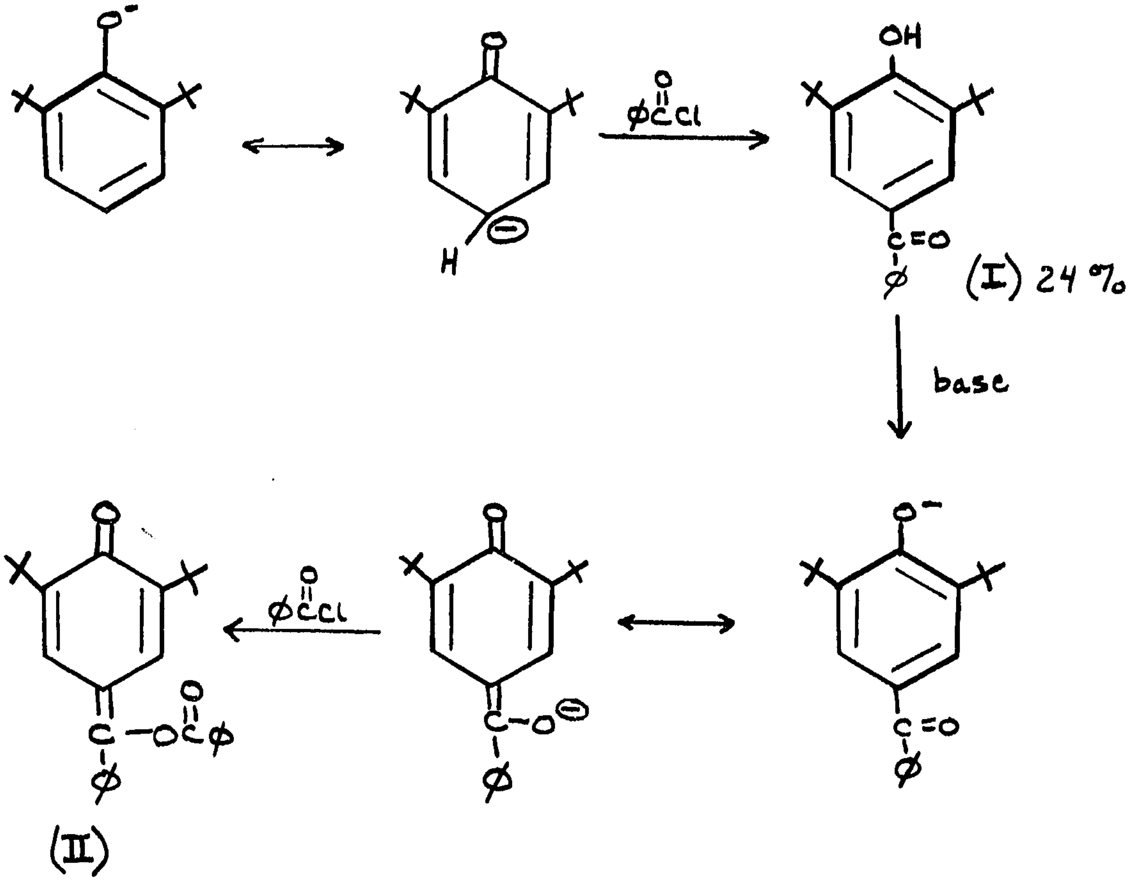
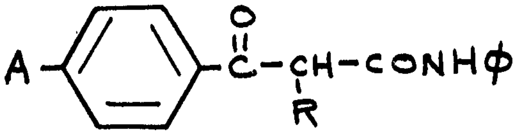


Figure 9

Cohen[19] prepared the methyl ethers of various 2,4,6-trisubstituted phenols in 58-65% yield by treating the sodium salts with methyl iodide. When a bulky alkylating agent is used to alkylate ambident anions, instead of obtaining the expected C-alkylated product, several examples of N-alkylation to give ketenimines have been reported[20,21,22]. Steric factors have also been found to operate in the alkylation of salts of monoalkylated benzoylacetanilides[23] (Figure 10).



A = H, NO_2

R = alkyl

Figure 10

When the entering group is methyl, C-alkylation is favored. As the bulk of the entering group increases, O-alkylation predominates.

(3)Attack by Carbonium Ions----When carbonium ions are generated in solutions containing the phenoxide ion, alkylation on carbon as on oxygen is observed. Para alkylation is diagnostic of carbonium ion intermediacy. Since carbon alkylation of sodium phenoxide using allylic and benzylic halides occurs only at the ortho positions[11,24,25], it is likely that these reactions do not involve carbonium ions.

(4)Variation in the Proportion of S_N1 and S_N2 Character of the Transition State----The greater the S_N2 contribution to the transition state, the greater will be the carbon alkylation and the greater the S_N1 contribution to the transition state of such graded nucleophilic displacements, the greater will be the proportion of O-alkylation[8,26].

The compounding of heterogeneity with these factors gives rise to increased carbon alkylation. When the nucleophilicity of carbon is sufficiently enhanced relative to that of oxygen, carbon alkylation occurs even in solution[5].

Another important factor in the alkylation of ambident anions has been shown to be the role of the solvent. In 1940, Hammett[27] pointed out that salt-dissolving solvents have a high dielectric constant and a considerable tendency to solvate ions. Such solvation often depends upon the hydrogen bonding capacity of the solvent. In aprotic solvents, the dielectric factor and the solvating ability of the solvent influence the course of the reaction. Aprotic solvents possess significant capabilities for solvating cations[28,29]. In protic solvents, both the hydrogen bonding factor and the dielectric factor influence the course of the reaction. These two factors, namely, the dielectric constant and the hydrogen bonding capacity of the solvent were studied by Kornblum[2] in order to account for the ability of solvents to control the course of homogeneous ambident phenoxide anion alkylations. In this investigation, it was found that in certain solvents(water, phenol and fluorinated alcohols), solutions of phenolic salts react to give much C-alkylation(see Table VII).

Table VII[2,a]

Homogeneous Reaction of Sodium Phenoxide with Alkyl Halides

Solvent	Salt	Alkylating Agent	% O-Alk.	% C-Alk.
Water	Sodium phenoxide	Allyl Cl	49	41
		Allyl Br	51	38
		Benzyl Cl	65	24
	Sodium p-cresoxide	Allyl Cl	67	25
		Allyl Br	58	30
Phenol[b]	Sodium phenoxide	Allyl Cl	22	78
		Allyl Br	23	77
		Benzyl Cl	22	69
	Potassium phenoxide	Benzyl Cl	30	70
2,2,3,3-Tetrafluoropropanol-1	Sodium phenoxide	Allyl Cl	58	37
2,2,2-Trifluoroethanol	Sodium phenoxide	Allyl Br	37	42
		Benzyl Cl	62	26

a. Reactions were conducted at 27° except where noted; b. Conducted at 43°.

In solvents not capable of hydrogen bonding, only oxygen alkylation was obtained. Neither carbon nor oxygen alkylation is a carbonium ion process, but rather, have been shown to be second-order displacements. Only a change in solvent produces a profound change in the reaction course. It was proposed that the transition states of reactions conducted in water, phenol and fluorinated alcohols are different from the transition states of reactions carried out in the solvents which are not capable of hydrogen bonding. This is attributed to (1)"Selective solvation" of phenoxide anion and (2) enhanced solvation of the leaving group of the alkylating agent. "Selective solvation" is defined by Kornblum as "the intense solvation of an anion by substances which are usually effective at forming hydrogen bonds so that the availability of the oxygen for nucleophilic displacement is decreased and displacements can occur at the ortho and para carbons."

In a more recent paper, Kornblum and coworkers[3] have correlated the dielectric constant of an aprotic solvent with its influence on the alkylation process. Sodium 2-naphthoxide was employed as the ambident anion. The 2-naphthoxide ion is capable of covalency formation at oxygen or at the alpha carbon[8]. Solutions of sodium 2-naphthoxide were alkylated with benzyl bromide, methyl iodide and n-propyl bromide in a variety of solvents(see Table VIII, IX and X).

Table VIII

Reaction of Benzyl Bromide with Sodium 2-Naphthoxide[3,a]

Solvent	Dielectric Constant	% O-Alkylation	% C-Alkylation
DMF[b]	37	97	0
DMSO	45	95	0
Ethylene glycol dimethyl ether	7	70	22
THF	7	60	36
Methanol	33	57	34
Ethanol	24	52	28
2,2,2-Trifluoroethanol	27	7	85
Water	80	10	84
Benzene-water		7	83

a.All reactions were conducted at room temperature except where noted; b.Conducted at 10-15°.

Table IX

Reaction of Methyl Iodide with Sodium 2-Naphthoxide[3,a]

DMF[b]	91	3
DMSO[b]	90	4
Ethylene glycol dimethyl ether	86	10
THF	80	13
Ethanol	83	12
2,2,2-Trifluoroethanol	57	34
Water	66	30

a.All reactions were conducted at room temperature except where noted; b.Conducted at 30°.

Table X

Reaction of n-Propyl Bromide with Sodium 2-Naphthoxide[3,a]

Solvent	% O-Alkylation	% C-Alkylation
DMF[b]	98	0
DMSO[b]	95	0
Ethylene glycol dimethyl ether	96	0
THF	96	0
Ethanol	95	Trace
2,2,2-Trifluoroethanol	81	10
Water	88	5

a. All reactions were conducted at room temperature except where noted; b. Conducted at 35°.

The fact that benzylation of sodium 2-naphthoxide (Table VIII) in DMF and DMSO results in oxygen alkylation, while in the excellent hydrogen bonding solvents trifluoroethanol and water, carbon alkylation preponderates derives from the hydrogen bonding capacities of trifluoroethanol and water[2]. Benzylation of sodium 2-naphthoxide reveals differences within the aprotic solvent group(DMF, DMSO, ethylene glycol dimethyl ether and THF) which are not found in the benzylation of sodium phenoxide(vide supra). The phenoxide ion is much more disposed toward oxygen alkylation than the 2-naphthoxide ion is. With sodium 2-naphthoxide, the reaction of benzyl bromide in THF or ethylene glycol dimethyl ether gives carbon alkylation to a substantial extent. The results in THF cannot be explained by hydrogen bonding. They can be attributed to the ability of the solvent to increase the importance of electrostatic interactions as a result of its dielectric effect, a measure of which is the dielectric constant of the solvent. In the four aprotic solvents employed, O-alkylation is favored with high dielectric constant solvents while solvents of low dielectric constant bring about a shift toward C-alkylation. In a medium of low dielectric constant, sodium 2-naphthoxide exists as ion-pairs and higher aggregates. The transition state for oxygen alkylation of an ion-pair is as follows:

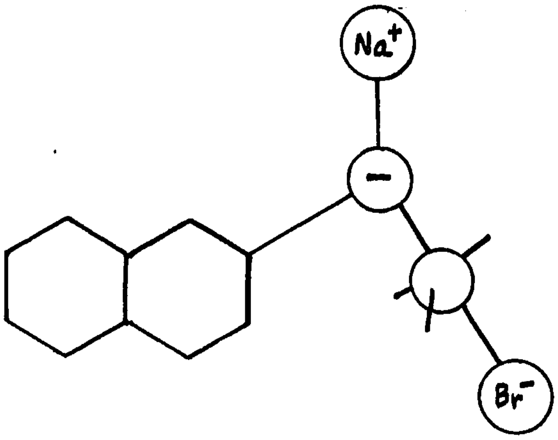


Figure 11

Oxygen alkylation involves the transfer of charge from oxygen to bromine and since the bromine is relatively remote from the sodium, this must be accomplished against the attractive force exerted by the sodium ion. In a medium of low dielectric constant, the attractive force exerted by the sodium ion on the departing bromide ion is the greatest and this would tend to disfavor the oxygen alkylation.

Carbon alkylation proceeds through a non-linear arrangement in which the developing bromide ion is relatively close to the sodium ion as follows:

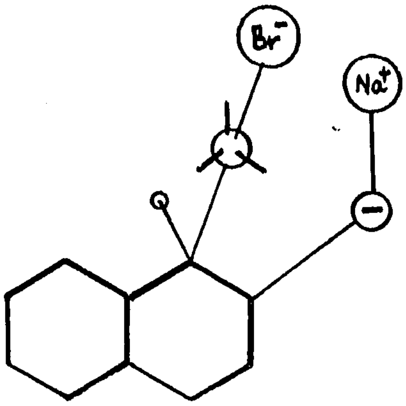


Figure 12

This transition state, because it involves relatively little removal of charge from the vicinity of the sodium ion, will be comparatively insensitive to the dielectric constant of the medium. The overall result is that a solvent of low dielectric constant favors carbon alkylation by disfavoring oxygen alkylation.

In an aprotic solvent of high dielectric constant such as DMF, the reacting specie may either be the ion-pair or the free 2-naphthoxide ion if the solution is dilute enough. In the case of the ion-pair, the transition state leading to O-alkylation is of lower energy in THF than in a high dielectric constant solvent like DMF since the DMF shields the departing bromide ion from the attractive force exerted by the sodium ion. Therefore, this coulombic factor loses its importance when the reaction is carried out in a medium of high dielectric constant. In contrast, the transition state leading to C-alkylation, as before, is insensitive to the dielectric constant of the medium. The overall result is that a high dielectric constant solvent favors O-alkylation by minimizing a force which opposes O-alkylation.

In a high dielectric solvent such as DMF or DMSO, the free 2-naphthoxide ion may take part in the reaction. It is presumed that in DMF and DMSO, solvation of the anion is minimal. With the sodium ion absent, a force which resists the transfer of charge from oxygen to bromine in the O-alkylation process is removed and the 2-naphthoxide ion is able to exercise its preference for nucleophilic displacements involving oxygen.

Another important solvent factor is the ability of the solvent to form hydrogen bonds. If the dielectric constants are approximately equal, the solvent which can form hydrogen bonds produces a shift in favor of carbon alkylation. The greater the hydrogen bonding capacity, the greater is the percentage of C-alkylated product(see Tables VIII, IX and X).

In aprotic solvents having a low dielectric constant such as THF and diethyl ether, the anion is likely to be part of an ion aggregate when it reacts. With a small cation such as lithium, the ion pairs will be relatively tight and the electrostatic restraint to ether formation relatively large. As we traverse the series Li^+, Na^+, K^+, NR_4^+, a progressive decrease in the yield of C-alkylation is observed[3].

In contrast, aprotic solvents having a high dielectric constant(DMF and DMSO) are especially effective at solvating the positive ion but relatively ineffective at solvating the 2-naphthoxide anion. Therefore, in DMF and DMSO we have a "free" anion with a high degree of reactivity. Even if the 2-naphthoxide ion reacts as an ion pair, in a medium of high dielectric constant such as DMF or DMSO, the electrostatic constraint to O-alkylation is minimized so that the influence of the cation on the course of the alkylation is minimized. Since the degree of solvation will decrease in the order Li^+, Na^+, K^+, NR_4^+, and since the charge is dispersed through solvation, the electrostatic influence of the of the various cations on the 2-naphthoxide ion in an ion pair will tend to even out(leveling effect).

In protic solvents(alcohols), the nature of the cation will be relatively unimportant as a factor in C/O alkylation due to the high dielectric constant, the "leveling effect" and the most important "selective solvation". Selective solvation of the 2-naphthoxide ion will favor C-alkylation and, in hydrogen-bonding media, it will minimize the role of the cation.

In general, the solvent dependence of cation effects is as follows: alkylations conducted in methanol and ethanol exhibit little variation in product ratio as the cation is changed. In contrast, alkylations conducted in diethyl ether, THF, benzene and toluene result in a decrease in the proportion of C-alkylation as the cation is changed from Li^+ to Na^+ to K^+ to NR_4^+ [3].

Certain solvents are especially effective at solvating cations; these include the dimethyl ether of ethylene glycol, DMF and DMSO[28,29,30,31]. When a cation is well solvated, the charge dispersal will minimize the coulombic restraint to O-alkylation. This factor is most significant in aprotic solvents of low dielectric strength(THF and ethylene glycol dimethyl ether) with THF being the poorer in solvating power.

These data can be explained on the basis of an earlier suggestion of C.K.Ingold[32] that factors which increase dissociation of the phenolic salt favor ether formation and factors which increase ion aggregates favor dienone formation.

Kornblum and coworkers[3] have refuted this proposition that free ions favor O-alkylation while ion-pairs favor C-alkylation. They cite the O/C ratios obtained by Forsblad[33] in the reaction of methyl iodide with the Li, Na, K and bis-piperidinium salts of beta-hydroxycoumarilic acid. Forsblad actually obtained more carbon alkylation with the dissociated anion than with any of the ion pairs. The results can be explained on the basis of solvation. In methanol, the dissociated anion,

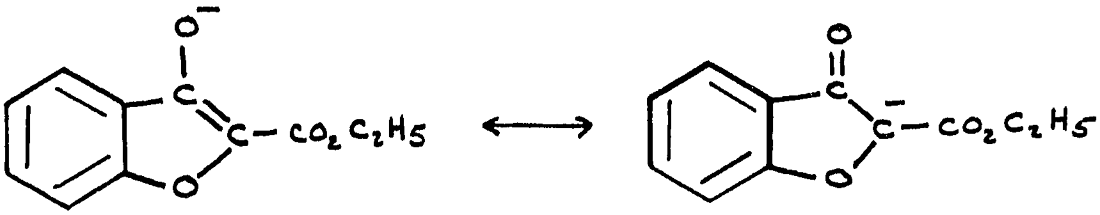


Figure 13

is selectively solvated[2] at oxygen and this shielding operates in favor of carbon alkylation. In this instance, it appears that hydrogen bonding is more effective in favoring C-alkylation(by shielding the oxygen atom) than is ion-pairing; which favors C-alkylation by providing a transition state having minimal charge separation(vide supra). This strongly hydrogen-bonded dissociated anion in methanol must be very different from a dissociated anion in an aprotic solvent. In DMF, for example, the dissociated anion would be expected to give less C-alkylation than the ion-pairs. The influence of solvents in the reaction of sodium 2-naphthoxide with methyl iodide and n-propyl bromide is easily seen in Tables IX and X.

The leaving group has also been shown to be a factor in the alkylation of ambident anions[34,35]. In this instance, the ambident anion,

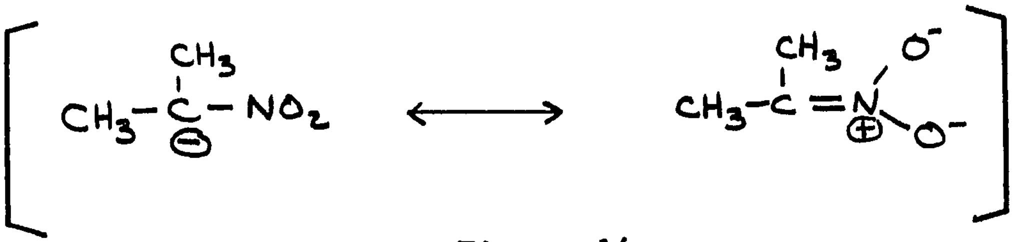


Figure 14

derived from an aliphatic nitro compound(the lithium salt of 2-nitropropane), was alkylated with p-$NO_2C_6H_4CH_2X$. It was found that the uniqueness of the p-nitrobenzyl system depends not only on the p-NO_2 group but also on the leaving group. The results are summarized in Table XI.

Table XI

Reaction of the Lithium Salt of 2-Nitropropane with p-NO_2-$C_6H_4CH_2X$ in Dimethylformamide at -16°C.[34,35]

X	% C	% O
NMe_3	93	0
Cl	95	1
OTos	40	32
Br	17	65
I	9	81

Zagorevsky[36] found that carbon substitution in metal 2-naphthoxides increased with increasing reactivity of the halide and decreasing electrophilic character of the metal used[37]. He also observed that use of the tetramethylammonium salt strongly favored alkylation at the oxygen atom.

Curtin[11] has reported that in the reaction of alkali metal salts of phenols, C-alkylation was increased at the expense of O-alkylation by the use of the following: non-polar solvents, salts of less acidic phenols, higher salt concentration, salts of less electropositive alkali metals, and more reactive halides(i.e. allylic rather than saturated halides). This is supported by the data given in Table XII.

Table XII

Reactions of Sodium 2,6-Dimethylphenoxide with Allyl and Benzyl Halides at 17-20°C.[11]

Solvent	Halide	C/O
Anhyd. diethyl ether	Allyl bromide	0.29, 0.31
	Benzyl chloride	0.36
	Benzyl bromide	0.36
Diethyl ether + H_2O	Allyl bromide	0.51
	Benzyl chloride	1.0
	Benzyl bromide	0.57
Diethyl ether sat'd with $Bu_4N^+Br^-$	Allyl bromide	0.12
Dioxane	Benzyl chloride	0.03
Toluene	Benzyl chloride	4.2
Toluene + THF	Benzyl chloride	3.0
Benzene	Allyl bromide	12
Diisopropyl ether	Benzyl chloride	1.8
THF	Benzyl chloride	0.01
	Benzyl iodide	0.0
THF + NaI	Benzyl iodide	0.0
Ethanol	Allyl bromide	0.16
	Benzyl iodide	0.09
Ethanol sat'd with NaI	Benzyl iodide	0.18

Acylation. The essential feature of the process of acylation is the attachment to a substrate of a group R•C=O which is derived from an acylating agent. The latter usually has the form R•COX where X is a halogen. Structural features and other circumstances which in any way enhances the electrophilicity of the acylating agent will usually favor the reaction. These general considerations when applied to particular cases, provide the basis of both substituent effects and the roles played by catalysts.

A reasonable generalization concerning acylation is that the power of an acylating agent R•COX increases with the strength of the acid HX. The origin of the parallelism is clear: the separation of the anion X^- is involved in both phenomena. In R•COX the carbonyl group is always polarized, some net positive charge being located on the carbon atom. Groups X which attract electrons and possess some stability as X^- will enhance this positive charge, promote cleavage into $R{\cdot}CO^+$ and X^-, and thus aid reaction. Groups which repel electrons and provide anions of little stability will have the opposite effect[38]. The same generalization applies for subtler variations in the leaving group, achieved within a given type of reagent. Thus, acyl bromides are more reactives than the corresponding chlorides[39].

The effects on reactivity of changes in R are not as straightfoward as for changes in X. Substituents which, by providing electrons, favor the departure of X^- and stabilize the acylium ion have the effect of reducing the charge on the carbonyl carbon atom in both the acylium ion and the polarized reagent. Electron-withdrawing substituents increase this charge but hinder ionization. The effect of changes in R will depend, therefore, on whether the substrate reacts primarily with the ionized or with the unionized acylating agent, and, moreover, on which particular phase of the overall process is rate determining. Similar effects are involved in other nucleophilic substitutions. Steric effects of substituents may lead to changes in mechanism.

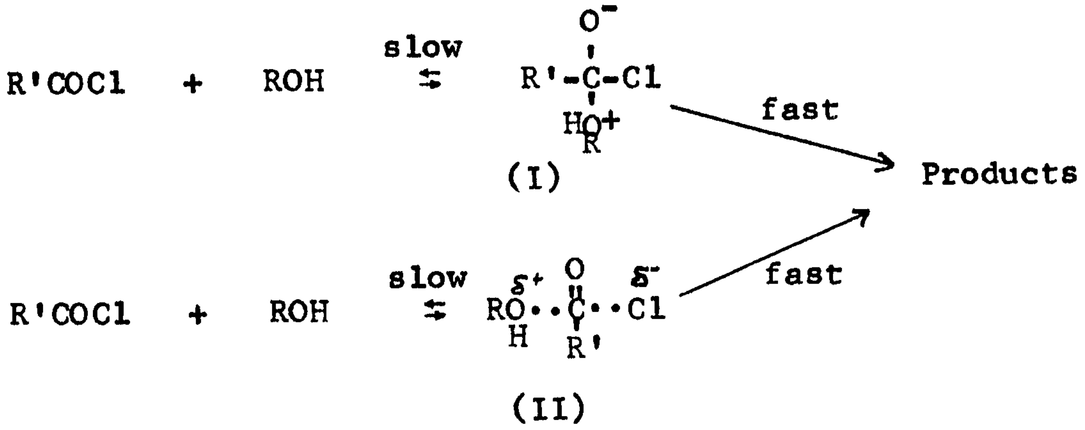
As noted above, a substrate S may react with either the ionized or the polarized acylating agent. On this basis, mechanisms of acylation may be divided into two types[4].

$$\text{(i)}\quad \mathrm{R{\cdot}COX} \overset{a}{\rightleftharpoons} \mathrm{R{\cdot}CO^{+}} + \mathrm{X^{-}}(\text{or } \mathrm{R{\cdot}CO^{+}X^{-}}) \xrightarrow[b]{S} \text{Products}$$

$$\text{(ii)}\quad \mathrm{R{\cdot}COX} + \mathrm{S} \longrightarrow \text{Products}$$

Bender is of the opinion that mechanism (ii) occurs via addition of the substrate to the carbonyl group, rather than via a direct synchronous displacement of X by S[1]. Satchell[40] and Bunton[41] however, consider that the formation of carbonyl addition products as intermediates in bimolecular acylation has been too uncritically accepted. In fact, Satchell[40] has proposed such a synchronous displacement of X by S in the reaction of phenols with chloroacetyl and 2-chloropropionyl chlorides in acetonitrile. The results of his study are presented at the end of this section.

Another opinion is offered on the mechanism of bimolecular acylation by Hudson and Saville[42] who feel that the transition state is probably best represented by an intermediate between (I) and (II).



In water, ions are dissociated and step (i)(b) will usually be fast so that hydrolysis either involves a slow ionization (i)(a) or a rate-determining attack by the substrate oxygen atom (ii). The ionization route is favored by substituents R which either help to stabilize the acylium ion(e.g. p-methoxyphenyl) or hinder route (ii) by blocking access to the unionized carbon atom(e.g. 2,6-xylyl)[38,39]. Mechanism (ii) is usually favored by substituents which withdraw electrons from the carbonyl carbon atom(vide supra).

Acylation of alcohols and phenols produces esters. The considerations here as before are much the same as for water, except that the reaction(alcoholysis) will be generally less likely to exhibit mechanism (i)[4]. This is because the lower dielectric constant of alcohols will inhibit ionization. However, in the alcoholysis of substituted benzoyl chlorides, both extreme mechanisms appear to operate within the same reaction series[43,44,45]. Specifically, all groups except para-methyl, meta-methyl and para-methoxy increase the rate of reaction with alcohols(see Table XIII).

Table XIII

Reaction of Substituted Benzoyl Chlorides with Ethanol at 0°C.[43,44,45] k_o/min. ØCOCl = 0.0044

Substituent(X)	$\frac{k_{XC_6H_4COCl}}{k_{C_6H_5COCl}}$
o-CH_3	3.7
m-CH_3	0.85
p-CH_3	0.78
o-OCH_3	29
m-OCH_3	1.1
p-OCH_3	0.81
o-Cl	3.5
m-Cl	5.6
p-Cl	1.9
o-Br	3.4
m-Br	4.6
p-Br	2.1
o-I	2.9
m-I	4.1
p-I	1.9
o-NO_2	2.2

Table XIII(continued)

m-NO_2	20.5
p-NO_2	21.6
o-C_2H_5	2.73
o-OC_2H_5	41.6
o-ϕCO	too fast
m-ϕCO	4.35
p-ϕCO	4.31
m-ϕCH_2-	1.04
p-ϕCH_2-	0.75
m-CH_2Cl	1.64
p-CH_2Cl	1.30
2,4-di CH_3	6.75
2,6-di OCH_3	too fast
2,4-di NO_2	31.6
3,5-di NO_2	too fast
2,4-di Cl	7.7
2,5-di Cl	14.4
3,4-di Cl	7.22
2,4,6-tri C_2H_5	too fast
2,4,6-tri NO_2[a]	too slow to measure
2,4,6-tri Br[a]	0.0008

a. Reacted with methanol at 25°C.

As noted before, in the absence of strong nucleophiles and in highly polar solvents, mechanism (i) tends to predominate, whereas in non-polar solvents and in the presence of strong nucleophiles mechanism (ii) tends to predominate [46,47,48]. Substituent effects on the nucleophilic reactions of substituted benzoyl chlorides indicate that electron-withdrawing groups facilitate the bimolecular reaction as expected[47,49,50].

It further appears that the solvolysis of acyl chlorides may undergo a change in mechanism as the polarity of the solvent is changed. The relative rates of solvolysis of the p-substituted benzoyl chlorides shown in Table XIV, for example, suffer an almost complete reversal in order as the reaction is transferred from 40/60 ethanol-ether(dielectric constant 12.8) to 50/50 water-acetone(dielectric constant 51.5)[49].

Table XIV

Effect of Solvent Change on Relative Solvolysis Rates of p-Substituted Benzoyl Chlorides(25°)[49]

Medium	D[a]	Relative Solvolysis Rates NO_2	Br	Cl	CH_3	CH_3O
40% EtOH + 60% Et_2O..	12.8	32	2.5	2.1	0.47	0.25
EtOH................	25.7	21.6	2.1	1.9	0.70	0.81
5% H_2O + 95% $COMe_2$...	22.2	35	3.2	---	0.55	0.60
50% H_2O + 50% $COMe_2$..	51.5	11.5	0.92	0.85	2.9	~30

a. Dielectric constant.

Note that in the alcohol-ether mixture, the trend in reactivities is much the same as that observed for the saponification of esters and the basic hydrolysis of amides----- typical bimolecular processes. That is, electron-attracting groups tend to accelerate the reaction while electron-donating groups tend to decelerate the reaction[46]. When the reaction is transferred to 100% ethanol or 5/95 water-acetone, the p-methoxy compound moves into the borderline region, since it now reacts more rapidly than the p-methyl compound. In 50/50 water/acetone, the solvolysis of only the p-nitro compound appears to have retained its bimolecular character. The hydrolysis of the remaining acyl halides have become distinctly "S_N1-like", and are now subject to acceleration by electron-donating groups.

The solvolysis of aromatic acid chlorides has been found to be accelerated by the addition of base(see Table XV).

Table XV

Effect of Alkali on the Solvolysis of Acid Chlorides[51,52,53]

1)80% alcoholic acetone at 10.75°

	Benzoyl Chloride	p-Nitrobenzoyl Chloride
$10^6 k_1 (sec^{-1})$	4.97	212
$k_2{}^a (M^{-1} sec^{-1})$	> 3	> 3

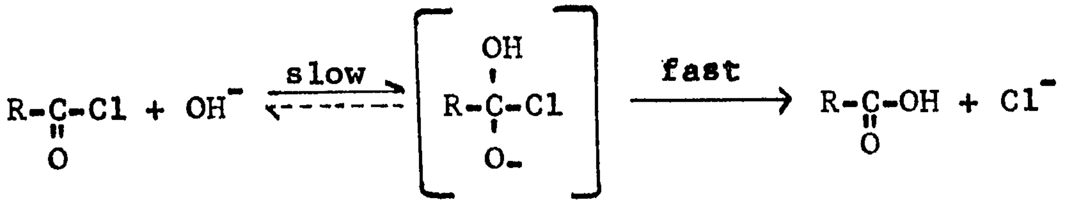
a. 0.02M OEt^-

2)25% aqueous acetone at 0.2°

	p-Nitrobenzoyl Chloride	p-Anisoyl Chloride
$10^6 k_1 (sec^{-1})$	20.32	2.82
$k_2{}^a (M^{-1} sec^{-1})$	6.82	0.405

a. 0.003M OH^-

A possible mechanism for such a base-catalyzed solvolysis has been suggested by Minato[53] and involves the following:



$$R-\underset{\overset{\|}{O}}{C}-Cl + OH^- \underset{}{\overset{slow}{\rightleftharpoons}} \left[R-\underset{\underset{O^-}{|}}{\overset{\overset{OH}{|}}{C}}-Cl \right] \xrightarrow{fast} R-\underset{\overset{\|}{O}}{C}-OH + Cl^-$$

In aqueous solution, the reaction of acetyl chloride is not acid catalyzed and predominantly of type (ii) mechanism [54]. Satchell and Briody[40] have provided kinetic data for the reactions of acetyl, propionyl, butyryl, 2-chloropropionyl and chloroacetyl chloride with phenols in acetonitrile. The effects of added salts(i.e. tetramethylammonium chloride and bromide) have been studied. The behavior of the acetyl, propionyl and butyryl compounds fits reasonably into the pattern established for acetyl chloride in nitromethane[55] and acetyl bromide in acetonitrile[56]. The mechanism of acylation is presumably similar in all these systems, acylium ion routes predominating. In the presence of added salt, the reaction rate is reduced, eventually becoming constant. This effect is shown in Table XVI for the reaction of acetyl chloride with 2-naphthol in acetonitrile.

Table XVI

Acylation by Acetyl Chloride at 25.1°C[40]

Initial conc. 2-naphthol = 10^{2}M; k_{obs} in min^{-1}

(a)Order in acetyl chloride in absence of salt

Conc. AcCl..........	0.42	0.56	0.70	0.98	1.12
$10^{3}k_{obs}$.............	1.59	2.08	2.70	3.45	3.89

(b)Effect of added Et_4NCl(conc. AcCl = 0.70)

10[Et_4NCl]..........	0.0	0.114	0.238	0.495	0.830	1.10
$10^{3}k_{obs}$.............	2.70	1.47	1.21	0.55	0.35	0.35

(c)Order of acetyl chloride in presence of 0.13M Et_4NCl

Conc. AcCl..........	0.42	0.56	0.70	0.84
$10^{3}k_{obs}$.............	0.19	0.27	0.35	0.44

The mechanism proposed to explain this behavior is as follows[55,56]:

$$HCl \overset{K_1}{\rightleftharpoons} (H^{+})_{solv.} + Cl^{-} \qquad (1)\text{fast}$$

$$HCl + Cl^{-} \overset{K_2}{\rightleftharpoons} HCl_2^{-} \qquad (2)\text{fast}$$

$$\begin{tikzcd}
RCOCl + HCl \arrow[r, phantom, "\rightleftharpoons"] \arrow[d, "(4)" right, "ArOH" left, "slow" {right, yshift=-8pt}] & RCO^{+}Cl^{-} + HCl \arrow[r, phantom, "\rightleftharpoons"] \arrow[d, "(4')" right, "ArOH" left, "slow" {right, yshift=-8pt}] & RCO^{+} + HCl_2^{-} \arrow[d, "(5)" right, "ArOH" left, "slow" {right, yshift=-8pt}] & (3)\text{fast} \\
Ester + HCl & Ester + HCl & Ester + HCl &
\end{tikzcd}$$

The hydrogen chloride is presumed to arise during the early stages of the reaction, or before reaction begins from the acylation of traces of water. Step (5) is removed as Et_4NCl

is added.

For the reaction of chloroacetyl chloride with p-methoxyphenol, the mechanism is proposed to involve a synchronous displacement of covalently bound chlorine by the phenol. This process is powerfully catalyzed by added salt as shown by the data in Table XVII.

Table XVII

Acylation of p-Methoxyphenol by Chloroacetyl Chloride[40]
(Temp.= 70.2°C)

(a)Effect of added Et_4NCl; $ClCH_2COCl$ conc. = 0.70M

$10^2[Et_4NCl]$	0.0	0.64	1.27	1.36	2.54
10^2k_{obs}	0.02	1.01	2.15	2.56	4.24

(b)Order in Acyl Halide in presence of chloride salt

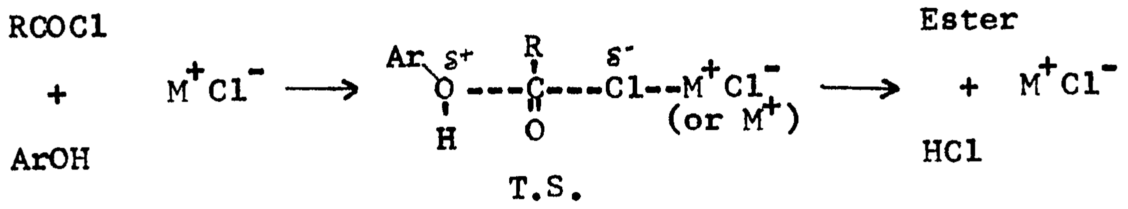
$10^2[Et_4NCl] = 2.54$

$ClCH_2COCl$	0.395	0.53	0.70	0.87
10^2k_{obs}	2.18	3.22	4.24	5.06

(c)Effect of added bromide salt(conc. $ClCH_2COCl$ = 0.70M)

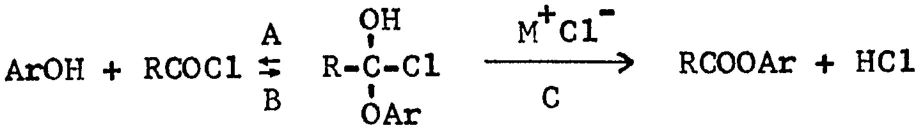
$10^2[Et_4NBr]$	0.0	0.21	0.50	0.92
10^2k_{obs}	0.02	0.32	0.93	2.13

Chloroacetyl chloride, in the absence of added salt, is found to be ca. 8000 fold slower than acetyl chloride in its reaction with p-methoxyphenol. Since propionyl and n-butyryl chlorides react at rates similar to that exhibited by acetyl chloride, steric effects are ruled out. The salt is believed to accelerate this synchronous displacement process in the following manner:



Satchell and Briody[40] conclude that, in acetonitrile, chloroacetyl chloride always reacts via the unionized acyl halide molecule and that this unexpectedly slow process is greatly facilitated by the presence of a suitable acceptor for the leaving group. In acetonitrile, and presumably in solvents of lower polarity, this departure clearly dominates the kinetics and accounts for the slowness of the reaction of chloroacetyl compared with acetyl chloride. Another result which argues strongly against any ionization route for chloroacetyl chloride is that added tetraethylammonium bromide has about the same effect on the rate as has the chloride. This effect is shown in Table XVII. If ionization equilibria were involved, chloroacetyl bromide would form rapidly and give considerably faster rates. The behavior of 2-chloropropionyl chloride falls satisfactorily between that of the acetyl and chloroacetyl derivatives.

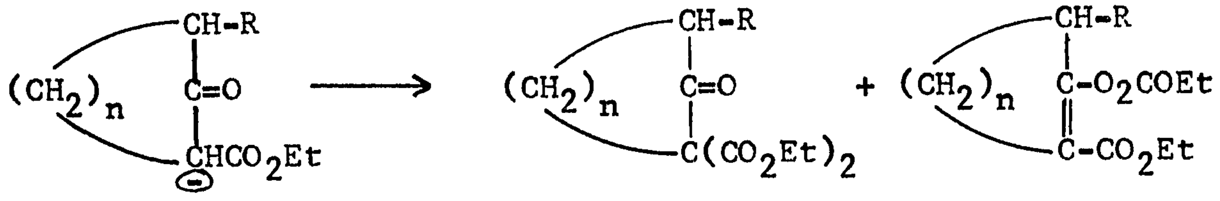
The dominance of bond-breaking(at moderate salt concentrations) for the reactions of chloroacetyl and 2-chloroacetyl chlorides means that these processes must be synchronous, rather than modifications of the carbonyl addition mechanism [e.g. (1)[53]].

(1) 

$$\text{ArOH} + \text{RCOCl} \underset{B}{\overset{A}{\rightleftarrows}} \text{R-}\underset{\text{OAr}}{\overset{\text{OH}}{\text{C}}}\text{-Cl} \xrightarrow[C]{M^{+}Cl^{-}} \text{RCOOAr} + \text{HCl}$$

This follows because, if step C is slow, B must surely be slow also[57], and the addition intermediate would accumulate and no kinetic or spectrophotometric evidence for this was found[40].

Recently, Ferris and coworkers[56] have reported a study of the steric factors which direct the point of attack in the acylation of cyclic beta-keto ester anions. They studied the reaction of ethylchloroformate with various cyclic beta-keto esters whose ring size ranged from five to seven carbon atoms. The reaction scheme is shown below:



	n	R		n	R		n	R
I	2	H	II	2	H	III	2	H
IV	2	$-CH_2CH_2CO_2Et$	V	2	$-CH_2CH_2CO_2Et$	VI	2	$-CH_2CH_2CO_2Et$
VII	3	H	VIII	3	H	IX	3	H
X	4	H	XI	4	H	XII	4	H

Figure 15

In each instance, the sodium salt of the cyclic beta-keto ester was used and the reaction was carried out in benzene. The anions of the cyclic compounds would be expected to be planar about the carbon atoms joined to the ester and carbonyl groups. This requires an axial attack on the ethyl chloroformate by the anion of the keto ester. By systematically changing the ring size of the beta-keto ester, the geometry of the transition state should be affected so as to tilt the balance in favor of either carbon- or oxygen-acylation. The results of their study, summarized in Table XVIII, show that the proportion of carbon-acylation decreases as the ring size changes from C_7 to C_5 to C_6.

Table XVIII

Products of the Reaction of Ethyl Chloroformate with Cyclic Beta-Keto Esters[58]

Keto Ester	Temp. (°C)	% C- and O-acylation C:O
I	R.T.	17:83
I	80	23:77
IV	80	10:90
VII	110	1:99
VII	R.T.	1:99
X	80	50:50
X	R.T.	50:50

This reaction is an irreversible process since a nonpolar solvent was used and no rearrangement occurred. The heterogeneous reaction where the sodium salt was insoluble in benzene was found not to be different from the homogeneous reaction with the system studied by Kornblum and Lurie[5]. The other factors which have been found to affect the course of the reaction of the ambident anion(e.g. solvent and the metal ion used) were held constant so that only the steric requirement of the anions being acylated was held to be responsible for changes in the C/O acylation ratio. The transition state for the carbon-acylation reaction is best represented by Figure 16[59].

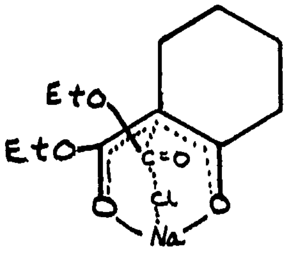


Figure 16

The attack of the acylating agent is facilitated by polarization of the carbon-halogen bond by the metal of the chelate ring. The oxygen-acylation reaction involves a four-centered transition state as shown by Figure 17[60].

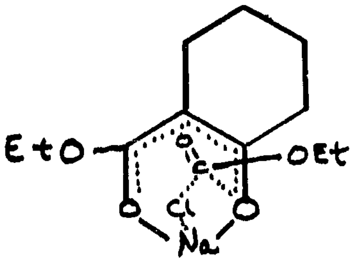


Figure 17

Therefore, one would expect that only a small change in the steric requirements of the anion being acylated would change the nature of the transition state. The greatest hindrance is found in the axial attack on the 2-carbethoxycyclohexanone chelate, somewhat less in the cyclopentanone chelate and least in the cycloheptanone ring as is evidenced by the following structural models.

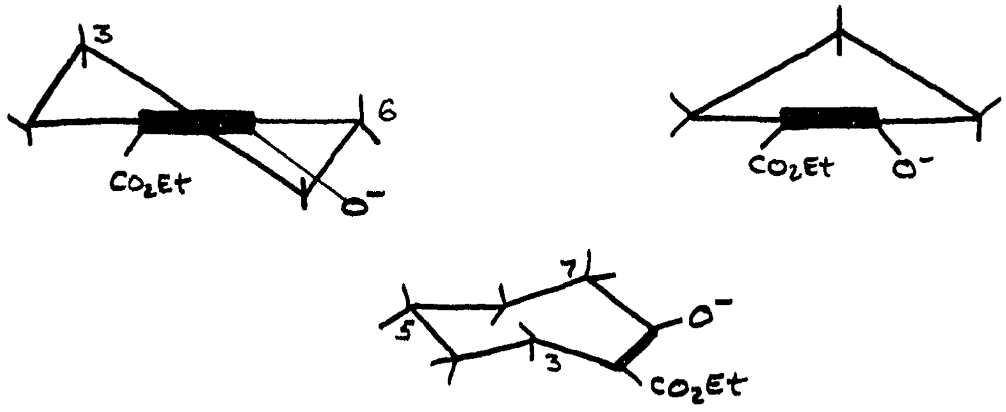
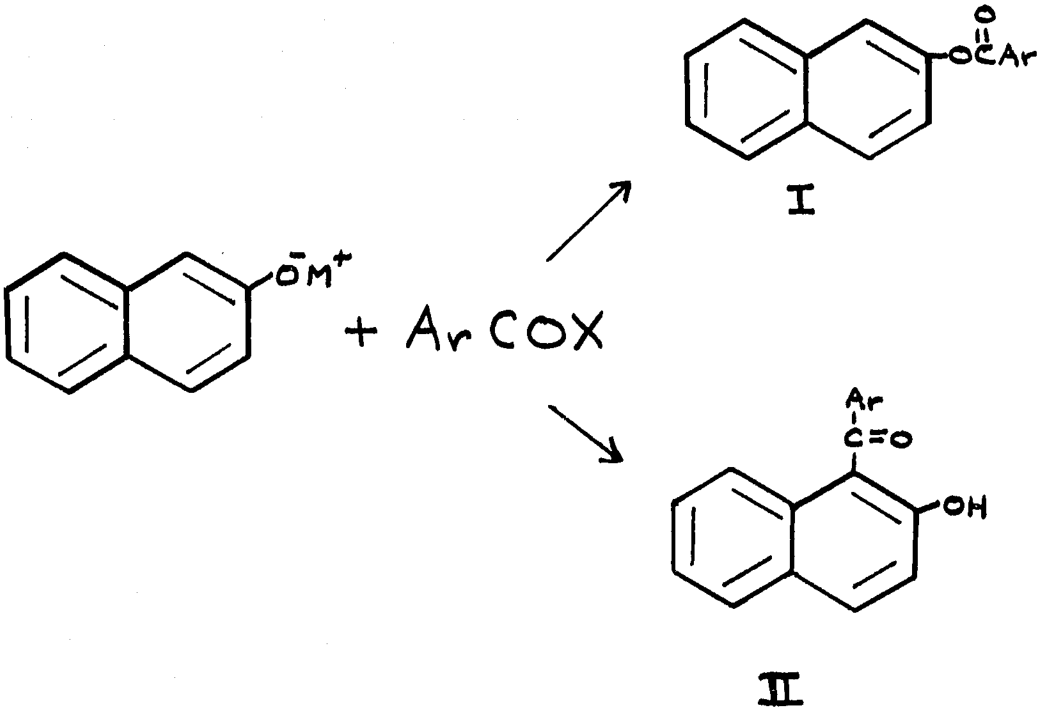


Figure 18

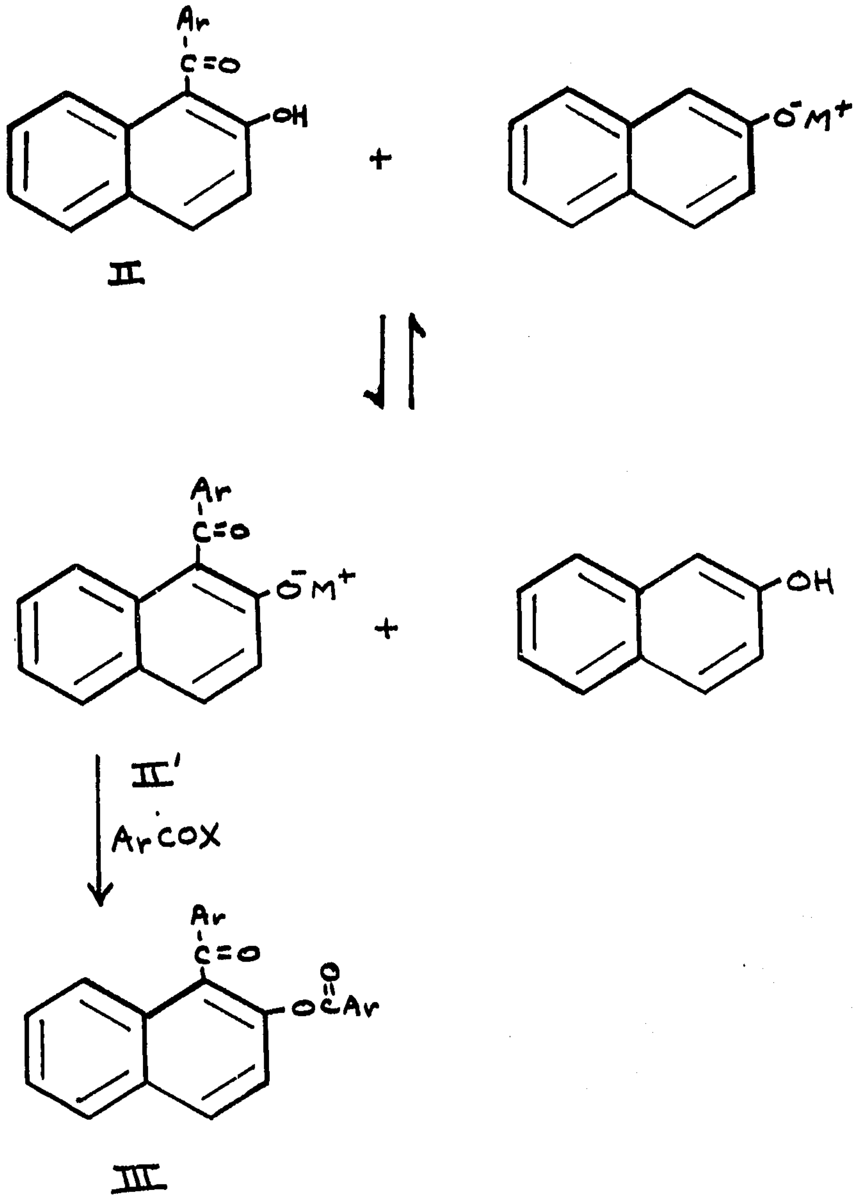
As the hindrance in the vicinity of the carbon atom increases, the acylation takes place on the more accessible oxygen atom.

III.RESULTS AND DISCUSSION

When the alkali salts of 2-naphthol are treated with an acyl halide, the following reactions may take place:



An ester(I) and/or a keto-naphthol(II) may be obtained. The keto-naphthol(or rather its metal salt) may further react with ArCOX to give the keto-ester(III). The reaction of the ester (I) with the acylating agent ArCOX to give rise to the keto-ester(III) is excluded on the basis of experimental evidence(see experiment 65).



Effect of Solvent Change. The results of conducting the reaction of sodium 2-naphthoxide with benzoyl chloride in a variety of solvents are recorded in Table XIX.

Table XIX

Reactions of Para-substituted Benzoyl Halides($\underline{p}$-Y-C_6H_4COX) with 2-Naphthoxide Salts($M^+C_{10}H_7O^-$)[a]

Exp.	Y	X	M^+	Solvent	D[b]	Physical State[c]	% O[d]	% C[e]	O/C
5[g]	H	Cl	Na	Benzene	2.27	Het.	88.3 82.6	0.86 0.75	103 110
2[g]	H	Cl	Na	Hexane	1.9	Het.	83.8	0.62	135
3[g]	H	Cl	Na	CCl_4	2.24	Het.	78.0	0.47	166
1[g]	H	Cl	Na	TFE[f]	27	Hom.	18.1	0.05	362
4[g]	H	Cl	Na	1-4-1[h]	7	Hom.	60.4	----	>10,000[i]
6[g]	H	Cl	Na	THF[j]	7	Hom.	68.5	----	>10,000[i]
7	H	Br	Na	Hexane	1.9	Het.	73.8 76.2	2.38 2.61	31.0 29.2
8	H	Br	Na	Benzene	2.27	Het.	85.0	2.09	40.7
10	H	Br	Na	TFE	27	Hom.	36.0	0.14	257
9	H	Br	Na	1-4-1	7	Hom.	68.9	----	>10,000[i]
12	H	Cl	Li	Hexane	1.9	Het.	82.4	4.00	20.6
11	H	Cl	Li	Benzene	2.27	Het.	83.6 86.3	2.32 2.53	36.0 34.1
20	H	Cl	Li	Water	80	Hom.	51.7	0.13	398
13	H	Cl	Li	THF	7	Hom.	86.7	----	>10,000[i]
15	H	Br	Li	Hexane	1.9	Het.	84.1	5.12	16.4
14	H	Br	Li	Benzene	2.27	Het.	84.0 87.7	4.64 4.50	18.1 19.5
21	H	Br	Li	Water	80	Hom.	46.4	0.17	273
16	H	Br	Li	THF	7	Hom.	86.7	----	>10,000[i]

Table XIX(continued)

Exp.	Y	X	M^+	Solvent	D[b]	Physical State[c]	% O[d]	% C[e]	O/C
17	H	I	Li	Hexane	1.9	Het.	67.5	15.1	4.5
18	H	I	Li	Benzene	2.27	Het.	77.8	13.0	6.0
19	H	I	Li	THF	7	Hom.	91.3	----	>10,000[i]
29[k]	NO_2	Cl	Na	Hexane	1.9	Het.	89.0	2.53	35.1
30[k]	NO_2	Cl	Na	Benzene	2.27	Het.	91.0	2.12	42.9
28[k]	NO_2	Cl	Na	THF	7	Hom.	100	----	>10,000[i]
25	NO_2	Cl	Li	Hexane	1.9	Het.	70.0	11.7	6.0
26[k]	NO_2	Cl	Li	Benzene	2.27	Het.	73.0	10.5	7.0
27	NO_2	Cl	Li	Benzene	2.27	Het.	72.6	9.73	7.5
23	NO_2	Cl	Li	THF	7	Hom.	100	0.64	156
24[k]	NO_2	Cl	Li	THF	7	Hom.	100	----	>10,000[i]
35	OCH_3	Cl	Na	Benzene	2.27	Het.	86.2 86.2	1.39 1.43	62 60
34	OCH_3	Cl	Na	Hexane	1.9	Het.	84.1	0.46	182
36	OCH_3	Cl	Na	THF	7	Hom.	100	----	>10,000[i]
41	OCH_3	Br	Na	Benzene	2.27	Het.	80.6	2.23	36
40	OCH_3	Br	Na	Hexane	1.9	Het.	81.7	1.97	41
42	OCH_3	Br	Na	THF	7	Hom.	100	----	>10,000[i]
38	OCH_3	Cl	Li	Benzene	2.27	Het.	84.1 89.7	7.33 9.31	11 10
37	OCH_3	Cl	Li	Hexane	1.9	Het.	89.1 91.2	3.34 3.44	28 27
39	OCH_3	Cl	Li	THF	7	Hom.	98.7	----	>10,000[i]

Table XIX(continued)

Exp.	Y	X	M^+	Solvent	D[b]	Physical State[c]	% O[d]	% C[e]	O/C
43	OCH_3	Br	Li	Hexane	1.9	Het.	80.6	3.61	22
44	OCH_3	Br	Li	Benzene	2.27	Het.	81.8 75.4	2.99 2.71	27 28
45	OCH_3	Br	Li	THF	7	Hom.	97.7	----	>10,000[i]

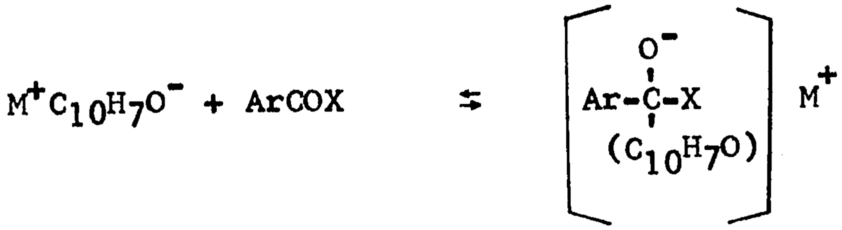
a. All reactions were conducted at room temperature and at a concentration of 0.61M except where noted; b. Dielectric constant[61]; c. Het. (heterogeneous) means that a solid phase was visible before the addition of the acyl halide; Hom. (homogeneous) means that no solid phase was visible before the addition of the acyl halide; d. Percent yield of ester; e. Total percent yield of both keto-naphthol and keto-ester; f. 2,2,2-Trifluoroethanol; g. Concentration = 0.55M; h. Ethylene glycol dimethyl ether; i. Maximum limits of detection; j. Tetrahydrofuran; k. Inverse addition (i.e. addition of the naphthoxide to a solution of the acid chloride).

It is clear that the course which the reaction takes depends on the solvent employed. For example, reactions of benzoyl chloride with sodium 2-naphthoxide conducted in ethylene glycol dimethyl ether(Exp. 4) and tetrahydrofuran(Exp. 6) solution stand at one extreme: both solvents yielded only the ester thereby resulting in an O/C acylation ratio of greater than 10,000(i.e. in these solvents carbon acylation occurs to the extent of less than 0.01%). In contrast, the reactions of benzoyl chloride with sodium 2-naphthoxide in benzene(Exp. 5), hexane(Exp. 2) or carbon tetrachloride (Exp. 3) result, in addition to the ester product, in the formation of small amounts of C-acylated products(0.86, 0.62 and 0.42%, respectively). The O/C acylation ratios for these latter reactions are found to be 107, 135 and 166 respectively. Thus a simple change in the solvent produces a change in the course of reaction of the ambident anion.

Two likely mechanisms may be considered for a bimolecular acylation reaction: A <u>concerted mechanism</u> involving a direct displacement by the nucleophile on the carbonyl carbon("S_N2-like")

$$M^+C_{10}H_7O^- + ArCOX \longrightarrow ArCO(C_{10}H_7O) + M^+X^-$$

and an <u>addition-elimination mechanism</u>,



$$M^+C_{10}H_7O^- + ArCOX \rightleftharpoons \left[\begin{array}{c} O^- \\ | \\ Ar-C-X \\ | \\ (C_{10}H_7O) \end{array}\right] M^+$$

the usual mechanism by which carbonyl compounds undergo substitution reactions.

In a medium of low dielectric constant(e.g. hexane, benzene etc.[61]), the reaction is found to be heterogeneous (see definition in Table XIX footnotes). Proof that the reaction takes place on the crystal surface is presented in a later part of the Discussion Section. Consider now the oxygen acylation transition state(Figure 19) for the concerted mechanism.

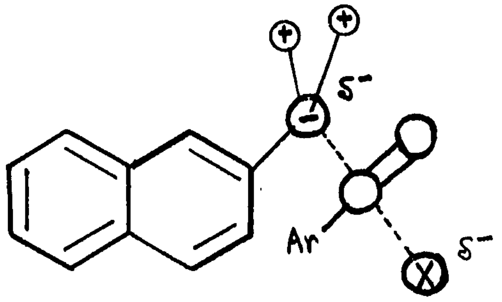


Figure 19

Ester formation by a naphthoxide ion which is part of a crystal lattice would proceed through a linear transition state, the negative charge originally resident on oxygen progressively being transferred to halogen. In the non-polar solvents, e.g. hexane, benzene and carbon tetrachloride, the departing halide ion would be poorly solvated. The loss of this charge on oxygen will cause strong electrostatic repulsions between the sodium ions. Since the sodium ions in the crystal lattice cannot move away from one another, the energy of the system must increase sharply.

In contrast to ester formation, C-acylation which occurs via a <u>concerted mechanism</u> does not proceed through a transition state having the linear oxygen-carbon-halogen disposition of Figure 19. The transition state for attack at the 1-carbon has a non-linear arrangement in which the sodium ion lies between the oxygen and halogen atoms[2] (Figure 20).

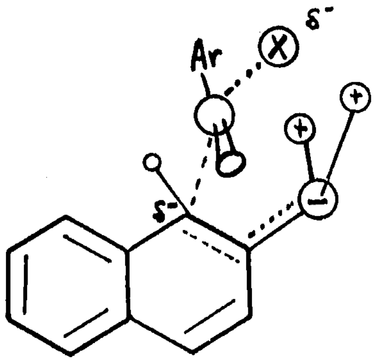


Figure 20

The halide ion which is leaving is solvated by ion-pair formation with a sodium ion(as contrasted with the poor solvation furnished by the non-polar solvent in the ester formation). Also, the removal of positive charge from the group of positive sodium ions surrounding the oxygen, even as the oxygen is losing its negative charge, prevents the build-up of coulombic repulsions between sodium ions which is an energy-raising factor in ester formation(Figure 19). It is clear then, why a naphthoxide ion which is part of a crystal lattice yields carbon acylated product in spite of its intrinsic tendency to react at oxygen(vide supra).

In contrast to the transition states for oxygen and carbon acylation for the heterogeneous reaction proceding via a concerted mechanism, the O- and C-acylation transition states for the addition-elimination mechanism(Figures 21 and 22) differ very little in their geometry in regard to the factors discussed above for a process proceding through an "S_N2-like" pathway.

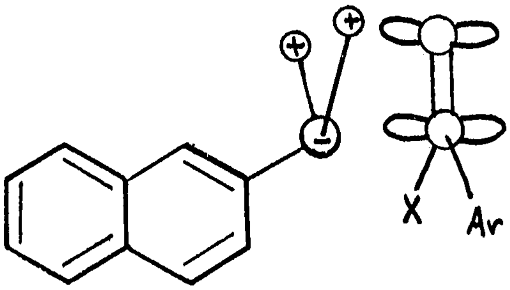


Figure 21

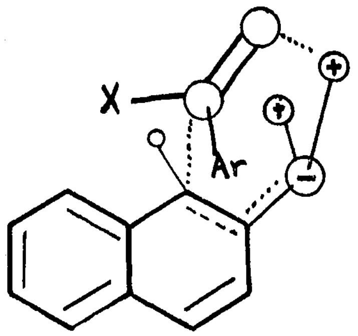


Figure 22

Ester formation by a naphthoxide ion in solution presents none of the problems such as the ones discussed above for the heterogeneous reaction. The reacting species may be the ion-pair, or, if the solution is dilute enough, it may be the free 2-naphthoxide ion[62]. The reaction, if it proceeds via the concerted mechanism and if it involves the ion-pair, will react via the transition state shown in Figure 23(O-acylation) and Figure 24(C-acylation).

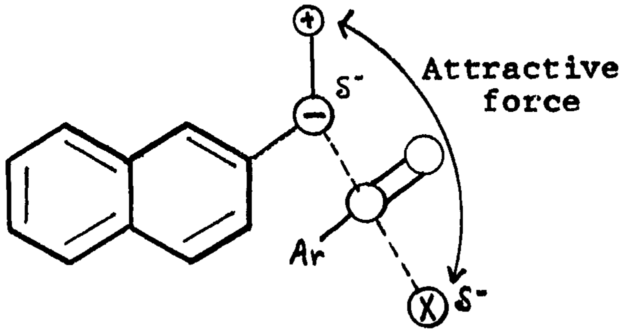


Figure 23

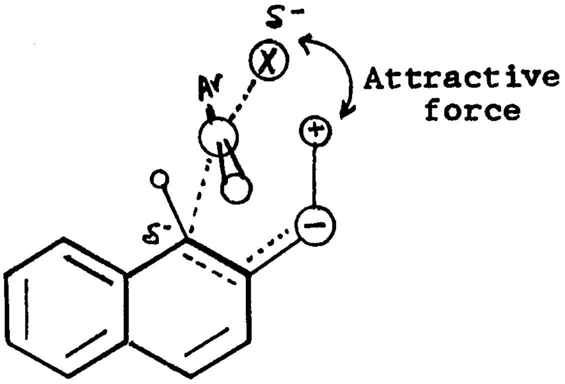


Figure 24

As the charge of oxygen is lost in the course of displacing the halide ion from the acylating agent(Figure 23), the metal cations are not constrained to remain as they were in the crystal lattice; instead, they are free to move so that electrostatic repulsions do not become important[5]. Further, solvents such as THF and ethylene glycol dimethyl ether, which are relatively more polar than hexane, benzene and carbon tetrachloride[61], will better shield the departing halide ion from the attractive force exerted by the sodium ion. Consequently, this latter force, which in a relatively low dielectric solvent operates as a deterent to oxygen acylation, loses its importance. Therefore, the factors which disfavor the O-acylation transition state in the heterogeneous reaction and in the homogeneous reaction(conducted in a solvent of relatively low dielectric constant) are no longer important and the naphthoxide ion is again free to exercise its intrinsic preference for nucleophilic attack by oxygen[3].

If the reaction in solution proceeds via an addition-elimination mechanism, the O- and C-acylation transition states may be pictured as follows in Figures 25 and 26:

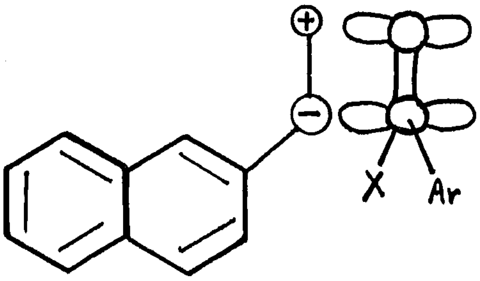


Figure 25

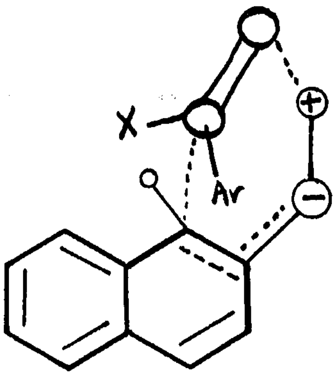


Figure 26

There are no obvious advantages to be seen for the C-acylation transition state as compared with the O-acylation transition state. Therefore, it is expected that attack by the more nucleophilic oxygen will predominate.

It is also conceivable that acylation involves the free 2-naphthoxide ion in aprotic solvents of high dielectric constant. With the metal ion absent, a force which resists the transfer of charge from oxygen to halogen in the oxygen acylation process(Figure 23) is removed and once again there are no restrictions against naphthoxide's intrinsic preference for nucleophilic displacement involving oxygen. The latter conclusion will also apply for an addition-elimination process since the free ion should not react any differently than the ion-pair.

In 2,2,2-trifluoroethanol(Exp.1), in spite of its high dielectric constant(i.e. D = 27[61]), an O/C acylation ratio of 362 is obtained for the homogeneous reaction of benzoyl chloride with sodium 2-naphthoxide. The fact that benzoylation of sodium 2-naphthoxide in ethylene glycol dimethyl ether and THF results only in oxygen acylation, while in the excellent hydrogen-bonding solvents 2,2,2-trifluoroethanol and water, a small amount of C-product is obtained, is fully consonant with previous experience involving the alkylation of sodium phenoxide and sodium 2-naphthoxide[2,3]: i.e. the transition states of the reaction of benzoyl halide with naphthoxide conducted in 2,2,2-trifluoroethanol(or water) are significantly different from those of homogeneous reactions carried out in 1-4-1 and THF because of "selective solvation" of the naphthoxide anion[2](see Historical Section). The similarity of effects between this acylation reaction and S_N2 reactions is striking.

Note must be taken at this point of the low yields obtained for the acylation reactions conducted in TFE and water(i.e. experiments 1, 10, 20 and 21). It is clear that the low yields of acylated naphthalene compounds are due to the reaction of the solvent with the acyl halide. This would result in the formation of 2,2,2-trifluoroethyl benzoate and benzoic acid for the reactions conducted in TFE and water, respectively.

The solvent effects discussed above for the homogeneous and heterogeneous reaction have also been observed for the reaction of both sodium and lithium 2-naphthoxide with a variety of p-substituted benzoyl halides(Table XIX). In each case, the same pattern of results was obtained.

Effect of Leaving Group Change. When the acylating agent was changed from benzoyl chloride to benzoyl bromide, it was expected that an increase in the O/C acylation ratio should result since there would be less electrostatic constraint for removal of the larger, more diffusely charged bromide ion than for the chloride ion(as regards oxygen acylation transition states---see Figures 19,21,23 and 25). However a smaller O/C acylation ratio(and a larger amount of C-acylated product) was obtained for the reactions of benzoyl bromide with sodium 2-naphthoxide than for the corresponding benzoyl chloride reactions(see Table XX).

For the reactions of lithium 2-naphthoxide with benzoyl halides, this "leaving group effect" is again observed and even extended to include the reaction of benzoyl iodide with lithium 2-naphthoxide(Table XX). The results observed fit in nicely with the trend previously observed for the reactions of sodium 2-naphthoxide with acyl halides; i.e. an increase in the leaving group facility will be accompanied by an increase in the percent of C-acylated product formed. A total yield for C-product of 15.1% and an O/C ratio of 4.5 was obtained for the reaction conducted in hexane(Exp. 17). In benzene(Exp. 18), a somewhat lower yield of total C-product was obtained: 13.0% and an O/C ratio of 6.0. Conversely, if the ease of leaving group facility is decreased relative to the chloride ion, as in the reaction of phenyl benzoate with lithium 2-naphthoxide in refluxing benzene(Exp. 64), only ester(i.e. 2-naphthyl benzoate) is obtained.

This increase in C-product which accompanies a change in the leaving group from chloride to bromide to iodide was also observed(but not explained) by le Noble and Puerta[63] for the alkylation of ethyl acetoacetate anion in dimethyl sulfoxide, a reaction which clearly proceeds via a concerted displacement mechanism. The amount of C-alkylation increased as the halide was varied from chloride to bromide to iodide. This trend is covered by an "S_N2-rule" which states that "increased S_N2 reactivity is correlated with a decreased O/C product ratio."

Table XX presents a comparison of the effect of a leaving group change for the reactions of 2-naphthoxides(both sodium and lithium) with benzoyl and anisoyl halides. With the benzoyl system, for both the reactions of sodium and lithium salts, an increase in the facility of the leaving group leads to a decrease in the O/C product ratio. However, as the "S_N1-character" of the reaction is increased by changing the p-substituent of the acyl halide from -H to $-OCH_3$, this leaving group effect is diminished and finally for the reaction of anisoyl halide with lithium 2-naphthoxide in benzene, this effect is reversed, chloride giving a smaller O/C product ratio than bromide. These results are in good agreement with le Noble's "S_N2-rule" discussed above and is further evidence that bimolecular acylation may occur via a concerted displacement mechanism.

Table XX

Change of Leaving Group[a]

Experiment	Reaction	O/C Acylation Ratio			
		OPh[b]	Cl	Br	I
	Hexane:				
2,7	$C_{10}H_7O^-Na^+$ + BzX[e]	___	135	30.1[f]	___
12,15,17	$C_{10}H_7O^-Li^+$ + BzX	___	20.6	16.4	4.5
34,40	$C_{10}H_7O^-Na^+$ + AnsX[d]	___	182	41	___
37,43	$C_{10}H_7O^-Li^+$ + AnsX	___	28[f]	22	___
	Benzene:				
5,8	$C_{10}H_7O^-Na^+$ + BzX	___	107[f]	40.7	___
11,14,18,64	$C_{10}H_7O^-Li^+$ + BzX	>1800[c]	35[f]	18.8[f]	6.0
35,41	$C_{10}H_7O^-Na^+$ + AnsX	___	61[f]	36	___
38,44	$C_{10}H_7O^-Li^+$ + AnsX	___	11[f]	28[f]	___
	2,2,2-Trifluoroethanol:				
1,10	$C_{10}H_7O^-Na^+$ + BzX	___	362	257	___
	Water:				
20,21	$C_{10}H_7O^-Li^+$ + BzX	___	398	273	___

a. All reactions were conducted at room temperature except where noted; b. Conducted in refluxing benzene; c. Maximum limits of detection; d. Anisoyl = Ans; e. Bz = benzoyl; f. Average value of duplicate determinations.

Effect of Metal Cation Change. Consider again the transition state for the heterogeneous reaction(Figures 19,20,21 and 22). When the counter-ion is changed from sodium to lithium, the bond strength of the bond between the metal cation and the oxygen of the naphthoxide is expected to increase. No data is available in the literature for a comparison of the Na-O vs the Li-O bond strength. However, it is reasonable to assume that the difference between the Na-Cl and Li-Cl bond strengths(for which literature data is available) is a good measure of this difference. The Li-Cl bond is 14.4 kcal/mole stronger than the Na-Cl bond[64]. The Li-O bond should be stronger than the Na-O bond by at least this amount. For the concerted mechanism transition states(Figures 19 and 20), decrease in the O/C ratio is expected when the metal cation is changed from sodium to lithium. This is because the internal solvation furnished by the proximate halide ion in the C-acylation transition state(Figure 20) becomes more important as the strength of the metal-oxygen bond is increased. This will lower the energy of the C-acylation transition state relative to that of the O-acylation transition state and bring about the anticipated decrease in the O/C ratio when the metal cation is changed from sodium to lithium.

No such change in the energy differences between the O- and C-acylation transition states is evident from an examination of the transition states for an acylation reaction which proceeds via an addition-elimination pathway(see Figures 21 and 22).

With the preceding arguments in mind, a number of benzoylations using both sodium and lithium salts of 2-naphthoxide were carried out. A comparison of the results obtained in presented in Table XXI. In every case, the lithium salt of 2-naphthoxide yielded a smaller O/C product ratio than did the sodium salt.

Table XXI

Change of Metal Cation

		O/C Acylation Ratio	
Experiment	Reaction	Li^+	Na^+
	Hexane:		
37,34	AnsCl	28[a]	182
43,40	AnsBr	22	41
12,2	BzCl	20.6	135
15,7	BzBr	16.4	30.1[a]
25,29	*p*-NO_2BzCl	6.0	35.1
	Benzene:		
38,35	AnsCl	11[a]	61[a]
44,41	AnsBr	28[a]	36
11,5	BzCl	35[a]	107[a]
14,8	BzBr	18.8[a]	40.7
26,27,30	*p*-NO_2BzCl	7.3[a]	42.9

[a] Average value of duplicate determinations.

Exclusion of Acylium Ion Contribution. In order to exclude the possibility that the anisoyl acylium ion participates in the reaction of anisoyl halides with naphthoxide ion, both anisoyl chloride and anisoyl bromide were treated with a solution of 2-naphthol in benzene in the presence of calcium carbonate to supress any acid-catalyzed process. The weaker nucleophile, 2-naphthol, would certainly be expected to enhance any acylium ion reaction relative to the displacement reaction by naphthoxide ion. No C- or O-acylated product was obtained and therefore it is reasonable to assume that there is no acylium ion reaction of any consequences competing with the bimolecular acylation process.

Effect of the Para-substituent Change in the Acyl Halide. For a reaction which proceeds via a concerted displacement, when the para-substituent is changed from methoxy to hydrogen to nitro, all other conditions being the same(i.e. same leaving group, metal cation and solvent), the "S_N2-character" of the reaction should increase and, in accord with le Noble's "S_N2-rule" cited previously, the O/C product ratio will decrease. A comparison of the results obtained when the para-substituent of the acyl halide is changed from methoxy to hydrogen to nitro(Table XXII) lends some support to this prediction. For example, the reactions of p-substituted benzoyl chlorides with both sodium and lithium 2-naphthoxides in hexane exhibit a decrease in the O/C product ratio as the para-substituent is changed from p-OCH_3 to p-H to p-NO_2. Likewise, a decrease in O/C product ratio is obtained for the reaction of p-substituted benzoyl bromides with both lithium and sodium 2-naphthoxide in hexane. However, when the solvent is changed to benzene, the O/C product ratio is found to increase as the p-substituent is changed from p-OCH_3 to p-H. A further change of the para-substituent to p-NO_2(in the reaction of para-substituted benzoyl chlorides with sodium and lithium 2-naphthoxide) again decreases the O/C product ratio.

Consider again the transition states for the concerted displacement pathway(Figures 19,20,23 and 24). Two opposing factors may affect the nature of these transition states; (1)a change in carbonyl carbon-halogen bond length(bond-

Table XXII

Change of Para-substituent in the Acyl Halide

Experiment	Reaction	O/C Acylation Ratio $\underline{p}$-OCH_3	$\underline{p}$-H	$\underline{p}$-NO_2
	Hexane:			
34,2,29	$\underline{p}$-X-C_6H_4COCl + $C_{10}H_7O^-Na^+$	182	135	35.1
37,12,25	$\underline{p}$-X-C_6H_4COCl + $C_{10}H_7O^-Li^+$	28[a]	20.6	6.0
40,7	$\underline{p}$-X-C_6H_4COBr + $C_{10}H_7O^-Na^+$	41	30.1[a]	———
43,15	$\underline{p}$-X-C_6H_4COBr + $C_{10}H_7O^-Li^+$	22	16.4	———
	Benzene:			
35,5,30	$\underline{p}$-X-C_6H_4COCl + $C_{10}H_7O^-Na^+$	61[a]	107[a]	42.9
38,11,26,27	$\underline{p}$-X-C_6H_4COCl + $C_{10}H_7O^-Li^+$	11[a]	35[a]	7.3[a]
41,8	$\underline{p}$-X-C_6H_4COBr + $C_{10}H_7O^-Na^+$	36	40.7	———
44,14	$\underline{p}$-X-C_6H_4COBr + $C_{10}H_7O^-Li^+$	18.8[a]	28[a]	———

a. Average value of duplicate determinations.

length factor) and (2) a change in the electrophilicity of the carbonyl carbon(electrophilicity factor). For those reactions which are conducted in hexane, when the para-substituent is a methoxy group, an increase in the C-X bond length is expected on the basis of Swain's rule[65]. As the electron-donating ability od the para-substituent is decreased(i.e. change in the p-substituent from methoxy to hydrogen), the bond length should also decrease. As the bond length increases, the energy of the bond decreases[66]. In the C-transition states(Figures 20 and 24), the decrease in the C-X bond energy is expected to strengthen the bond between the halogen and the metal cation. For the O-transition state, the metal cation is far enough removed from the halide ion so that an increase in the C-X bond length will have a smaller effect on the metal halide attraction energy. The overall effect for a change from a p-H to a p-OCH_3 group should be a lowering of the energy of the transition state for carbon acylation relative to the O-transition state and a decrease in the O/C product ratio.

Consider now the effect of the electrophilicity factor. The p-OCH_3 group will decrease the electrophilicity of the carbonyl carbon(i.e. relative to that of the p-H) thereby making it a less reactive electrophile relative to an unsubstituted benzoyl halide. A less reactive electrophile is more selective and attack(or attack by) the more nucleophilic oxygen is expected. The result should be that for a p-OCH_3 group, the O/C product ratio should increase relative to that obtained for the reaction of the unsubstituted benzoyl halide. The assumption is now made that the second factor, electrophilicity, be accorded a greater weight than the bond-length factor in the consideration of the influence of the p-OCH_3 group. This assumption is supported by the relative rate data(Table XXIII), the significance of which is discussed in a later section. The change from a p-H to a p-OCH_3 benzoyl halide causes a decrease in the rate of reaction with naphthoxide ion relative to the unsubstituted benzoyl halide. For example, the relative rate of reaction of sodium 2-naphthoxide with anisoyl chloride in hexane is 0.78 while the relative rate of benzoyl chloride for the same reaction is 1.00. The electrophilicity factor must be more important than the bond-length factor for a change in the para-sunbtituent from p-H to p-OCH_3 or anisoyl chloride would be more reactive than benzoyl chloride. The net effect of these two opposing factors should result in an increase in the O/C ratio relative to that obtained for the unsubstituted halide.

When the para-substituent is changed from p-H to p-NO_2, these two factors again exert their influence in opposite directions. The p-NO_2 group should shorten the C-X bond length according to Swain's rule[65]. Using the same argument presented above, this shortening of the C-X bond should raise the energy of the C-transition state relative to the C-acylation transition state of the unsubstituted benzoyl halide. The energy of the O-transition state(relative to the unsubstituted benzoyl halide O-transition state) is increased, but to a lesser extent. Opposing this factor is the more important electrophilicity factor. The presence of the p-NO_2 group should enhance greatly the electrophilicity of the carbonyl group, raising its energy and making it a more reactive and less selective electrophile. The net effect of these two opposing factors should be a decrease in the O/C product ratio relative to that obtained for the unsubstituted acyl halide.

Consider now these same two factors when the solvent is changed from hexane to benzene. The p-OCH_3 benzoyl halide should be a less electrophilic species in the more polar benzene[61]. This will lessen the effect of factor (2), perhaps to the extent wherein factor(1) will assume major importance. If this happens, the net result will be a decrease in the O/C acylation ratio relative to the unsubstituted benzoyl halide. Benzene will also decrease the electrophilicity of the carbonyl carbon of a p-NO_2 benzoyl halide relative to the reaction of this same acyl halide in hexane. Although this should cause a slight decrease in the O/C product ratio (relative to the O/C ratio obtained for the reaction in hexane), the very large electron-withdrawing effect of the p-NO_2 group(as compared to the magnitude of the p-OCH_3 group's electron-donating ability; i.e. $\sigma_{\underline{p}\text{-OCH}_3} = -0.27$, $\sigma_{\underline{p}\text{-NO}_2} = 0.78$[67]) should still bring about a large decrease in the O/C product ratio relative to the unsubstituted benzoyl halide.

The above considerations and the conclusions resulting thereto concerning the effect of a change in the para-substituent in the acyl halide for a reaction which proceeds via a *concerted-displacement mechanism* are in excellent agreement with the actual results obtained(see Table XXII).

Alternatively, for a reaction which proceeds through an *addition-elimination* pathway, only factor (2), the *electrophilicity factor*, is expected to be of any importance in determining the O/C product ratio since the breaking of the C-X bond does not take part in the rate-determining step. A consideration of the *electrophilicity factor* leads one to conclude that the O/C acylation ratio should be in the order $\underline{p}\text{-OCH}_3$ $\underline{p}\text{-H}$ $\underline{p}\text{-NO}_2$. This does not agree with the results shown in Table XXII.

Heterogeneity. The questions presents itself whether the reaction of naphthoxide with acyl halides in hexane and benzene takes place on the crystal surface or in solution. Visually, the reaction appears to be heterogeneous(i.e. a solid phase is visible before the acyl halide is added). However, a small amount of salt could be dissolved and react at a faster rate than the undissolved salt. An experiment was carried out to determine if any 2-naphthoxide salt could be dissolved in pentane(pentane was used in place of hexane to facilitate the experimental procedure, the dielectric constant of pentane being identical with that of hexane[61]). This dissolved salt could then be reacted with an acyl halide to determine the O/C acylation ratio for the homogeneous reaction(i.e. that reaction in which no solid phase is visible before the addition of the acyl halide). In the experiment carried out(Exp. 48), pentane was transported by means of distillation into a Sohxlet cup which contained lithium 2-naphthoxide(the lithium salt was found to be the more soluble of the two salts----for example in the preparation of the lithium salt, diethyl ether, the solvent used to precipitate the sodium salt from a THF solution, could not be used because it was found to partially solubilize the lithium salt). This pentane extract was then returned to the distillation reservoir pot which also contained an acyl halide. This experiment was run for a period of 138.5 hours. At the end of this time, analysis of the reservoir pot showed that no naphthoxide salt had dissolved in the refluxing pentane. A similar experiment with benzene(Exp. 49) gave like results. These experiments suggest that under the usual reaction conditions, no homogeneous reaction of any consequences could be taking place. This means then that the reaction in benzene and hexane must be taking place on the crystal surface. It is possible however, that under the conditions of the acylation reaction, the presence of dissolved acyl halide increases the dielectric constant of the medium sufficiently to cause the solution of some of the naphthoxide salt thereby resulting in a homogeneous reaction component. To exclude this possibility, a sample of lithium 2-naphthoxide in benzene was stirred with an equivalent of nitrobenzene(whose dielectric constant is 36, approximately twice that of benzoyl chloride[61]) to determine if any of the salt would dissolve in the nitrobenzene-benzene mixture. No salt was found to dissolve after 2 hours stirring. Therefore, one may reasonably presume that the reaction of naphthoxide ion in hexane and benzene is a reaction between solid naphthoxide and the dissolved acyl halide.

Trans-esterification Controls. The possibility that C-acylation can take place via attack of the ambident naphthoxide ion or by the ambident keto-naphthoxide ion on the ester product cannot be overlooked. This reaction may be pictured as follows:

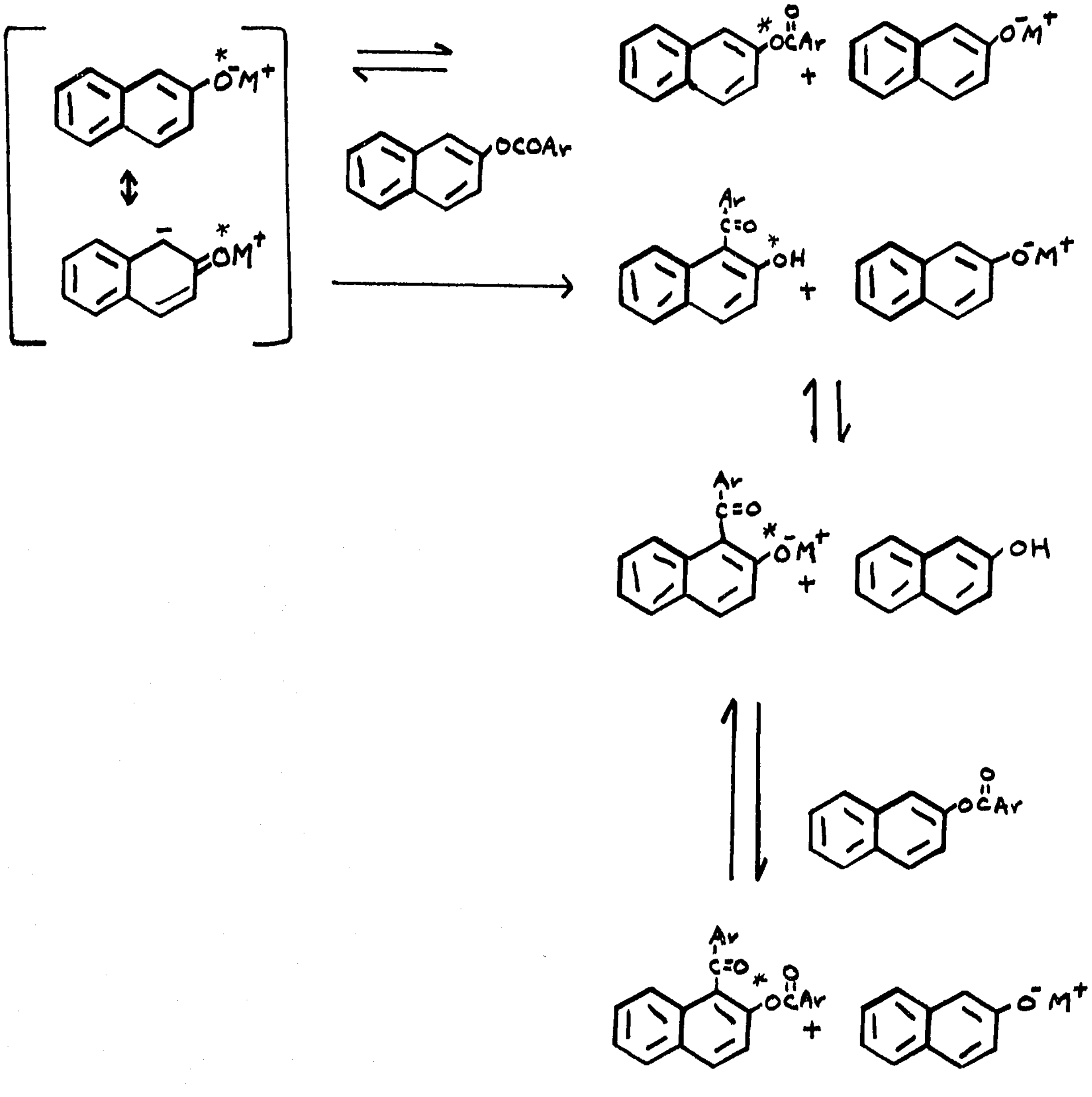


Figure 27

To exclude the above reaction from consideration, control experiments were carried out for every reaction in which any C-acylated product(either keto-naphthol or keto-ester) was obtained. The control experiments were set up so as to maximize trans-esterification conditions. One eqivalent of naphthoxide salt was allowed to react with ten equivalents of ester for ca. 20 hours using the same conditions under which the acylation experiment is carried out except that the contact time for these controls was increased some 40 fold.

For the benzoyl system(i.e. the series of reactions utilizing a benzoyl halide as an acylating agent), no C-acylated product was obtained and the starting ester was recovered essentially quantitatively.

Therefore one may conclude that the C-acylated product has arisen via another pathway; namely, reaction of the naphthoxide with the acyl halide.

For the reaction of p-nitrobenzoyl chloride with the lithium salt of 2-naphthol, the normal addition procedure (i.e. adding the acid halide to a 10% excess of salt solution or suspension) gave somewhat unexpected results(see Table XIX). In benzene(Exp. 27), an O/C acylation ratio of 7.5 was found. However, in tetrahydrofuran(Exp. 23), 0.64% of C-acylated product(keto-naphthol) was obtained which resulted in an O/C acylation ratio of 156.

In order to explain the anomalous THF results, an exchange reaction may be invoked(vide supra). That this pathway may actually be responsible for the anomaly observed is born out by the results obtained from the reaction of lithium 2-naphthoxide with a ten-fold excess of 4-nitronaphthyl benzoate in hexane, benzene and THF(Exp.31,32 and 33, respectively). Trans-esterification leading to C-acylated product was found to occur in all three solvents.

To minimize the formation of C-product via this pathway, it was thought that if the ester product could be formed in the presence of an excess of p-nitrobenzoyl chloride rather than in an excess of naphthoxide anion, then there would be no excess base to catalyze the trans-esterification reaction. To accomplish this, an inverse addition of lithium 2-naphthoxide to an excess of p-nitrobenzoyl chloride was carried out in benzene(Exp.26),hexane (Exp. 25) and THF(Exp. 24). The results of these experiments are recorded in Table XIX. For the reactions which were conducted in benzene and hexane, an O/C acylation ratio was obtained which was very close to that obtained using regular addition. However, this inverse addition method completely eliminated the C-product for the THF reaction and a quantitative yield of ester was obtained. Therefore, it would appear from these results that C-product formed in the benzene(and undoubtedly in the hexane reaction) arises not via a base-catalyzed trans-esterification pathway but rather from the reaction of p-nitrobenzoyl chloride with the naphthoxide ion. However, the base-catalyzed trans-esterification pathway does appear to be responsible for the unexpected 0.64% yield of C-product in the THF reaction which can be eliminated(to give a meaningful O/C acylation ratio) by the use of inverse addition.

For the anisoyl system(i.e. the series of reactions utilizing an anisoyl halide as an acylating agent), no C-acylated product was obtained and the starting ester was recovered essentially quantitatively.

Relative Rates. By means of competitive reactions in the presence of acetophenone and benzophenone, Entemann and Johnson[68] have determined that the order of reactivity toward phenyl magnesium bromide of the benzoyl halides is the reverse of that encountered in hydrolytic[69,70], alcoholytic[71,72], phenolytic[73] and Friedel-Crafts reactions[74]. That is, the fluoride is more reactive than the chloride which is, in turn, more reactive than the bromide. They state "since the acid fluoride is actually found to be the most reactive, it is obvious that the reaction occurs through addition to the carbonyl group.......". Therefore, it was of interest to us to determine the relative rates of reaction of the acyl halides with naphthoxide ion in order that we might acquire additional information whcih would aid us in distinguishing between the alternative pathways available for base-catalyzed acylation.

To determine the relative rates of reaction, a competition method was employed. For the competition reaction, pairs of acyl halides(whose para-substituents were different) were permitted to compete for a naphthoxide substrate in hexane. Relative rates were then calculated from the amount of ester obtained from each acyl halide after a correction had been made for the amount of C-product formed. As a check on the method, relative rate values for benzoyl bromide were determined by two different competition experiments. The deviation from the average relative rate value was less than 5%. The relative rates of reaction of acyl halides with sodium 2-naphthoxide and lithium 2-naphthoxide in hexane are as follows:

Table XXIII

Relative Rates of Reaction of Acyl Halides with $M^+C_{10}H_7O^-$

	$Na^+C_{10}H_7O^-$		$Li^+C_{10}H_7O^-$	
p-Substituted Acyl Halide	Cl	Br	Cl	Br
p-OCH_3	0.78	0.95	0.62	1.13
p-H	1.00	1.32	1.00	2.27
p-NO_2	8.03	____	48.7	____

The wider range of values obtained for the relative rate of the lithium salt vs. the sodium salt is intelligible on the basis that lithium 2-naphthoxide should be a weaker nucleophile than sodium 2-naphthoxide and hence more discriminating between pairs of acyl halides. The sodium 2-naphthoxide, being the stronger nucleophile, will exhibit a kind of leveling effect and will tend to be less discriminating between pairs of acyl halides. For the sodium salt then, a smaller range of relative rate values is expected.

Two important trends are noted from the relative rate data.

(1)When the leaving group is changed from chloride to bromide, the rate of reaction is increased. For the reaction of benzoyl halide with sodium 2-naphthoxide, the chloride to bromide change is accompanied by a 32% increase in rate while the same change in leaving group for the reaction with lithium is attended by a 127% rate increase. Similar effects are obtained from the reaction of sodium and lithium 2-naphthoxides with anisoyl halides. This rate enhancement when the leaving group facility is increased indicates that the transition state for the reaction involves a great deal of bond-breaking. This latter indication is not unexpected if the acylation reaction is proceding by a concerted displacement mechanism. However, an addition-elimination mechanism would probably require that a change in leaving group from chloride to bromide decrease the rate of reaction(as the reaction of phenyl magnesium bromide has shown------vide supra) since the decrease in electronegativity of the halide should cause a concomitant decrease in the electrophilicity of the carbonyl carbon. If we now consider the substitution reactions of aromatic halides which are activated by electron-withdrawing groups(a model system which is known to proceed through an addition-elimination mechanism[75]), the expected rate decrease as the leaving group is changed from chloro to bromo is observed (see Table XXIV).

Table XXIV

Relative Rates for Leaving Groups in an Addition-Elimination Reaction

Reaction	Temp. (°C)	k_{Cl}/k_{Br}	Ref.
Sodium methoxide[a] with:			
1-Halo-2,4-dinitrobenzenes	15	1.38	76
	25	1.52	77
	35	1.56	77
	50	1.61	78
2-Cyano-1-halo-4-nitrobenzenes	25	1.27	79
4-Cyano-1-halo-2-nitrobenzenes	25	1.39	80
2-Halo-1,6,8-trinitronaphthalenes	0	1.8	81
	15	2.7	81
	25	3.7	81
1-Halo-2-nitrobenzenes	0	2.46	82
	50	1.43	82
1-Halo-4-nitrobenzenes	0	1.63	78
	50	1.34	78
Sodium ethoxide[b] with:			
1-Halo-2,4-dinitrobenzene	15	1.60	77
	25	1.73	77
4-Halonitrobenzenes	90.8	1.15	83

Table XXIV(continued)

Ammonia in methanol with:			
1-Halo-2,4-dinitrobenzene	25	1.08	84
1-Halo-2,4-dinitronaphthalenes	25	1.36	85
	45	1.57	85
Methylamine with:[b]			
1-Halo-2,4-dinitrobenzenes	25	1.24	77

a.Methanol; b.Ethanol.

Alternatively, the order of leaving in a typical S_N2 reaction is known to be Br greater than Cl. Examples of such an order are listed in Table XXV.

Table XXV

Relative Displacement Rates for Leaving Groups in S_N2 Rxs.

T(°C)	Reagent	k_{Br}/k_{Cl}	Reference
20	ϕCH_2X + MeO^- in MeOH	41.0	86
25	ϕCH_2X + NH_3 in abs. EtOH	51.6	87
30.5	ϕCH_2X + pyridine in 90% aqueous EtOH	50	88
30	C_3H_7X + OEt^- in EtOH	63	89
24	AllylX + OEt^- in EtOH	52	89
40	EtX + OEt^- in EtOH	42	90
20	CH_3X + $S_2O_3^=$ in water	44	88

(2)When the para-substituent is changed from methoxy to hydrogen to nitro, the relative rate of reaction with naphthoxide ion is increased(see Table XXIII). The reaction of sodium 2-naphthoxide with acyl chlorides yields the order 0.78:1.00:8.03 for p-OCH_3, p-H and p-NO_2, respectively. The reaction of lithium 2-naphthoxide gives the same order for the corresponding reactions with the sodium salt(i.e. 0.62:1.00:48.7). For the competition of anisoyl bromide and benzoyl bromide for naphthoxide ion(both sodium and lithium), the presence of a p-OCH_3 substituent is found to lower the relative rate of reaction. These relative rate data can easily be accomodated by an addition-elimination mechanism wherein an electron-withdrawing group in the para-position would be expected to facilitate attack by a nucleophile and an electron-donating group in this position should hinder attack by a nucleophile[91]. However, there are S_N2 reactions in the literature which are also facilitated by the presence of a p-nitro group. Examples of this effect in reactions of benzyl chlorides are given in Table XXVI.

Table XXVI

Relative Displacement Rates for Para-substituents in S_N2 Reactions of ϕCH_2Cl

T(°C)	Reagents	$k_{p\text{-}NO_2}/k_{p\text{-}H}$	References
0.1	KI in acetone	6.82	92
20	KI in acetone	6.20	92
30	$Na_2S_2O_3$ in 60% aqueous acetone	2.55	93

This effect of electron-withdrawing substituents in the para-position in the S_N2 reactions of benzyl compounds has been considered by Swain[94] in terms of "loose" and "tight" transition states. Electron-withdrawing substituents place a fractional positive charge on the benzylic carbon atom of the initial state and stabilize the somewhat more negative charge in the "tight" transition state.

Alternatively, the introduction of a nitro group into the para-position of a system which is known to undergo reaction with a nucleophile via an addition-elimination mechanism also results in an increased rate. However, this increase in rate is much greater than that obtained for a typical S_N2 reaction(vide supra). For example, in the saponification of substituted ethyl benzoates at 30°, the $k_{p\text{-}NO_2}/k_{p\text{-}H}$ is found to be 104[95].

For an addition-elimination pathway, the presence of a p-methoxy group substantially decreases the rate of saponification of substituted ethyl benzoates(i.e. $k_{p\text{-}OCH_3}/$

$k_{\underline{p}\text{-}H}$= 0.22)[95]. For a reaction which proceeds via an S_N2 mechanism, the influence of an electron-donating p-methoxy group is not clear. Gould has stated that ".....we cannot compare the quantity of electron density that has been supplied with that which has been removed at the instant the system passes through the transition state. We therefore cannot say whether the carbon at the reaction site is more positive or more negative in the activated complex than in the reaction; consequently, an S_N2 reaction might be accelerated or retarded by electron-rich substituents on the substrate".[96] Bunton[97] concurs with this latter statement.

Finally it was of interest to calculate the partial relative rates for the reaction of 2-naphthoxides with acyl halides in hexane in order that a further insight into the effect of a change in leaving group and of a change in para-substituent(of the acyl halide) on the nature of the C- and O-acylation transition states might be gained. The partial relative rates are shown in Table XXVII.

Table XXVII

Partial Relative Rates for the Reaction of Naphthoxides with Acyl Halides in Hexane

Metal Cation	Acyl Halide	C-Acylation	O-Acylation
Li	AnsCl	0.487	13.0
Li	BzCl	1.00	20.6
Li	p-NO_2BzCl	156	934
Li	AnsBr	1.05	23.3
Li	BzBr	2.78	45.7
Na	AnsCl	0.575	105
Na	BzCl	1.00	135
Na	p-NO_2BzCl	30.4	1083
Na	AnsBr	3.02	126
Na	BzBr	5.63	175

Two of the factors discussed before, Effect of a Change in Leaving Group and of a Change in the Para-substituent in the Acyl Halide, may now be considered in terms of their influence on the partial relative rates of the C- and O-acylation processes. The data in Table XXVII shows a larger increase in relative rate for the C-acylation process than for the O-acylation process as the leaving group on the acyl halide is changed from Cl to Br. This is an indication that there is more bond-breaking in the C-acylation transition state than in the O-acylation transition state. This leaving group effect is again in accord with what one might predict, a priori, for a reaction which proceeds via a concerted displacement mechanism; i.e. since a displacement involves the breaking of the C-X bond in the rate-determining step, we would expect to see a rate increase for both the C- and O-acylation processes as the leaving group is changed from Cl to Br. The rate enhancement however, should be greater for the C-process than for the O-process since a consideration of the transition states for the two processes(vide supra) indicates that there is more bond-breaking in the C-acylation transition state due to the proximate metal cation which helps the halide ion to leave. These relative rate differences are not predicted for a reaction which proceeds through an addition-elimination pathway since the breaking of the C-X bond is not rate-determining[75].

The data is Table XXVII also shows that for a change in para-substituent from p-OCH_3 to p-H to p-NO_2, there is an overall rate enhancement(both O- and C-) but the C-acylation process exhibits a larger increase in rate than does the C-process. This is evidence which supports a concerted displacement mechanism as arguments previously(vide supra), in terms of the two factors electrophilicity and bond-length, have shown.

Structure Proof. The synthesis of 1-benzoyl-2-naphthol (II, Figure 28) was carried out via a Fries rearrangement of 2-naphthyl benzoate. The position of the keto group in compound(II) was established using the synthetic scheme outlined in Figure 28.

Since the other keto-naphthols used in this study [i.e. 1-(4'-nitrobenzoyl)-2-naphthol and 1-anisoyl-2-naphthol] were also synthesized via a Fries rearrangement of the respective 2-naphthyl esters, it is presumed that the position of the keto group in these compounds is also established.

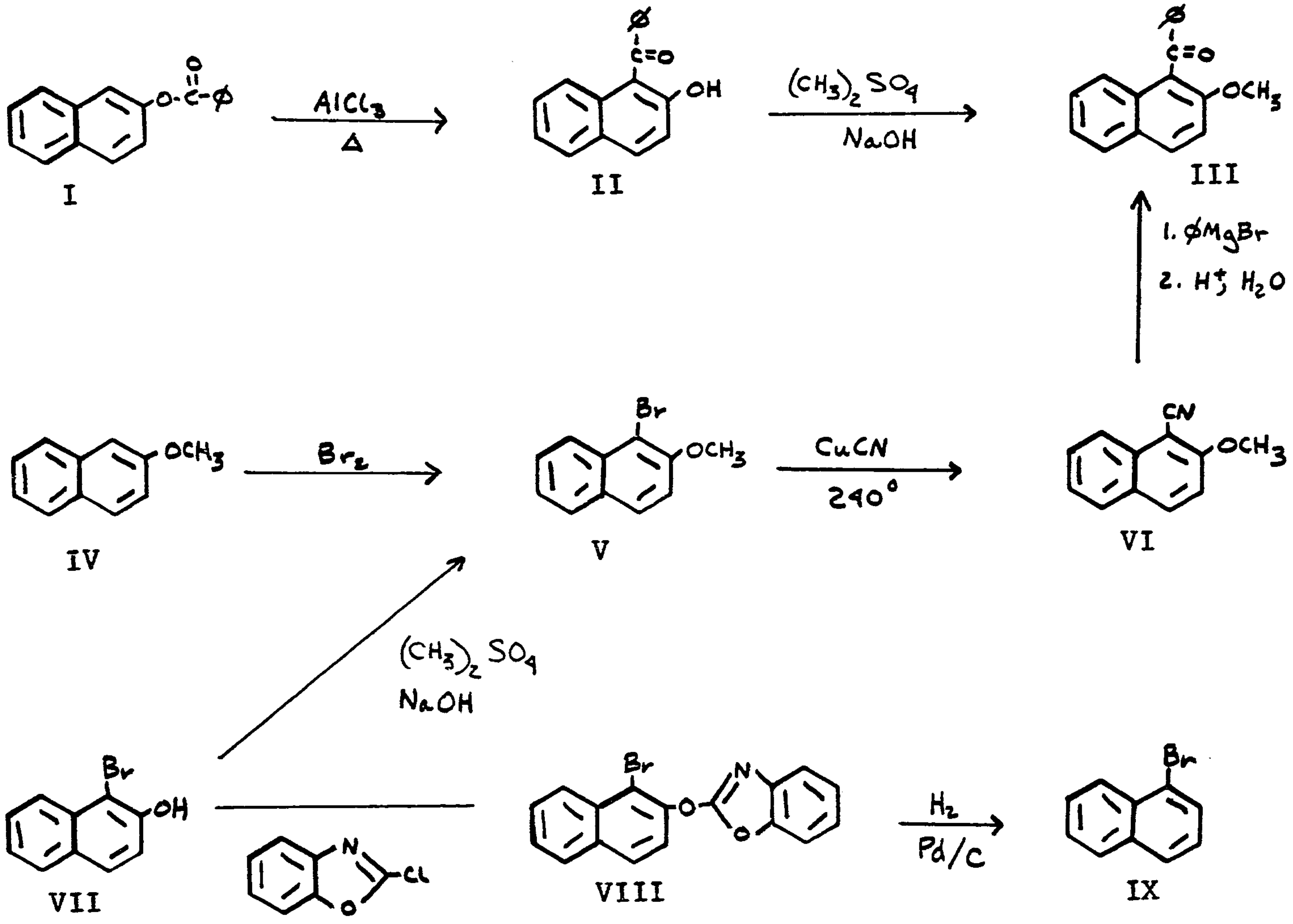

I
AlCl₃
Δ
II
(CH₃)₂ SO₄
NaOH
III
1. ϕMgBr
2. H⁺; H₂O
IV
Br₂
V
CuCN
240°
VI
(CH₃)₂ SO₄
NaOH
VII
VIII
H₂
Pd/C
IX

Figure 28

IV.EXPERIMENTAL

Analyses were by Schwarzkpf Microanalytical Laboratory, Queens New York. The infrared absorption spectra were determined on a Perkin-Elmer Model 237 spectrophotometer.

Eastman Kodak Co. white label 2-naphthol(m.p. 121-122°) and 2-naphthyl benzoate(m.p. 108°) were used without further recrystallization. Tetrahydrofuran(Matheson) was refluxed over potassium hydroxide for 24 hours and then distilled from lithium aluminum hydride. Benzene(Baker, reagent) was distilled from sodium wire. 2,2,2-Trifluoroethanol(Pennsalt) was allowed to stand over sodium carbonate, then over anhydrous magnesium sulfate and, finally, distilled[2]. The carbon tetrachloride used was Fisher anhydrous grade. Hexane(Eastman, purified) was distilled from sodium wire. Ethylene glycol dimethyl ether(Eastman) was distilled from sodium. All acyl halides(commercial samples) were used directly provided the physical constants agreed with the literature values. If not, they were either sublimed(in the case of p-nitrobenzoyl chloride) or distilled(in the case of the other halides) until the correct melting point or refractive index was realized.

Vapor Phase Chromatography. Analyses of the benzoylated products were carried out on a Wilkens Aerograph VPC(Model 600-D, Flame Ionization Detector) using a 4.5 ft.(1/8" copper)silicone rubber(5% SE-30) column on Chromosorb G (70/80 mesh, AW-DMCS). VPC analyses were conducted at a flow rate of 25 ml./min. and at a column temperature of 220°. For the analyses of the products obtained from the reaction of benzoyl chloride and bromide with the salts of 2-naphthol, a procedure was devised whereby 0.01% of 1-benzoyl-2-naphthol could be detected in the acidic(base-soluble) fraction. An aliquot from a standard containing 0.990g.(99%) of 2-naphthol and 0.010g.(1%) of 1-benzoyl-2-naphthol dissolved in 10 ml. of ethanol was analyzed by VPC. 1-Benzoyl-2-naphthol could readily be detected to the extent of 0.01%. Under these conditions, 2-naphthol and 1-benzoyl-2-naphthol have retention times of 0.3 and 2.0 minutes, respectively. In analyzing unknowns, the acidic fraction was made up to the same concentration(by weight) as the standard and a 1 microliter aliquot was analyzed; absence of 1-benzoyl-2-naphthol meant that less than 0.01% was present in the acidic fraction. An analogous procedure was devised whereby 0.01% of 1-benzoyl-2-naphthyl benzoate could be detected in the neutral(base-insoluble) fraction. A standard of 0.990g.(99%) of 2-naphthyl benzoate and 0.010g.(1%) of 1-benzoyl-2-naphthyl benzoate was made up to a volume of 10 ml. with chloroform and a 1 microliter aliquot was analyzed. 1-Benzoyl-2-naphthyl benzoate could readily be detected to the extent of 0.01%. Under these conditions, 2-naphthyl benzoate and 1-benzoyl-2-naphthyl benzoate have retention times of 2.2 and 15.6 minutes, respectively. In analyzing unknowns, the neutral fraction was made up to the same concentration(by weight) as the standard and a 1 microliter aliquot was analyzed; absence of 1-benzoyl-2-naphthyl benzoate meant that less than 0.01% of C-acylate was present in the neutral fraction. In all quantitative analyses, retention times and relative responses to the flame ionization detector were determined using an authentic sample of each component. A sample calculation of the data found in Table XIX may be shown as follows for the reaction of benzoyl chloride with sodium 2-naphthoxide in the dimethyl ether of ethylene glycol(1-4-1):

Area of chromatogram peak for unknown 2-naphthyl benzoate
= 325 units

Conversion factor obtained from standard solution of 2-naphthyl benzoate = 0.000234 mg./unit

325 units x 0.000234 mg./unit = 0.0728mg. ester per 0.100mg.
of sample injected(1 microliter of a 10% solution)

% ester in sample = 72.8

Actual yield of neutral fraction = 7.2113g.

Recalculated yield of neutral fraction = 0.728 x 7.2113
= 5.250g.

Moles of ester = 0.0217(68.9%)

For the analysis of the products obtained from the reaction of benzoyl iodide with lithium 2-naphthoxide an internal standard, 2-naphthyl 4-nitrobenzoate, was used to measure the amount of products formed. For the analysis of the base-soluble product, a synthetic mixture of the authentic keto-naphthol and the internal standard were dissolved in tetrahydrofuran and a sample analyzed by VPC. Under the above-stated conditions, the keto-naphthol and the internal standard exhibited retention times of 2.0 and 7.2 minutes, respectively. To analyze the experimentally obtained base-soluble product, a known weight of internal standard was added to it and the entire mixture was completely dissolved in tetrahydrofuran. A sample of this solution was then chromatographed and from the ratio of the areas of the peaks obtained for the synthetic mixture to that obtained for the experimental mixture, the yield of keto-naphthol can be calculated via a simple proportion. In this manner, 0.01% of keto-naphthol can easily be detected. In an identical manner, the yields of ester and keto-ester can also be determined. The keto-ester can easily be detected to the extent of 0.01%. Under these conditions, the ester and keto-ester have retention times of 2.2 and 15.6 minutes, respectively.

Analyses of the p-nitrobenzoylated products were carried out on a Wilkens Aerograph(vide supra) at a flow rate of 38 ml./min. and a column temperature of 274°. An internal standard, 2-naphthyl 4-nitrobenzoate, was used to quantitatively measure the amount of products formed. Under the above-stated conditions, the ester, keto-naphthol, internal standard and keto-ester exhibited retention times of 1.8, 1.8, 6.6 and 16.5 minutes, respectively.

For the analysis of the products obtained from the reaction of p-methoxybenzoyl chloride and bromide with the metal salts of 2-naphthol an internal standard method was utilized. The analysis of the keto-naphthol was carried out at 228^{o} and at a flow rate of 25 ml./min. using 2-naphthyl 3,4,5-trimethoxybenzoate as the internal standard. The keto-naphthol and internal standard exhibited retention times of 4.1 and 11.6 minutes, respectively. The analysis of the ester and keto-ester was conducted at a column temperature of 268^{o} and at a flow rate of 25 ml./min. using 1-(4'-nitrobenzoyl)-2-naphthyl benzoate as the internal standard. The ester, internal standard and keto-ester exhibited retention times of 1.4, 6.5 and 11.8 minutes, respectively.

In each set of reactions(i.e. benzoyl, anisoyl and 4-nitrobenzoyl systems), trapping experiments were carried out to confirm the identity of the chromatogram peaks. In all cases, the infrared spectrum of the trapped compound was identical with that exhibited by an authentic sample.

All vapor phase chromatographic analyses were conducted in triplicate. The peak areas were determined by planimetry and an average peak area was calculated. The deviation from this average peak area was found to be on the order of 2%.

As a check on the analytical method, weighed amounts of authentic samples of each of the products expected in each series of reactions were mixed together and then separated by the method presented in experiments 1, 23 and 34. VPC analysis of the separated materials accounted for more than 99% of the material taken.

Selected duplicate experiments were also conducted as a check on the analytical method. The O/C acylation ratios of these duplicate experiments were found to agree to within 10%.

Sodium 2-Naphthoxide.[3] To 75.0 g.(0.521 mole) of 2-naphthol dissolved in 260 ml. of methanol was added 20.0 g.(0.500 mole) of Baker analyzed reagent quality sodium hydroxide dissolved in 40 ml. of water. The methanol and water were removed under reduced pressure at 60°. The crude salt was dissolved in 120 ml. of tetrahydrofuran and the solution was filtered. The filtrate was treated with 300 ml. of benzene and the precipitated sodium 2-naphthoxide was isolated by filtration, washed thoroughly with ethyl ether and dried at 100°(1 mm.) for 24 hours; yield, 40-50g.(48-60%).

Anal. Calcd. for $C_{10}H_7ONa$: neut. equiv., 166. Found: neut. equiv., 166-169.

Lithium 2-Naphthoxide. To 37.5 g.(0.26 mole) of 2-naphthol dissolved in 130 ml. of methanol was added 6.0 g.(0.25 mole) of anhydrous lithium hydroxide(Baker analyzed reagent) in 100 ml. of water. The solvent was removed under reduced pressure at 60°. The crude salt was dissolved in 80 ml. of THF and the solution was filtered. The filtrate was treated with 200 ml. of benzene and the precipitated lithium 2-naphthoxide was collected by filtration, washed with pentane and dried at 100° and 1 mm. pressure for 24 hours. The reprecipitation of the crude salt was carried out in a dry-box under a nitrogen atmosphere. Yield, 20.4 g.(54%).

Anal. Calcd. for $C_{10}H_7OLi$: neut. equiv., 150. Found: neut. equiv., 148-150.

1-Benzoyl-2-naphthol. An intimate mixture of 41 g. of aluminum chloride and 30 g. of 2-naphthyl benzoate was heated in an oil bath at 120° for 2 hours. The reaction mixture was then permitted to cool to room temperature and a solution containing 70 ml. of concentrated hydrochloric acid and 400 g. of ice was added to it. The resulting precipitate was collected by suction filtration, washed with water, then with 5% sodium bicarbonate solution and finally with water again. This material was recrystallized from aqueous ethanol to give 13.54 g.(45%) of product. M.p. 140°; lit.[98], 140°.

1-Benzoyl-2-naphthyl Benzoate. 1-Benzoyl-2-naphthol, 7.44 g., was dissolved in 24 ml. of 5% sodium hydroxide solution and cooled to 0°. Benzoyl chloride, 4.22 g., was added dropwise to this solution. The flask was stoppered after addition was completed and shaken vigorously for 10 minutes. The precipitate formed was collected by suction filtration and recrystallized three times from aqueous ethanol to give 1.64 g.(16%) of product. M.p.,95.5-96.5°. The product exhibited no O-H bands in its infrared absorption spectrum.

Anal. Calcd. for $C_{24}H_{16}O_3$: C, 81.81; H, 4.55. Found: C, 81.57; H, 4.58.

1. Reaction of Benzoyl Chloride with Sodium 2-Naphthoxide in 2,2,2-Trifluoroethanol:

To a solution of 6.850g.(0.0413 mole) of sodium 2-naphthoxide in 75 ml. of 2,2,2-trifluoroethanol was added 5.27 g.(0.0315 mole) of benzoyl chloride dissolved in 7 ml. of tetrahydrofuran. The reaction mixture was permitted to stir for 30 minutes after the addition of the benzoyl chloride was completed. The solvent was removed under reduced pressure and the residue suspended in 150 ml. of benzene. This suspension was extracted with three 50 ml. portions of ice-cold 10% potassium hydroxide solution. The benzene extract was then washed with water until neutral and dried over anhydrous magnesium sulfate. The drying agent was removed by filtration and the filtrate evaporated to give the base-insoluble(neutral) fraction which weighed 6.174g.

The base-extract was acidified with ice-cold 6N hydrochloric acid and extracted with three 50 ml. portions of benzene. The combined benzene extracts were washed with water until neutral and dried over anhydrous magnesium sulfate. The drying agent was removed by filtration and the filtrate evaporated to dryness to give the base-soluble (acidic) fraction which weighed 4.428g. The VPC analyses of these fractions gave the following results:

Ester, 18.1%	Keto-naphthol, 0.052%	Keto-ester, 0.000%

2.Reaction of Benzoyl Chloride with Sodium 2-Naphthoxide in Hexane:

A duplicate of experiment 1 was carried out in hexane. The VPC analyses of the products obtained are given as follows:

Ester, 83.8% Keto-naphthol, 0.624% Keto-ester, 0.000%

3.Reaction of Benzoyl Chloride with Sodium 2-Naphthoxide in Carbon Tetrachloride:

A duplicate of experiment 1 was carried out using carbon tetrachloride as the solvent. The VPC analyses of the products obtained are as follows:

Ester, 78.0% Keto-naphthol, 0.468% Keto-ester, 0.000%

4.Reaction of Benzoyl Chloride with Sodium 2-Naphthoxide in Ethylene Glycol Dimethyl Ether(1-4-1):

A duplicate of experiment 1 was carried out in 1-4-1. VPC analyses of the products obtained are as follows:

Ester, 60.4% Keto-naphthol, 0.000% Keto-ester, 0.000%

5.Reaction of Benzoyl Chloride with Sodium 2-Naphthoxide in Benzene:

A duplicate of experiment 1 was carried out using benzene as the solvent. VPC analyses of the products obtained are as follows:

Ester,	88.3%	Keto-naphthol,	0.641%	Keto-ester,	0.223%
"	82.5%	"	0.638%	"	0.113%

6.Reaction of Benzoyl Chloride with Sodium 2-Naphthoxide in Tetrahydrofuran(THF):

A duplicate of experiment 1 was carried out in THF. VPC analysis of the products obtained is as follows:

Ester, 68.5% Keto-naphthol, 0.000% Keto-ester, 0.000%

7.Reaction of Benzoyl Bromide with Sodium 2-Naphthoxide in Hexane:

A duplicate of experiment 2 was carried out except that benzoyl bromide was used in place of benzoyl chloride. VPC analysis of the products obtained is as follows:

Ester, 73.8% Keto-naphthol, 2.23% Keto-ester, 0.085%
" 76.2% " 2.48% " 0.13%

8.Reaction of Benzoyl Bromide with Sodium 2-Naphthoxide in Benzene:

A duplicate of experiment 5 was carried out using benzoyl bromide as the acylating agent. VPC analyses of the products obtained are as follows:

Ester, 85.0% Keto-naphthol, 2.09% Keto-ester, 0.000%

9.Reaction of Benzoyl Bromide with Sodium 2-Naphthoxide in 1-4-1:

A duplicate of experiment 4 was carried out using benzoyl bromide as the acylating agent. VPC analyses of the products obtained are as follows:

Ester, 68.9% Keto-naphthol, 0.000% Keto-ester, 0.000%

10. Reaction of Benzoyl Bromide with Sodium 2-Naphthoxide in 2,2,2-Trifluoroethanol(TFE):

A duplicate of experiment 1 was carried out using benzoyl bromide as the acylating agent. VPC results are as follows:

Ester, 36.0%   Keto-naphthol, 0.036%   Keto-ester, 0.101%

11. Reaction of Benzoyl Chloride with Lithium 2-Naphthoxide in Benzene:

The same procedure as had been employed for experiment 5 was utilized except that the lithium salt of 2-naphthol was used in place of sodium 2-naphthoxide. VPC analyses of the products obtained are as follows:

Ester, 83.6%   Keto-naphthol, 0.874%   Keto-ester, 1.45%
"   86.3%   "   1.20%   "   1.33%

12. Reaction of Benzoyl Chloride with Lithium 2-Naphthoxide in Hexane:

A duplicate of experiment 11 was carried out except that hexane was used as the solvent. VPC analyses of the products obtained are as follows:

Ester, 82.4%   Keto-naphthol, 0.482%   Keto-ester, 3.52%

13. Reaction of Benzoyl Chloride with Lithium 2-Naphthoxide in Tetrahydrofuran:

A duplicate of experiment 11 was carried out except that tetrahydrofuran was used in place benzene. VPC analyses of the products obtained are as follows:

Ester, 86.7% Keto-naphthol, 0.000% Keto-ester, 0.000%

14. Reaction of Benzoyl Bromide with Lithium 2-Naphthoxide in Benzene:

A duplicate of experiment 11 was carried out except that benzoyl bromide was used as the acylating agent in place of benzoyl chloride. VPC analyses of the products obtained are as follows:

Ester,	84.0%	Keto-naphthol,	1.23%	Keto-ester,	3.41%
"	87.7%	"	1.72%	"	2.78%

15. Reaction of Benzoyl Bromide with Lithium 2-Naphthoxide in Hexane:

A duplicate of experiment 14 was carried out in hexane. VPC analyses of the products obtained are as follows:

Ester, 84.1% Keto-naphthol, 0.166% Keto-ester, 4.95%

16. Reaction of Benzoyl Bromide with Lithium 2-Naphthoxide in Tetrahydrofuran:

A duplicate of experiment 14 was carried out in tetrahydrofuran. VPC analyses of the products obtained are as follows:

Ester, 86.7% Keto-naphthol, 0.000% Keto-ester, 0.000%

Benzoyl Iodide.[99] Dry, powdered sodium iodide, 30 g., was mixed with 30 g. of benzoyl chloride under anhydrous conditions. The mixture was gradually warmed to 50° with occasional shaking. The temperature of the reaction mixture was then raised to 70° for 3.5 hours. The red-brown liquid was decanted off and distilled at 12 mm. and 110°. Yield, 14.4 g.(29%).

17.Reaction of Benzoyl Iodide with Lithium 2-Naphthoxide in Hexane:

A duplicate of experiment 15 was carried out except that benzoyl iodide was used in place of benzoyl bromide. VPC analyses of the products obtained are as follows:

Ester, 67.5% Keto-naphthol, 0.225% Keto-ester, 14.9%

18.Reaction of Benzoyl Iodide with Lithium 2-Naphthoxide in Benzene:

A duplicate of experiment 17 was carried out using benzene as the solvent. VPC analyses of the products obtained are as follows:

Ester, 77.8% Keto-naphthol, 0.216% Keto-ester, 12.8%

19.Reaction of Benzoyl Iodide with Lithium 2-Naphthoxide in Tetrahydrofuran:

A duplicate of experiment 17 was carried out using tetrahydrofuran as the solvent. VPC analyses of the products obtained are as follows:

Ester, 91.3% Keto-naphthol, 0.000% Keto-ester, 0.000%

20. Reaction of Benzoyl Chloride with Lithium 2-Naphthoxide in Water:

A duplicate of experiment 11 was carried out using water as the solvent. VPC analyses of the products obtained are as follows:

Ester, 51.7% Keto-naphthol, 0.127% Keto-ester, 0.000%

21. Reaction of Benzoyl Bromide with Lithium 2-Naphthoxide in Water:

A duplicate of experiment 14 was carried out using water as the solvent. VPC analyses of the products obtained are as follows:

Ester, 46.4% Keto-naphthol, 0.099% Keto-ester, 0.171%

22. Trans-esterification Control Experiment for the Reaction of Sodium 2-Naphthoxide with 2-Naphthyl Benzoate in Hexane:

Sodium 2-naphthoxide, 0.1918 g.(0.00115 mole), and 2.85 g.(0.0115 mole) of 2-naphthyl benzoate were suspended in 21 ml. of hexane(conc.=0.55M in ester). This suspension was stirred under nitrogen at 25° for 20 hours. The solvent was removed under reduced pressure and the residue was worked up in the manner previously described in experiment 1. No keto-naphthol or keto-ester(i.e. less than 0.01%) could be detected.

Control experiments were carried out for each naphthoxide salt(sodium and lithium) and every solvent wherein C-acylation was obtained. In all instances, no trans-esterification(leading to C-acylation) occurred and the starting ester was recovered essentially quantitatively.

2-Naphthyl 3,4,5-Trimethoxybenzoate. 3,4,5-Trimethoxybenzoyl chloride, 11.5 g.(0.05 mole), was dissolved in 100 ml. of pyridine and the solution brought to reflux. To this was added a solution of 10 g.(0.069 mole) of 2-naphthol in 25 ml. of pyridine. The solution was refluxed for 1 hour and then permitted to cool to room temperature. The reaction mixture was then added to an ice-cold solution containing 100 ml. of 5% sulfuric acid and 500 ml. of water. A white precipitate was collected, washed well with water, leached with 25 ml. of ice-cold 2% sodium hydroxide solution and air dried. This material was then recrystallized from ethanol. Yield, 6.3 g.(43%); m.p. 124-125°.

2-Naphthyl 4-Nitrobenzoate. To 20 g. of 4-nitrobenzoyl chloride dissolved in 200 ml. of pyridine was added, in a portionwise manner, a solution of 20 g. of 2-naphthol dissolved in 50 ml. of pyridine. The solution was heated at reflux for 1 hour and then poured into a solution containing 150 ml. of 5% sulfuric acid and 1 liter of water. The precipitate was collected, leached with 50 ml. of ice-cold 2% sodium hydroxixde solution, washed well with water and recrystallized from hexane:benzene to yield 14 g.(32%) of product which melted at 168-169°; lit.[100], m.p. 169°.

1-(4'-Nitrobenzoyl)-2-naphthol. An intimate mixture of 39.8 g. of 2-naphthyl 4-nitrobenzoate and 23.66 g. of aluminum chloride was heated in an oil bath at 120° for 2 hours. The reaction mixture was permitted to cool to room temperature and a solution containing 50 ml. of 6N hydrochloric acid and 200 g. of ice was added to it. A bright yellow solid was collected by suction filtration, triturated with water, then with 5% sodium bicarbonate solution and finally with water again. The solid was suspended in 400 ml. of acetone and filtered to remove a small amount of insoluble material. Hexane was added to the filtrate until it became turbid. It was then permitted to cool in the refrigerator overnight. This crude product was collected by suction filtration and recrystallized from acetone:hexane to give 4.03 g.(9%) of product which melted at 187-188°; lit.[101], m.p. 186°.

Anal. Calcd. for $C_{17}H_{11}NO_4$: C, 69.66; H, 3.76; N, 4.78. Found: C, 69.72; H, 3.85; N, 4.56.

1-(4'-Nitrobenzoyl)-2-naphthyl 4-Nitrobenzoate. 1-(4'-Nitrobenzoyl)-2-naphthol, 1.4 g., was dissolved in 10 ml. of pyridine. To this solution was added 0.8 g. of 4-nitrobenzoyl chloride and the mixture was heated at reflux for 1 hour. After cooling, the solution was poured into 50 ml. of ice-cold water. The precipitate was collected by suction filtration, triturated with 5% sodium bicarbonate solution, washed with water and recrystallized from benzene to give 1.2 g.(59%) of a material which melted at 218-219°. This material exhibited no O-H bands in its infrared absorption spectrum.

Anal. Calcd. for $C_{24}H_{14}N_2O_7$: C, 65.16; H, 3.17; N, 6.34. Found: C, 65.43; H, 3.37; N, 6.41.

23. Reaction of 4-Nitrobenzoyl Chloride with Lithium 2-Naphthoxide in Tetrahydrofuran:

A duplicate of the experimental procedure employed in experiment 1 was carried out in tetrahydrofuran except that 4-nitrobenzoyl chloride was used as the acylating agent. After the addition of the acid chloride was completed, the solution was permitted to stir for 1/2 hour. The solvent was then removed under reduced pressure and the residue suspended in 150 ml. of benzene. The benzene solution was extracted with three 10 ml. portions of ice-cold 5% potassium hydroxide. The benzene layer was washed with water until neutral and then evaporated to dryness to yield the neutral fraction.

The base extract was separated from the benzene layer and neutralized with 6N hydrochloric acid. This mixture was then extracted with five 10 ml. portions of chloroform. The chloroform extract was washed successively with three 25 ml. portions of 5% sodium bicarbonate and then with water until neutral. The chloroform was removed under reduced pressure to give the acidic product. Both the acidic and neutral fractions were analyzed by VPC(vide supra) to give the following results:

Ester, 100% Keto-naphthol 0.64% Keto-ester, 0.00%

24. Reaction of 4-Nitrobenzoyl Chloride with Lithium 2-Naphthoxide in Tetrahydrofuran Using Inverse Addition:

To 1.09 g.(0.00588 mole) of 4-nitrobenzoyl chloride dissolved in 9.63 ml. of tetrahydrofuran was slowly added a solution of 0.8397 g.(0.00560 mole) of lithium 2-naphthoxide in 7.0 ml. of tetrahydrofuran. The reaction was permitted to stir for 1/2 hour. See experiment 23 for work-up procedure. VPC analyses of the products obtained gave the following results:

Ester, 100% Keto-naphthol, 0.00% Keto-ester, 0.00%

25.Reaction of 4-Nitrobenzoyl Chloride with Lithium 2-Naphthoxide in Hexane Using Inverse Addition:

Aduplicate of experiment 24 was carried out in hexane except that the lithium 2-naphthoxide was added as a solid in a portionwise fashion to a suspension of the 4-nitrobenzoyl chloride in hexane. VPC analyses of the products obtained gave the following results:

Ester, 70.0% Keto-naphthol, 0.00% Keto-ester, 11.7%

26.Reaction of 4-Nitrobenzoyl Chloride with Lithium 2-Naphthoxide in Benzene Using Inverse Addition:

A duplicate of experiment 25 was carried out in benzene. The VPC results are as follows:

Ester, 73.0% Keto-naphthol, 0.00% Keto-ester, 10.5%

27.Reaction of 4-Nitrobenzoyl Chloride with Lithium 2-Naphthoxide in Benzene:

A duplicate of experiment 23 was carried out in benzene. The VPC analyses of the products obtained are as follows:

Ester, 72.6% Keto-naphthol, 0.35% Keto-ester, 9.38%

28. Reaction of 4-Nitrobenzoyl Chloride with Sodium 2-Naphthoxide in Tetrahydrofuran Using Inverse Addition:

A duplicate of experiment 24 was carried out except that sodium 2-naphthoxide was used in place of lithium 2-naphthoxide. The VPC analyses of the products obtained are as follows:
Ester, 100% Keto-naphthol, 0.00% Keto-ester, 0.00%

29. Reaction of 4-Nitrobenzoyl Chloride with Sodium 2-Naphthoxide in Hexane Using Inverse Addition:

A duplicate of experiment 25 was carried out except that sodium 2-naphthoxide was used in place of lithium 2-naphthoxide. The VPC analyses of the products obtained are as follows:
Ester, 89.0% Keto-naphthol, 0.00% Keto-ester, 2.53%

30. Reaction of 4-Nitrobenzoyl Chloride with Sodium 2-Naphthoxide in Benzene Using Inverse Addition:

A duplicate of experiment 28 was carried out in benzene. The VPC analyses of the products obtained are as follows:
Ester, 91.0% Keto-naphthol, 0.00% Keto-ester, 2.12%

31. Reaction of Lithium 2-Naphthoxide with 2-Naphthyl 4-Nitrobenzoate in Hexane:

Lithium 2-naphthoxide, 0.1315 g.(0.000877 mole), and 2.57 g.(0.00877 mole) of 2-naphthyl 4-nitrobenzoate were suspended in 14.4 ml. of hexane and permitted to stir for 21.5 hours at 25°. The reaction was worked up in the usual manner. An exchange reaction was found to occur(as evidenced by the formation of keto-naphthol to the extent of 10.1%.

32. Reaction of Lithium 2-Naphthoxide with 2-Naphthyl 4-Nitrobenzoate in Benzene:

Lithium 2-naphthoxide, 0.0915 g.(0.00061 mole), and 1.79 g.(0.0061 mole) of 2-naphthyl 4-nitrobenzoate were suspended in 10 ml. of benzene and permitted to stir for 21.5 hours at 25°. The reaction was worked up in the usual manner. An exchange reaction was found to occur(as evidenced by the formation of keto-naphthol) to the extent of 25.2%.

33. Reaction of Lithium 2-Naphthoxide with 2-Naphthyl 4-Nitrobenzoate in Tetrahydrofuran:

Lithium 2-naphthoxide, 0.1248 g.(0.000832 mole), and 2.44 g.(0.00832 mole) of 2-naphthyl 4-nitrobenzoate were suspended in 8.82 ml. of tetrahydrofuran and permitted to stir for 22 hours at 25°. The reaction was worked up in the usual manner. An exchange reaction was found to occur(as evidenced by the formation of keto-naphthol) to the extent of 28.8%.

2-Naphthyl Anisate. To 12.46 g.(0.0730 mole) of anisoyl chloride dissolved in 10 ml. of pyridine was added 9.8 g. (0.068 mole) of 2-naphthol. The solution was heated on a steam-bath for 10 minutes and then poured into an ice-cold solution containing 30 ml. of 5% sulfuric acid and 200 ml. of water. A white precipitate was collected by suction filtration, washed thoroughly with water, then with 5% sodium bicarbonate solution and finally with water again. The product was recrystallized from absolute ethanol. Yield: 18 g. (95%). M.p. 114-114.5°; lit.[102] m.p. 113-114°.

1-Anisoyl-2-naphthol. An intimate mixture of 10 g. of 2-naphthyl anisate and 10 g. of aluminum chloride was heated in an oil bath at 180° for 2 hours. The reaction mixture was permitted to cool to room temperature and a solution containing 35 ml. of 6*N* hydrochloric acid and 100 g. of ice was added to it. The resulting precipitate was collected by suction filtration, leached with water, 5% sodium bicarbonate solution and finally with water again. This precipitate was dissolved in 100 ml. of 5% sodium hydroxide solution and a small amount of insoluble material was removed by filtration. The filtrate was neutralized with 6*N* hydrochloric acid and the resulting precipitate was extracted into 100 ml. of chloroform. The chloroform extract was washed successively with three 10 ml. portions of 5% sodium bicarbonate solution, then washed with water until neutral. The chloroform layer was dried over magnesium sulfate. The drying agent was removed by filtration and the filtrate evaporated to dryness. The residue was recrystallized three times from aqueous ethanol to give 1.52 g.(15%) of pale yellow needles which melted at 115°; lit.[103] m.p. 115-116°.

Anal. Calcd. for $C_{18}H_{14}O_3$: C, 77.69; H, 5.03. Found: C, 77.39; H, 5.09.

1-(4'Methoxybenzoyl)-2-naphthyl 4-Methoxybenzoate. To 1 ml. (0.0073 mole) of anisoyl chloride dissolved in 3 ml. of pyridine was added 1 g.(0.0036 mole) of 1-anisoyl-2-naphthol. The solution was heated at reflux for 1 hour, cooled and added to a solution containing 3 ml. of 5% sulfuric acid and 20 ml. of an ice-water mixture. The resulting oil was separated and dissolved in 150 ml. of benzene. The benzene solution was washed with three 10 ml. portions of ice-cold 2% sodium hydroxide solution, then with water until neutral. The benzene was removed under reduced pressure and the residue recrystallized twice from benzene:ethanol to give 0.655 g.(44%) of a product which melted at 150.5-151.5°. This material exhibited no O-H bands in its infrared absorption spectrum.

Anal. Calcd. for $C_{26}H_{20}O_5$: C, 75.68; H, 4.86. Found: C, 75.63; H, 4.90.

Anisoyl Bromide.[9] Oxalyl bromide(Aldrich), 25 g.(0.116 mole), was dissolved in 50 ml. of benzene. To this was added 13.5 g.(0.077 mole) of sodium anisate in small portions. The reaction mixture was then heated at reflux while stirring for 24 hours. The resulting sodium bromide was removed by filtration. The benzene was removed under reduced pressure and the remaining liquid was distilled at 135°(10 mm.) to give 13.83 g.(83%) of a colorless liquid. Lit.[104] 183-186 (27 mm.).

34.Reaction of Anisoyl Chloride with Sodium 2-Naphthoxide in Hexane:

To a stirred suspension of 0.6224 g.(0.00371 mole) of sodium 2-naphthoxide in 6.1 ml. of hexane was added, in a dropwise fashion, 0.577 g.(0.00338 mole) of anisoyl chloride dissolved in 7.0 ml. of hexane. The reaction was permitted to stir for 1/2 hour at room temperature after the addition of the acid chloride was completed. The solvent was removed under reduced pressure and the residue suspended in 150 ml. of benzene. This suspension was extracted successively with three 10 ml. portions of ice-cold 5% sodium hydroxide solution. The benzene layer was then washed with water until neutral and evaporated to dryness to give the neutral fraction. The base-extract was neutralized with 6N hydrochloric acid and successively extracted with five 10 ml. portions of chloroform. The chloroform extract was washed with three

25 ml portions of 5% sodium bicarbonate solution and then with water until neutral. The chloroform was removed under reduced pressure to give the acidic fraction. VPC analyses of the acidic and neutral fractions were carried out according to the procedure previously described(cf. VPC Analyses). The following results were obtained:

Ester, 84.1% Keto-naphthol, 0.331% Keto-ester, 0.131%

35.Reaction of Anisoyl Chloride with Sodium 2-Naphthoxide in Benzene:

The same procedure as had been employed for experiment 34 was utilized except that benzene was used as the solvent in place of hexane. The VPC analyses of the products obtained are as follows:

Ester, 86.2% Keto-naphthol, 0.874% Keto-ester, 0.513%
" 86.2% " 1.27% " 0.160%

36.Reaction of Anisoyl Chloride with Sodium 2-Naphthoxide in Tetrahydrofuran:

A duplicate of experiment 34 was carried out using tetrahydrofuran as the solvent. VPC analyses of the products obtained are as follws:

Ester, 100% Keto-naphthol, 0.000% Keto-ester, 0.000%

37.Reaction of Anisoyl Chloride with Lithium 2-Naphthoxide in Hexane:

A duplicate of experiment 34 was carried out except that lithium 2-naphthoxide was used in place of sodium 2-naphthoxide. VPC analyses of the products obtained are as follows:

Ester, 89.1%   Keto-naphthol, 0.127%   Keto-ester, 3.21%
"   91.2%   "   0.110%   "   3.33%

38. Reaction of Anisoyl Chloride with Lithium 2-Naphthoxide in Benzene:

A duplicate of experiment 35 was carried out except that lithium 2-naphthoxide was used in place of sodium 2-naphthoxide. VPC analyses of the products obtained are as follows:

Ester, 84.1%   Keto-naphthol, 0.978%   Keto-ester, 6.35%
"   89.7%   "   1.23%   "   8.08%

39. Reaction of Anisoyl Chloride with Lithium 2-Naphthoxide in Tetrahydrofuran:

A duplicate of experiment 36 was carried out except that lithium 2-naphthoxide was used in place of sodium 2-naphthoxide. VPC analyses of the products obtained are as follows:

Ester, 98.7%   Keto-naphthol, 0.00%   Keto-ester, 0.00%

40. Reaction of Anisoyl Bromide with Sodium 2-Naphthoxide in Hexane:

A duplicate of experiment 34 was carried out except that anisoyl bromide was used as the acylating agent in place of anisoyl chloride. VPC analyses of the products obtained are as follows:

Ester, 81.7%   Keto-naphthol, 1.48%   Keto-ester, 0.492%

41. Reaction of Anisoyl Bromide with Sodium 2-Naphthoxide in Benzene:

A duplicate of experiment 40 was carried out in benzene. VPC analyses of the products obtained are as follows:

Ester, 80.6%   Keto-naphthol, 1.07%   Keto-ester, 1.16%

42. Reaction of Anisoyl Bromide with Sodium 2-Naphthoxide in Tetrahydrofuran:

A duplicate of experiment 40 was carried out in tetrahydrofuran. VPC analyses of the products are as follows:

Ester, 100%   Keto-naphthol, 0.000%   Keto-ester, 0.00%

43. Reaction of Anisoyl Bromide with Lithium 2-Naphthoxide in Hexane:

A duplicate of experiment 40 was carried out except that lithium 2-naphthoxide was used in place of sodium 2-naphthoxide. VPC analyses of the products are as follows:

Ester, 80.6%   Keto-naphthol, 0.041%   Keto-ester, 3.61%

44. Reaction of Anisoyl Bromide with Lithium 2-Naphthoxide in Benzene:

A duplicate of experiment 43 was carried out in benzene. VPC analyses of the products are as follows:

Ester, 81.8%   Keto-naphthol, 0.087%   Keto-ester, 2.90%
"   75.4%   "   0.058%   "   2.65%

45. Reaction of Anisoyl Bromide with Lithium 2-Naphthoxide in Tetrahydrofuran:

A duplicate of experiment 43 was carried out in tetrahydrofuran. VPC analyses of the products obtained are as follows:

Ester, 97.7%   Keto-naphthol, 0.00%   Keto-ester, 0.00%

46. Reaction of Anisoyl Bromide with 2-Naphthol in Benzene:

To a solution of 0.699 g.(0.00479 mole) of 2-naphthol dissolved in 7.8 ml. of benzene was added 0.218 g.(0.00218 mole) of calcium carbonate. To this stirred mixture was added 0.9375 g.(0.00436 mole) of anisoyl bromide. The reaction was permitted to stir for 1 hour. The calcium carbonate was then removed by filtration and the filtrate was worked up in the manner previously described in experiment 34. Only 2-naphthol was recovered. No ester, keto-naphthol or keto-ester was found.

47. Trans-esterification Control Experiment for the Reaction of Sodium and Lithium 2-Naphthoxide with 2-Naphthyl Anisate:

A duplicate of experiment 22 using 2-naphthyl anisate in place of 2-naphthyl benzoate was carried out for each naphthoxide salt(sodium and lithium) and every solvent wherein C-acylation was obtained. In all instances, no transesterification(leading to C-acylation) occurred and the starting ester was recovered essentially quantitatively.

48.Heterogeneity Experiment in Pentane:

A 500 ml. round-bottom flask was equipped with a 1 ft. Vigreux column on top of which was mounted a Sohxlet extractor. In the cup of the extractor was placed 2.0681 g. (0.0138 mole) of lithium 2-naphthoxide. In the flask was placed 2.69 g.(0.0145 mole) of benzoyl bromide dissolved in 250 ml. of pentane. The flask was heated at reflux for 138.5 hours. In this manner, only lithium 2-naphthoxide which dissolved in the pentane(i.e. homogeneous reaction) would be available to react with the benzoyl bromide in the flask. The amount of naphthoxide in the Sohxlet cup did not appear to diminish during the reflux period. At the end of the reflux period, the pentane solution was worked up in the manner described in experiment 1. The lithium 2-naphthoxide remaining in the Sohxlet cup was subjected to a gravimetric bromide determination[105](i.e. $AgNO_3$) to determine the amount of benzoyl bromide which was carried up past the fractionating column to the Sohxlet cup. Yield of AgBr, 6.6%. VPC analyses of the products obtained from the work-up of the pentane solution are as follows:

Ester, 6.62% Keto-naphthol, 0.00% Keto-ester, 0.102%

49. Heterogeneity Experiment in Benzene:

A duplicate of experiment 48 was carried out in benzene. In place of the Vigreux column, a vacuum-jacketed packed column(glass helices, 1/8" I.D.) was used. Total reflux time was 232 hours. A quantitative gravimetric bromide determination[105] on the naphthoxide remaining in the Sohxlet cup yielded 15.7% AgBr. VPC analyses of the products obtained from the work-up of the benzene solution are as follows:

Ester, 29.2%   Keto-naphthol, 0.00%   Keto-ester, 0.203%

50. Solubility of Sodium 2-Naphthoxide in Nitrobenzene:Hexane Solution:

To 0.9161 g.(0.00552 mole) of sodium 2-naphthoxide suspended in 9.0 ml. of hexane was added 0.616 g.(0.00502 mole) of nitrobenzene dissolved in 7.0 ml. of hexane. The mixture was stirred at room temperature for 2 hours, then filtered and the filtrate evaporated to dryness under reduced pressure. No sodium 2-naphthoxide was found in this filtrate as evidenced by the zero titer obtained from a titration with 0.1N hydrochloric acid.

51. Solubility of Lithium 2-Naphthoxide in Nitrobenzene: Hexane Solution:

A duplicate of experiment 50 was carried out using lithium 2-naphthoxide in place of sodium 2-naphthoxide. The salt did not dissolve in the nitrobenzene:hexane solution as evidenced by the zero titer obtained from a titration of the filtered solution with 0.1N hydrochloric acid.

52. Competition of Anisoyl Bromide and Benzoyl Bromide for Lithium 2-Naphthoxide in Hexane:

To a stirred suspension of 0.869 g. (0.00579 mole) of lithium 2-naphthoxide in 9.5 ml. of hexane was added, at one time, a solution of 1.2439 g. (0.00579 mole) of anisoyl bromide and 1.072 g. (0.00579 mole) of benzoyl bromide in 10 ml. of hexane. The reaction was permitted to stir for 1/2 hour at room temperature. The reaction mixture was worked up in the manner previously described in experiment 1. Only the neutral fraction was analyzed for 2-naphthyl benzoate and 2-napthyl anisate. VPC analysis was conducted at a temperature of 235° and at a flow rate of 30 ml./min. A known mixture of 2-naphthyl anisate and 2-naphthyl benzoate was chromatographed and the ratio of the areas of the peaks for the two esters determined. From the ratio of the of the area of the peaks for the esters obtained from the experiment, it is possible to determine the relative amounts of anisate and benzoate ester present. A sample calculation is presented as follows:

$$\text{Exp. Mole Ratio} = \frac{(\text{Known Mole Ratio})(\text{Exp. Area Ratio})}{\text{Known Area Ratio}}$$

(The Ratio is always taken as benzoate/anisate)

$$\text{Exp. Mole Ratio} = \frac{(0.772)(1.85)}{0.715} = 2.00$$

$$\frac{\text{2-Naphthyl Benzoate}}{\text{2-Naphthyl Anisate}} = 2.00$$

This Mole Ratio was then corrected for the percentage of carbon acylation which contributes to the rate of reaction.

$$\text{Corrected Relative Rate} = \frac{\text{Benzoate} + \%\ \text{C-acylation}}{\text{Anisate} + \%\ \text{C-acylation}}$$

$$= \frac{2.00 + 0.12}{1.00 + 0.05} = \frac{2.02}{1.00}$$

These results are tabulated at the end of this series of competition reactions.

53. Competition of Anisoyl Chloride and Benzoyl Bromide for Lithium 2-Naphthoxide in Hexane:

A duplicate of experiment 52 was carried out for the competition reaction of 1 equiv. of anisoyl chloride with 3 equiv. of benzoyl bromide for 1 equiv. of lithium 2-naphthoxide. VPC analysis of the esters obtained is as follows:

Relative Molar Ratio:

$$\frac{\text{2-Naphthyl Benzoate}}{\text{2-Naphthyl Anisate}} = 3.84$$

54. Competition of Anisoyl Chloride and Benzoyl Bromide for Lithium 2-Naphthoxide in Hexane:

A duplicate of experiment 52 was carried out for the competition reaction of anisoyl chloride(3equiv.) with benzoyl bromide(1 equiv.) for 1 equiv. of lithium 2-naphthoxide. VPC analysis of the esters obtained is as follows:

Relative Molar Ratio:

$$\frac{\text{2-Naphthyl Benzoate}}{\text{2-Naphthyl Anisate}} = 4.14$$

55. Competition of Anisoyl Chloride and Benzoyl Bromide for Lithium 2-Naphthoxide in Hexane:

A duplicate of experiment 52 was carried out for the competition reaction of anisoyl chloride(1 equiv.) with benzoyl bromide(1 equiv.) for lithium 2-naphthoxide(1 equiv.). VPC analysis of the esters obtained is as follows:

Relative Molar Ratio:

$$\frac{\text{2-Naphthyl Benzoate}}{\text{2-Naphthyl Anisate}} = 3.64$$

56. Competition of Anisoyl Bromide and Benzoyl Chloride for Lithium 2-Naphthoxide in Hexane:

A duplicate of experiment 52 was carried out for the competition reaction of anisoyl bromide(1 equiv.) with benzoyl chloride(1 equiv.) for lithium 2-naphthoxide(1 equiv.). VPC analysis of the esters obtained is as follws:

Relative Molar Ratio:

$$\frac{\text{2-Naphthyl Benzoate}}{\text{2-Naphthyl Anisate}} = 0.95$$

57. Competition of Anisoyl Chloride and Benzoyl Chloride for Lithium 2-Naphthoxide in Hexane:

A duplicate of experiment 52 was carried out for the competition reaction of anisoyl chloride(1 equiv.) with benzoyl chloride(1 equiv.) for lithium 2-naphthoxide(1 equiv.). VPC analysis of the esters obtained is as follows:

Relative Molar Ratio:

$$\frac{\text{2-Naphthyl Benzoate}}{\text{2-Naphthyl Anisate}} = 1.59$$

58.Competition of Benzoyl Chloride with 4-Nitrobenzoyl Chloride for Lithium 2-Naphthoxide in Hexane:

A duplicate of experiment 52 was carried out for the competition reaction of benzoyl chloride(50 equiv.) with 4-nitrobenzoyl chloride(5 equiv.) for lithium 2-naphthoxide (1 equiv.).VPC analysis of the esters obtained is as follows:

Relative Molar Ratio:

$$\frac{\text{2-Naphthyl Benzoate}}{\text{2-Naphthyl 4-Nitrobenzoate}} = 0.023$$

59.Competition of Benzoyl Bromide with Anisoyl Bromide for Sodium 2-Naphthoxide in Hexane:

A duplicate of experiment 52 was carried out using sodium 2-naphthoxide in place of lithium 2-naphthoxide. VPC analysis of the esters obtained is as follows:

Relative Molar Ratio:

$$\frac{\text{2-Naphthyl Benzoate}}{\text{2-Naphthyl Anisate}} = 1.34$$

60.Competition of Benzoyl Bromide with Anisoyl Chloride for Sodium 2-Naphthoxide in Hexane:

A duplicate of experiment 55 was carried out except that sodium 2-naphthoxide was used in place of lithium 2-naphthoxide. VPC analysis of the esters obtained is as follows:

Relative Molar Ratio:

$$\frac{\text{2-Naphthyl Benzoate}}{\text{2-Naphthyl Anisate}} = 1.63$$

61. Competition of Benzoyl Chloride with Anisoyl Chloride for Sodium 2-Naphthoxide in Hexane:

A duplicate of experiment 57 was carried out except that sodium 2-naphthoxide was used in place of lithium 2-naphthoxide. VPC analysis of the esters obtained is as follows:

Relative Molar Ratio:

$$\frac{\text{2-Naphthyl Benzoate}}{\text{2-Naphthyl Anisate}} = 1.24$$

62. Competition of Benzoyl Chloride with Anisoyl Bromide for Sodium 2-Naphthoxide in Hexane:

A duplicate of experiment 56 was carried out except that sodium 2-naphthoxide was used in place of lithium 2-naphthoxide. VPC analysis of the esters obtained is as follows:

Relative Molar Ratio:

$$\frac{\text{2-Naphthyl Benzoate}}{\text{2-Naphthyl Anisate}} = 1.04$$

63. Competition of Benzoyl Chloride with 4-Nitrobenzoyl Chloride for Sodium 2-Naphthoxide in Hexane:

A duplicate of experiment 58 was carried out for the competition reaction of benzoyl chloride(20 equiv.) with 4-nitrobenzoyl chloride(2 equiv.) for sodium 2-naphthoxide (1 equiv.). VPC analysis of the esters obtained is as follows:

Relative Molar Ratio:

$$\frac{\text{2-Naphthyl Benzoate}}{\text{2-Naphthyl 4-Nitrobenzoate}} = 0.127$$

Calculation of the Relative Rates of Reaction of Acyl Halides with Lithium 2-Naphthoxide in Hexane:

Relative Molar Ratios

Experimentally Determined		Corrected[a]
$\frac{\text{BzBr}}{\text{AnsBr}}$	$\frac{2.00}{1.00}$	$\frac{2.02}{1.00}$
$\frac{\text{BzBr}}{\text{AnsCl}}$	$\frac{3.64}{1.00}$	$\frac{3.71}{1.00}$
$\frac{\text{BzCl}}{\text{AnsBr}}$	$\frac{0.95}{1.00}$	$\frac{0.95}{1.00}$
$\frac{\text{BzCl}}{\text{AnsCl}}$	$\frac{1.59}{1.00}$	$\frac{1.60}{1.00}$
$\frac{\text{BzCl}}{\underline{\text{p}}\text{-NO}_2\text{BzCl}}$	$\frac{0.023}{1.00}$	$\frac{0.0205}{1.00}$

Relative Rates

BzCl = 1.00

BzBr = 2.30[b], 2.24[c]

AnsCl = 0.62

AnsBr = 1.14[b], 1.11[c]

$\underline{\text{p}}$-NO_2BzCl = 48.7

---

a. Corrected for the percentage of C-acylate formed; b. Calculated from BzBr/AnsCl divided by BzCl/AnsCl; c. Calculated from BzBr/AnsBr divided by BzCl/AnsBr.

Calculation of the Relative Rates of Reactions of Acyl Halides with Sodium 2-Naphthoxide in Hexane:

Relative Molar Ratios

Experimentally Determined		Corrected[a]
$\frac{\text{BzBr}}{\text{AnsBr}}$	$\frac{1.37}{1.00}$	$\frac{1.38}{1.00}$
$\frac{\text{BzBr}}{\text{AnsCl}}$	$\frac{1.67}{1.00}$	$\frac{1.71}{1.00}$
$\frac{\text{BzCl}}{\text{AnsBr}}$	$\frac{1.07}{1.00}$	$\frac{1.06}{1.00}$
$\frac{\text{BzCl}}{\text{AnsCl}}$	$\frac{1.27}{1.00}$	$\frac{1.28}{1.00}$
$\frac{\text{BzCl}}{\underline{p}\text{-NO}_2\text{BzCl}}$	$\frac{0.127}{1.00}$	$\frac{0.124}{1.00}$

Relative Rates

BzCl = 1.00

BzBr = 1.33[b], 1,30[c]

AnsCl = 0.78

AnsBr = 0.96[b], 0.94[c]

$\underline{p}$-NO$_2$BzCl = 8.03

a. Corrected for the percentage of C-acylate formed; b. Calculated from BzBr/AnsCl divided by BzCl/AnsCl; c. Calculated from BzBr/AnsBr divided by BzCl/AnsBr.

Calculation of Partial Relative Rates of C- & O-Acylation:

Definitions:

C = partial relative rate of keto-naphthol and keto-ester formation.

O = partial relative rate of ester formation.

OC = partial relative rate of keto-ester formation.

Processes contributing to the rate of BzCl reaction may be written as follows:

$$BzCl = C_1 + O_1 + OC_1$$

Likewise, for BzBr:

$$BzBr = C_2 + O_2 + OC_2$$

Let $C_1/O_1 = A_1$, $C_1/OC_1 = B_1$ and set $C_1 = 1.00$

Let $C_2/O_2 = A_2$, $C_2/OC_2 = B_2$

Substituting and solving for C_2 we get

$$C_2 = \frac{1.00 + 1/A_1 + 1/B_1}{1.00 + 1/A_2 + 1/B_2} \times \frac{BzBr}{BzCl}$$

Once C_2 is known, O_2 and OC_2 may also be calculated. In this manner, the partial relative rates for the reaction of sodium and lithium 2-naphthoxides with acyl halides may be calculated. The results of these calculations are shown in Table XXVII.

64. Reaction of Lithium 2-Naphthoxide with Phenyl Benzoate in Refluxing Benzene:

Lithium 2-naphthoxide, 0.6043 g.(0.00403 mole), and 0.797 g.(0.00403 mole) of phenyl benzoate in 7.32 ml. of benzene was refluxed, while stirring, for 43 hours. The solvent was removed and the residue worked up in the manner described in experiment 1. Analysis of the products obtained gave the following results:

2-naphthyl benzoate, 17.2%

A duplicate of the above experiment was run for 71 hours. The yield of 2-naphthyl benzoate was 18.5%.

65. Reaction of 2-Naphthyl 4-Nitrobenzoate with 4-Nitrobenzoyl Chloride in Hexane:

To 1.000 g.(0.00341 mole) of 2-naphthyl 4-nitrobenzoate dissolved in 5.6 ml. of hexane was added 0.633 g.(0.00341 mole) of 4-nitrobenzoyl chloride. The reaction mixture was stirred at room temperature for 1/2 hour. See experiment 23 for work-up procedure. The starting ester was quantitatively recovered. No C-acylated product(keto-ester) was found.

1-Bromo-2-methoxynaphthalene. (a)To a stirred solution of 30 g.(0.19 mole) of 2-naphthylmethyl ether(Eastman) in 125 ml. of glacial acetic acid was added, in a dropwise fashion, 30.3 g.(0.19 mole) of bromine. Addition took 30 minutes. The solution was then poured into 300 ml. of an ice-water mixture. A white precipitate was collected by suction filtration and then fractionally distilled at 122-124°(0.24 mm.). Yield, 22 g.(49%). M.p. 84.5°; lit.[106] m.p. 85°.

(b)To a solution of 0.669 g.(0.003 mole) of 1-bromo-2-naphthol(M,C & B) in 4 ml. of 5% sodium hydroxide solution was added 0.378 g.(0.003 mole) of dimethyl sulfate. The solution was heated in an oil bath at 100° for 1 hour, then cooled in an ice-bath and the resulting crystals were collected by suction filtration. The product was successively washed with two 10 ml. portions of 5% sodium hydroxide, then washed thoroughy with water and dried on the filter. This material was recrystallized from absolute ethanol to give 0.459 g.(63%). M.p. 85°; lit.[106] m.p. 85°. A mixed m.p. with the product of reaction (a) was undepressed.

1-Cyano-2-methoxynaphthalene. An intimate mixture of 10 g. (0.0422 mole) of 1-bromo-2-methoxynaphthalene and 6.6 g. of cuprous cyanide was heated for 1 hour in an oil bath at 240°. The hot dark brown melt was then poured into a mortar and permitted to cool. The solidified product was then pulverized and the resulting brown powder was leached with a warm solution containing 30 ml. of concentrated ammonia in 100 ml.

of water. The insoluble material remaining was dissolved in 50 ml. of ethyl acetate, filtered and the filtrate evaporated to dryness. The residue was sublimed at 145°(0.3 mm.). Yield, 3.08 g.(40%). M.p. 93.5-94.5°; lit.[107] m.p. 94°.

1-Benzoyl-2-methoxynaphthalene. A solution of 1.8 g.(0.0105 mole) of 1-cyano-2-methoxynaphthalene in 8 ml. of benzene was slowly added to a gently refluxing ethereal solution (8 ml.) of phenyl magnesium bromide prepared from 1.56 ml. (0.0148 mole) of bromobenzene and 0.36 g.(0.0148 mole) of magnesium. The mixture was refluxed for 1 hour after the addition was completed, cooled and poured into a stirred mixture of ice and 50 ml. of 10 % sulfuric acid. The benzene and ether were removed by distillation and the aqueous solution was heated at reflux for 3 hours. The cooled solution was extracted with three 25 ml. portions of ethyl ether. The ether extract was evaporated to dryness on the steam-bath and the residue twice recyrstallized from ligroin. Yield, 0.80 g.(29%). M.p. 125°; lit.[108] m.p. 125°.

1-Benzoyl-2-methoxynaphthalene. To a solution of 0.744 g. (0.003 mole) of 1-benzoyl-2-naphthol(synthesized via a Fries rearrangement; vide supra) in 4 ml. of 5% sodium hydroxide was added 0.378 g.(0.003 mole) of dimethyl sulfate. The solution was heated in an oil bath at 95° for 1 hour, then cooled in an ice-bath and the resulting crystals were collected by suction filtration. The product was washed successively with two 10 ml. portions of 5% sodium hydroxide, then thoroughly washed with water and dried. This material was recrystallized from ligroin to give 0.399 g.(51%). M.p. 124-5°. A mixed melting point with the 1-benzoyl-2-methoxynaphthalene prepared by the reaction of phenyl magnesium bromide on 1-cyano-2-methoxynaphthalene(vide supra) was undepressed. The infrared spectra of the two materials were also identical.

Benzoxazole Ether of 1-Bromo-2-hydroxynaphthalene.[109] 1-Bromo-2-hydroxynaphthalene, 10 g.(0.0448 mole), 6.87 g. (0.0448 mole) of 2-chlorobenzoxazole(Eastman) and 11.85 g.(0.0856 mole) of potassium carbonate were suspended in 100 ml. of acetone and heated at reflux, while stirring, for 24 hours. The reaction mixture was permitted to cool to room temperature, filtered and the filtrate was chilled in an ice-bath. The white crystalline material which formed was collected by suction filtration. Yield, 12 g.(79%). M.p. 142-143°.

Hydrogenation of the Benzoxazole Ether of 1-Bromo-2-hydroxynaphthalene.[109] The ether, 5 g.(0.0147 mole), was dissolved in 50 ml. of THF and hydrogenated(Pd/C, 10%) in a Parr hydrogenator for 48 hours. The catalyst was filtered off and the filtrate was evaporated to dryness. The oily residue was dissolved in 25 ml. of benzene. The benzene solution was washed successively with three 10 ml. portions of 5% sodium hydroxide, then with water until neutral and finally dried over magnesium sulfate. The benzene was removed by distillation and the remaining oily residue was fractionally distilled at 148°(20 mm.). Yield, 0.50 g.(16%). The infrared spectrum of the product was identical with that of an authentic sample of 1-bromonaphthalene.

SUMMARY

Sodium and lithium 2-naphthoxide have been acylated in a variety of solvents with benzoyl chloride, benzoyl bromide, benzoyl iodide, p-nitrobenzoyl chloride, anisoyl chloride and anisoyl bromide. Acylation occurs at both carbon and oxygen. This is the first report of attack at carbon by a base-catalyzed acylation reaction on 2-naphthoxide anion. In hexane and benzene, the reaction has been shown to take place on the crystal surface.

Two likely mechanisms for this bimolecular acylation reaction have been considered: A concerted displacement and an addition-elimination mechanism. Analysis of solvent effects, leaving group effects, metal cation effects, para-substituent effects, relative rates of reaction and partial relative rates of reaction of the acyl halide is offered in support of the concerted displacement mechanism.

BIBLIOGRAPHY

1.M.L.Bender, Chem.Rev., 60, 53(1960).

2.N.Kornblum, P.J.Berrigan and W.J. le Noble, J.Am.Chem.Soc., 82, 1257(1960); ibid., 85, 1141(1963).

3.N.Kornblum, R.Seltzer and P.Haberfield, ibid., 85, 1148 (1963).

4.D.P.N. Satchell, Quart.Rev., XVII, 160(1963).

5.N.Kornblum et al., J.Am.Chem.Soc., 81, 2705(1959).

6.N.Kornblum et al., ibid., 76, 3209(1954).

7.N.Kornblum et al., ibid., 77, 5528(1955).

8.N.Kornblum et al., ibid., 77, 6269(1955).

9.K.H.Saunders, *The Aromatic Diazo-Compounds and Their Technical Applications*, 2nd edition, Arnold and Co., London, 1947, p.199.

10.D.S.Tarbell and J.F.Kincaid, J.Am.Chem.Soc., 62, 728(1940).

11.D.Y.Curtin et al., ibid., 80, 1391(1960).

12.K.Lauer, Ber., 70, 1130(1937).

13.H.Schenkel, Experientia, 4, 282(1948).

14.H.C.Brown, D.H.McDaniel and O.Häfliger, *Determination of Organic Structures by Physical Methods*, Edited by E.A. Braüde and F.C.Nachnod, Academic Press, Inc., New York, N.Y., 1955, p.598.

15.H.Conroy and R.A.Fireston, J.Am.Chem.Soc., 78, 2297(1958).

16.K.Kalberer and H.Schmid, Helv.Chim.Acta, 40, 780(1957).

17.N.Kornblum and R.Seltzer, J.Am.Chem.Soc., 83, 3668(1961).

18.T.H.Coffield et al., ibid., 79, 5019(1957).

19.L.A.Cohen, J.Org.Chem., 22, 1333(1957).

20.M.Prober, J.Am.Chem.Soc., 73, 2274(1956).

21.M.S.Newman et al., ibid., 82, 873(1960).

22.N.Robjohn and P.R.Stapp, J.Org.Chem., 26, 45(1961).

23.A.L.Searles and D.Ressler, J.Am.Chem.Soc.,80,3656(1958).

24.L.Claisen et al., Ann.,442,210(1925).

25.F.M.Elkobaisi and W.J.Hinkinbottom,J.Chem.Soc.,2431(1958).

26.H.Hart and H.S.Eleuteris, J.Am.Chem.Soc.,76,518(1954).

27.L.P.Hammett, Physical-Organic Chemistry, McGraw-Hill Book Co., Inc., New York, N.Y., 1940, p.39.

28.(a)H.D.Zook and T.J.Russo, J.Am.Chem.Soc.,82,1258(1960).
(b)H.D.Zook and W.L.Gumby, ibid.,82,1386(1960).

29.(a)H.E.Zaugg et al., ibid., 82,2895(1960).
(b)H.E.Zaugg, ibid., 82, 2903(1960); ibid.,83,837(1961).

30.G.Wittig and E.Stahnecker, Ann.,605, 69(1957).

31.J.F.Garst et al., J.Am.Chem.Soc.,83,5034(1961).

32.C.K.Ingold, Ann.Reports, 23,142(1926).

33.I.Forsblad,Arkiv.Kemi, 15, 403(1960).

34.N.Kornblum et al., J.Am.Chem.Soc.,83, 2779(1961).

35.N.Kornblum and P.Pink, Tetrahedron, 19,17(1963).

36.V.A.Zagorevsky, J.Gen.Chem.(USSR), 28,488(1958).

37.Iden., ibid., 27, 3055(1957).

38.C.K.Ingold, Structure and Mechanism in Organic Chemistry, Cornell University Press, Ithaca, New York,1953,p.758.

39.J.D.Roberts and M.C.Caserio, Basic Principles of Organic Chemistry, W.A.Benjamin, New York, N.Y., 1964,p.354.

40.J.M.Briody and D.P.N.Satchell, J.Chem.Soc.,168(1965).

41.C.A.Bunton, Ann.Reports Chem.Soc.,15, 186(1958).

42.R.F.Hudson and B.Saville, J.Chem.Soc.,4121(1955).

43.J.F.Norris et al., J.Am.Chem.Soc., **57**,1415(1935).

44.J.F.Norris and H.H.Young, ibid., **57**,1420(1935).

45.J.F.Norris and V.W.Ware, ibid., **61**, 1418(1939).

46.D.A.Brown and R.F.Hudson, J.Chem.Soc., 3352(1953).

47.R.F.Hudson and J.E.Wardhill, ibid., 1729(1950).

48.B.L.Archer et al., ibid., 888(1933).

49.D.A.Brown and R.F.Hudson, ibid., 883(1953).

50.E.W.Crunden and R.F.Hudson, ibid., 501(1956).

51.C.A.Bunton et al., Chem.Ind.(London), 1154(1954).

52.E.R.A.Peeling, J.Chem.Soc., 2307(1959).

53.H.Minato, Bull.Chem.Soc.(Japan), **37**, 316(1964).

54.V.Gold and J.Hilton, J.Chem.Soc., 3303(1955).

55.D.P.N.Satchell, ibid., 558(1963).

56.J.M.Briody and D.P.N.Satchell, ibid., 3724(1964).

57.M.L.Bender, *Techniques of Organic Chemistry*,Vol.8, Interscience, New York, N.Y., 1963.

58.J.P.Ferris et al., J.Org.Chem., **29**, 87(1964).

59.A.Brändström, Arkiv.Kemi, **6**, 155(1953).

60.H.D.Murdoch and D.C.Nonhebel, J.Chem.Soc.,2153(1962); D.C.Nonhebel, ibid., 670(1960).

61.A.A.Maryott and E.R.Smith, National Bureau of Standards, Circular 514(1951).

62.J.F.Garst et al., J.Am.Chem.Soc., **87**,4080(1965).

63.W.J.le Noble and J.F.Puerta, Tetrahedron Letters, 1087, (1966).

64.L.Brewer and T.E.Brackett, Chem.Rev., **61**, 425(1961).

65.C.G.Swain and E.R.Thorton, J.Am.Chem.Soc.,**84**,817(1962).

66.D.Wrinch and D.Harker, J.Phys.Chem.,**8**, 502(1940).

67. H.H.Jaffe, Chem.Rev., 53, 191(1953).

68. C.E.Entemann and J.R.Johnson, J.Am.Chem.Soc., 55, 2900 (1933).

69. H.Staudinger and E.Anthes, Ber., 46, 1417(1913).

70. D.Karve and K.K.Dole, J.Univ. of Bombay, 7, 108(1938).

71. A.T.Dann et al., J.Chem.Soc., 15(1933).

72. R.Leimu, Ber., 70B, 1040(1937).

73. A.L.Bernoulli and A.St.Goar, Helv.Chim.Acta,9,730(1926).

74. N.O.Calloway, J.Am.Chem.Soc.,59,1474(1937).

75. J.F.Bunnett, Quart.Res., 12, 1(1958).

76. E.Lulofs, Rec.trav.chim.,20, 292(1901).

77. A.L.Beckwith et al., J.Chem.Soc., 3552(1952).

78. G.P.Buner et al., ibid., 1265(1954).

79. M.Baudet, Rec.trav.chim., 43, 707(1924).

80. R.Mattaar, ibid., 41, 103(1922).

81. H.van der Kam, ibid., 45, 564(1926).

82. B.Bolto et al., J.Chem.Soc., 2926(1955).

83. G.W.L.Bevan, ibid., 2340(1951).

84. J.D.Reinheimer and J.F.Bunnett, J.Am.Chem.Soc., 81, 315 (1959).

85. R.C.Krauss and J.D.Reinheimer, Can.J.Chem.,45,77(1967).

86. A.J.Sisti and S.Lowell, J.Org.Chem.,29, 1635(1964).

87. S.H.Hendioz et al., Compt.rend., 244, 1203(1957).

88. J.W.Baker, J.Chem.Soc., 2631(1932).

89. A.Conrad and A.Bruckner, Z.Physik.Chem.,4,631(1889).

90. C.H.Grant and C.N.Hinshelwood, J.Chem.Soc.,258(1933).

91. J.Hine, Physical Organic Chemistry, 2nd edition, McGraw-

Hill, 1962, p.285.

92.G.M.Bennett and B.Jones, J.Chem.Soc., 1815(1935).

93.R.Fuchs and D.M.Carlton, J.Am.Chem.Soc.,85,105(1963).

94.C.G.Swain and W.P.Langsdorf, ibid.,73,2815(1951).

95.J.D.Roberts and M.C.Caserio, Basic Principles of Organic Chemistry, W.A.Benjamin, New York, N.Y.,1964, p.955.

96.E.S.Gould, Mechanism and Structure in Organic Chemistry, Holt,Rinehart and Winston, New York, N.Y., 1959, p.282.

97.C.A.Bunton, Nucleophilic Substitution at a Saturated Carbon Atom, Elsevier, New York, N.Y., p.34.

98.G.G.Joshi and N.M.Shah, J.Indian Chem.Soc., 29,225(1952).

99.D.W.Theobald and J.C.Smith, Chem.Ind.(London),1007(1958).

100.N.D.Cheronis and J.B.Entrikin, Semimicro Qualitative Analysis, Interscience, 2nd edition, 1958, p.585.

101.P.Donaldson, Naphthalene Compounds, Arnold, New York, N.Y., 1958.

102.W.Dilthey et al., J.prakt.Chem.,148, 210(1937).

103.R.D.Desai and R.M.Desai, J.Sci.Ind.Research(India), 14B, 505(1955).

104.R.Adams and L.H.Ulich, J.Am.Chem.Soc.,42,609(1920).

105.I.M.Kolthoff and E.B.Sandell, Quantitative Analysis 3rd edition, MacMillan Co.,New York, N.Y.,1952, p.307.

106.R.C.Ferris and D.Hamer, J.Chem.Soc., 1409(1961).

107.P.Karrer et al., Helv.Chim.Acta, 3, 268(1920).

108.H.E.Fierz-David and G.Jaccard, ibid., 11,1044(1928).

109.Procedure of W.J.Musliner and J.W.Gates,Jr., J.Am.Chem. Soc., 88, 4271(1966).