In presenting the dissertation as a partial fulfillment of the requirements for an advanced degree from the Georgia Institute of Technology, I agree that the Library of the Institute shall make it available for inspection and circulation in accordance with its regulations governing materials of this type. I agree that permission to copy from, or to publish from, this dissertation may be granted by the professor under whose direction it was written, or, in his absence, by the Dean of the Graduate Division when such copying or publication is solely for scholarly purposes and does not involve potential financial gain. It is understood that any copying from, or publication of, this dissertation which involves potential financial gain will not be allowed without written permission.

7/25/68

THE *ORTHO* EFFECT IN AROMATIC NUCLEOPHILIC SUBSTITUTION

A THESIS
Presented to
The Faculty of the Graduate Division
by
Richard Lawrence Karelitz

In Partial Fulfillment
of the Requirements for the Degree
Master of Science
in Chemistry

Georgia Institute of Technology
December, 1968

THE ORTHO EFFECT IN AROMATIC NUCLEOPHILIC SUBSTITUTION

Approved:

Chairman

Date Approved by Chairman 5/29/69

ACKNOWLEDGMENTS

I would like to thank Dr. Charles L. Liotta for suggesting this problem and for all the valuable aid and encouragement he provided both on the lab work and the writing.

Thanks are also due Drs. E. Grovenstein, Jr. and H. M. Neumann for serving on the reading committee and giving many helpful comments and suggestions about this thesis.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF ILLUSTRATIONS

SUMMARY

The object of this study was to examine the effect of ortho substituents on the acidity of phenols and the nucleophilicity of the respective anions toward 2,4-dinitrochlorobenzene (DNCB) in anhydrous methanol at 35°. Extensive studies have been carried out on the ortho substituted pyridines and benzoic acids but to date little is known about the ortho effect on phenols.

The second order reaction between phenoxide ion and DNCB to form the diphenyl ether is complicated by the simultaneous reaction of methoxide ion, formed by the equilibrium between phenoxide ion and methanol solvent, and DNCB. The rate of disappearance of total base, k_{obs}, may be expressed by the following equation

$$k_{obs} = (k_2 - k_{obs}) \frac{[MeOH]}{[ArOH]} K_{eq} + k_1$$

where [MeOH] is the measured concentration of solvent, [ArOH] is the calculated concentration of unionized phenol, and k_2 is the rate of reaction of methoxide ion with DNCB. The intercept of the line this equation define, k_1, is the desired rate constant for the reaction between phenoxide ion and DNCB and the slope is the equilibrium constant for the reaction between phenoxide ion and methanol which may be converted to the pK_a of the phenol in methanol by means of the autoprotolysis constant of methanol at 35°.

The substituents used in this study were H, CH_3, C_2H_5, i-C_3H_7,

<u>t</u>-C_4H_9, OCH_3, F, Cl, Br, and I. There are two primary ways by which a substituent may affect the reactivity of a compound, the electrical, or polar effect, and the steric effect. It was found that the alkyl and halo phenols and phenoxides differed in their response to these two types of effects and were discussed separately.

The acidity and nucleophilicity of the <u>ortho</u> alkyl substituted phenols and phenoxides were dependent only on the size of the substituent. The pK_a's of the phenols were proportional to the E_s values of the alkyl substituents. The decrease in acidity as the substituent increased in size was attributed to steric inhibition of solvation of the anion.

The nucleophilicity of <u>o</u>-methylphenoxide was less than that of phenoxide itself because of the primary steric effect of the methyl group. However as the series methyl, ethyl, and isopropyl was traversed, the nucleophilicity increased sharply. Despite the increasing size of these groups they are all able to assume a conformation of approximately the same primary steric effect in the transition state while the increasing steric inhibition of solvation eased the approach to the transition state for the more bulkily substituted phenoxides.

Both the steric and polar effect of the halo substituents affected the reactivity of the <u>ortho</u>-halophenols and phenoxides. The nucleophilicity of the <u>ortho</u>-halophenoxides was decreased in a linear fashion by the increasing size and polar effect of the halogens as the series F to I was traversed.

The polar effect of the halogen substituents increased the acidity of the _ortho_-halophenols about as much as the increasing steric effect decreased the acidity and the pK_a of these substituted phenols was about constant.

CHAPTER I

INTRODUCTION

The ortho effect of substituents is generally considered to be due to a combination of polar and steric effects. The polar effect may be divided into inductive effects, electrical effects transmitted either through polarization of sigma bonds or field effects transmitted by the electrostatic field associated with any electrical charge, and resonance effects, electrical effects transmitted to the reaction center through the π-electron framework. Likewise, steric effects may be classified as primary, where the substituent directly interferes with the reaction, and secondary steric effects as in steric inhibition of resonance and steric inhibition of solvation. Under certain conditions this may be further complicated by a superposition of solvation effects upon the afore mentioned polar and steric effects.[1,2,3]

The earliest attempts at a separation of polar and steric effects were made by Taft who defined a series of polar substituent constants, σ^*, which he considered to be free of steric effects and therefore suitable for use with aliphatic acids and their derivatives and ortho substituted benzoic acids and their derivatives.[3] The rationale behind Taft's treatment was his assumption that the steric and resonance effects of substituents should be nearly identical in the acidic and basic hydrolysis of esters. He defined his substituent constants by the equation

$$\rho^* = \frac{1}{2.48} \log \left(\frac{K_x}{K}\right)_B - \log \left(\frac{K_x}{K}\right)_A \qquad (1)$$

where 2.48 is a scale of factor which puts his constants on the same scale as those of Hammett's, K_x and K represent the rate constants for the hydrolysis of the substituted and unsubstituted esters, respectively, while subscript B and A denote basic or acidic hydrolysis conditions. Several reactions have been shown to obey the equation

$$\log \left(\frac{K_x}{K}\right) = \rho^* \sigma^* \qquad (2)$$

where σ^* represents the sensitivity of the reaction to the effect of the substituent. Taft also found that the rate of acidic hydrolysis of many substituted esters would provide an estimate of the steric effect of the substituent. This steric substituent constant, E_s, is given by

$$\log \left(\frac{K_x}{K}\right)_A = E_s \qquad (3)$$

and substituting (3) and (1)

$$\log \left(\frac{K_x}{K}\right)_B + E_s + 2.48\ \sigma^*$$

Although these polar and steric substituent constants provided by Taft are extremely valuable in many situations where Hammett's substituent constants are not applicable, it is preferable to define substituent constants without the aid of assumptions whose validity may be questioned.

Jones and Smith studied the rates of the unimolecular vapor phase pyrolysis of ortho substituted isopropyl benzoates to form propene and the corresponding benzoic acids.[4] They analyzed their data by means of the following equation,

$$\log \frac{K_x}{K} = \rho\sigma_{JS} \qquad (5)$$

making use of a value of ρ they had obtained previously, and were able to obtain polar substituent constants, σ_{JS}, for ortho substituents which are unaffected by either solvation or primary steric effects.

The apparent acidities of ortho substituted benzoic acids in benzene are the basis of another set of ortho polar substituent constants. Davis and Hetzler determined the apparent acidities of a series of substituted benzoic acids towards 1,3-diphenylguanidine in benzene.[5] Liotta found an excellent linear correlation between log K para and log K ortho for these acids.[6] By making use of the equation

$$\log\left(\frac{K_x}{K}\right)_{\underline{\text{ortho}}} = 1.41 \log\left(\frac{K_x}{K}\right)_{\underline{\text{para}}} = \sigma_o^o \qquad (6)$$

he was able to define a set of ortho substituent constants which are free from primary and secondary steric effects. The rates of esterification of ortho substituted benzoic acids by diphenyldiazomethane have been investigated in several solvents in Liotta's laboratories. While the reaction rates determined in toluene, a solvent nearly identical with benzene, correlate with σ_o^o, all points falling upon the line, those reaction rates determined in ethanol correlate rather poorly with σ_o^o. Ethanol, being polar and protic, strongly solvates the carboxyl group and makes the reaction susceptible to steric and solvation effects. Benzene and toluene, on the other hand, may be considered non-solvating for benzoic acids. In fact Liotta's sigma values obtained in benzene correlate with those of Jones and Smith obtained in the vapor phase (σ_{JS}):

$$\sigma_o^o = 2.38\,\sigma_{JS}. \tag{7}$$

Perhaps the most extensive series of <u>ortho</u> substituent constants has been compiled by Traynham and Tribble, who examined many substituted phenols in dimethylsulfoxide (DMSO) by means of nuclear magnetic resonance techniques.[7] Using the unsubstituted phenol as a standard they compared the chemical shifts of the hydroxyl proton in the <u>ortho</u> and <u>para</u> series and found an excellent linear correlation. The hydroxyl proton is very strongly hydrogen bonded to the DMSO solvent and the apparent lack of solvation effects in the <u>ortho</u> series is believed to be due to the orientation of the DMSO...HO moiety away from the <u>ortho</u> substituent. They defined their <u>ortho</u> substituent constant, σ_o^-, by the equation

$$\sigma_o^- = 0.720\Delta\sigma_o - 0.038 \tag{8}$$

where $\Delta\sigma_o$ is the chemical shift relative to the hydroxyl proton of the unsubstituted phenol. Tribble and Traynham state that in their system both steric and solvation effects are minimal and σ_o^- provides a very good measure of the electronic effect of <u>ortho</u> substituents.

In many reaction series of interest to organic chemists it is not possible to isolate the polar effect and examine it under conditions of minimum or constant steric effect when dealing with ortho substituted compounds. In this situation it is still possible to describe the effects of ortho substituents on rates and equilibria qualitatively in terms of a combination of polar, steric, and solvation effects. An example of this is the Yukawa-Tsueno equation in which polar and steric substituent parameters are combined.[8]

The esterification of a series of substituted benzoic acids with diphenyldiazomethane in ethanol and the pKa's of those acids in water were determined by Chapman, Shorter, and Utley.[9] They plotted their data in the form log rate constant versus pK_a for each substituted acid and the points fell on two lines, one consisting of the points for the ortho substituents and the other for the meta and para substituents. The authors suggested that the presence of any substituent in the ortho position causes a similar increase in the acidity of the acid. They further observed that for the ortho alkyl substituents both the rate of esterification and the acidity increased with increasing substituent size, presumably due to a secondary steric effect. The increase in log rate constant with Taft's E_s values is strictly linear for the alkyl groups. The pK_a of o-t-butylbenzoic acid falls below the line defined by the points for the methyl, ethyl, and i-propyl compounds in a plot of pK_a vs E_s. This is interpreted as being due to steric inhibition of solvation of the benzoate anion by the very bulky t-butyl group.

H. C. Brown and his co-workers have extensively studied the reactions of pyridine bases with alkyl iodides and Lewis acids of various types.[10] They found that in the reaction of alkyl pyridines with methyl iodide in nitrobenzene, substitution of any alkyl group for hydrogen in the 3- or 4- position results in an approximately twofold increase in rate over that for the unsubstituted compound but substitution of alkyl groups for hydrogen in the 2- position causes large decreases in the rate of reaction.[10a] The decrease has an approximately linear dependence on the Es value of the substitutent.

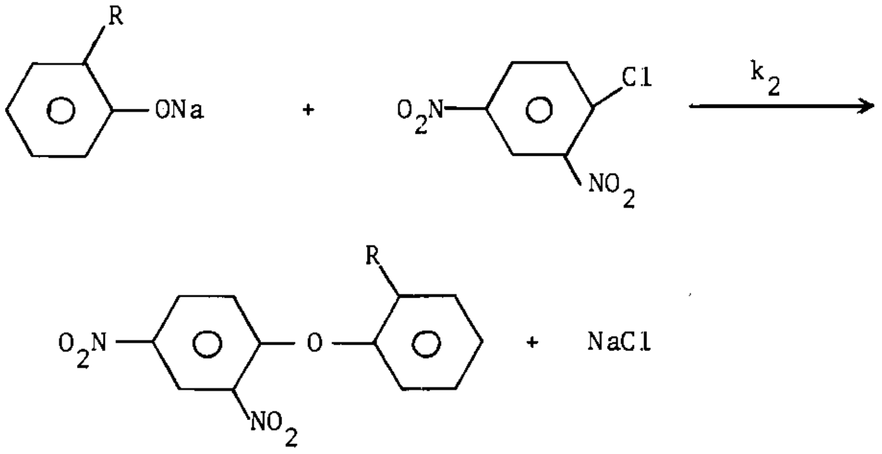
The similarity of the rate increases due to substitution by several different alkyl groups in the 3- and 4- positions was attributed to the similarity of the polar effects of the alkyl groups. The large decreases in rate brought about by alkyl substitution in the 2- position were considered to be the result of primary steric effects. Secondary steric effects would be absent in nitrobenzene. In the same paper it was stated that for the reaction of a base with a series of alkyl iodides the increase in energy of activation should be greater in going from ethyl to isopropyliodide than in going from methyl to ethyl iodide. They actually found this to be true for the reaction of pyridine with alkyl iodides in benzene solvent but the opposite was observed in nitrobenzene solution. Their explanation was that in the solvent of higher ionizing power, nitrobenzene, there was the possibility of a unimolecular mechanism becoming significant for the more highly branched alkyl iodides.

In a study of the base strengths of the alkyl pyridines in aqueous solution, it was observed that substitution of any alkyl group for hydrogen in the 3- or 4- position caused about the same increase in pK_a.[10b] Substitution for 2- hydrogen of methyl, ethyl, or n-propyl resulted in the same increase in base strength but i-propyl or t-butyl caused lesser increases. Brown believes this decreasing increase in base strength is the result of steric inhibition of solvation of the pyridinium cation by the very bulky 2 substituents.

It was desired to extend this type of study to the ortho substituted phenols. In terms of a compound's sensitivity to the steric effect of its ortho substituent, the phenols should be intermediate in properties between the pyridines and the benzoic acids. The large size of the carboxyl group makes it relatively easy for benzoic acids and benzoates to be solvated and minimizes interactions between solvent shell and ortho substituent. Brown believes that except in the case of very bulky substituents the base strengths of the pyridines are free of solvent effects;[10b] furthermore in the reactions with alkyl iodides the pyridines are not ionized and solvation would have a small effect on their reactivity although they are subject to large primary steric effects.

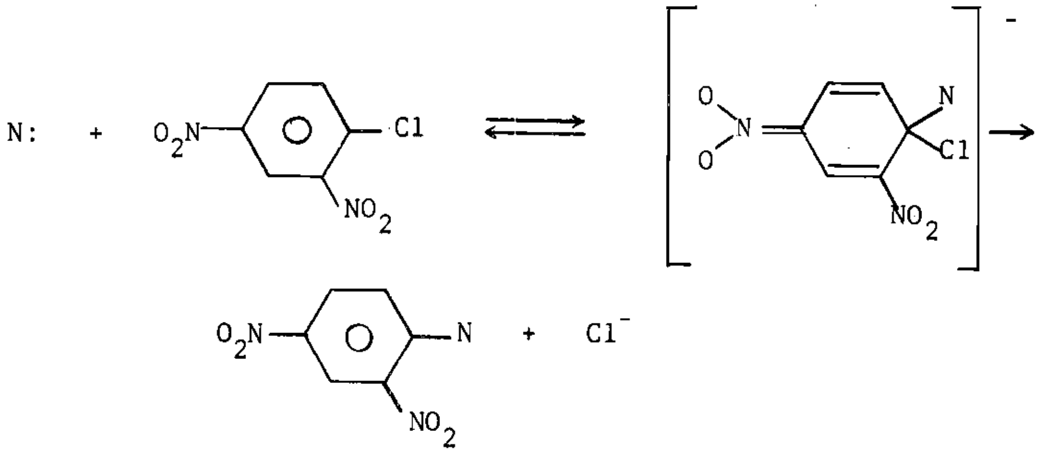
On the other hand, both the acidity of a phenol and the nucleophilic reactivity of a phenoxide would depend to a large extent on the ability of a protic solvent to surround the oxygen atom of the phenol. Any factors which alter this solvation should cause significant changes in the reactivity of the phenol.

The reaction chosen for the study was the nucleophilic displacement of chlorine from 2,3-dinitrochlorobenzene (DNCB) by ortho substituted phenoxide ions in methanol to form the substituted diphenylether.



(9)

The mechanism of this reaction is believed to proceed by the following steps.[11,12,13]



(10)

The reaction follows second order kinetics, first order in nucleophile and first order in substrate.[11,12] The pK_a values of the ten ortho substituted phenols included in the study were determined in the same solvent, anhydrous methanol.

CHAPTER II

EXPERIMENTAL

Derivation of the Rate Expression

The reaction between DNCB, [Ar'Cl], and phenoxide ion, $[ArO^-]$, in methanol is complicated by a simultaneous reaction between DNCB and methoxide ion, $[MeO^-]$, which is produced by the equilibrium between methanol, [MeOH], and phenoxide.

$$MeOH + ArO^- \overset{K_{eq}}{\rightleftharpoons} MeO^- + ArOH \tag{11}$$

The two simultaneous reactions are:

$$ArO^- + Ar'Cl \xrightarrow{k_1} ArOAr' + Cl \tag{12}$$

$$MeO^- + Ar'Cl \xrightarrow{k_2} MeOAr' + Cl \tag{13}$$

Since both nucleophiles are strongly basic, the rate of reaction can easily be determined by following the disappearance of total base. The rate of disappearance of base for the two simultaneous, second order reactions is given by

$$\frac{-d[base]}{dt} = k_1[ArO^-][Ar'Cl] + k_2[MeO^-][Ar'Cl] \tag{14}$$

Making use of the relationship defined by Equation 11,

$$K_{eq} = \frac{[MeO^-][ArOH]}{[MeOH][ArO^-]} \tag{15}$$

the rate law can be written in terms of only one basic ion

$$\frac{-d[\text{base}]}{dt} = \left(k_1 + \frac{k_2K_{eq}[\text{MeOH}]}{[\text{ArOH}]}\right) [\text{ArO}^-][\text{Ar'Cl}] \qquad (16)$$

The total concentration of base is given by

$$[\text{base}] = [\text{ArO}^-] + [\text{MeO}^-] \qquad (17)$$

Substituting for [MeO$^-$] by Equation 15

$$[\text{base}] = [\text{ArO}^-] \left(1 + K_{eq} \frac{[\text{MeOH}]}{[\text{ArOH}]}\right) \qquad (18)$$

solving Equation 18 for [ArO$^-$] and substituting it into Equation 16, the rate law becomes

$$\frac{-d[\text{base}]}{dt} = \left(\frac{k_1 + k_2K_{eq} \frac{[\text{MeOH}]}{[\text{ArOH}]}}{1 + K_{eq} \frac{[\text{MeOH}]}{[\text{ArOH}]}}\right) [\text{base}]\text{Ar'Cl}] \qquad (19)$$

which may be written

$$\frac{-d[\text{base}]}{dt} = k_{obs} [\text{base}][\text{Ar'Cl}] \qquad (20)$$

Equating the rate constants in Equation 19 and Equation 20

$$k_{obs} = \frac{k_1 + k_2K_{eq} \frac{[\text{MeOH}]}{[\text{ArOH}]}}{1 + K_{eq} \frac{[\text{MeOH}]}{[\text{ArOH}]}} \qquad (21)$$

and rearranging Equation 21, the useful expression is derived

$$k_{obs} = (k_2 - k_{obs})K_{eq} \frac{[MeOH]}{[ArOH]} + k_1 \qquad (22)$$

k_{obs} is the rate constant actually obtained from a single kinetic experiment. k_2, the rate of reaction of methoxide with DNCB, can be obtained from independent experiments in which only methoxide is present to react with the DNCB. The concentration of phenol and methanol can be determined from the amounts of reagents used to prepare the reaction mixture.

By performing a series of kinetic runs with various amounts of excess phenol, a graph may be made of k_{obs} vs $(k_2 - k_{obs}) \frac{[MeOH]}{[ArOH]}$ which has as slope K_{eq}, the equilibrium constant for the reaction between methanol and phenoxide, and as intercept k_1, the desired rate of reaction of the phenoxide with DNCB.

[ArOH] as is used in this derivation represents the equilibrium concentration of phenol in solution. This may be obtained from the weight of phenol used, the amount of $NaOCH_3$ added, and the equilibrium constant, K_{eq}. There are very few published values of the pK_a's of phenols in 100 percent methanol; consequently the equilibrium concentration of these phenols couldn't be calculated directly. If, as an approximation, the equilibrium constant for a particular phenol is assumed equal to zero, one could say that all the added methoxide is reacted with phenol to form phenoxide. Then, as an approximation, the equilibrium concentration of phenol is simply the concentration of total phenol minus the concentration of methoxide ion. A plot of k_{obs} vs $(k_2 - k_{obs}) \frac{[MeOH]}{[ArOH]_{app}}$ will have as slope K'_{eq}, an approximate value of the equilibrium constant -- but this will be a somewhat better approximation than zero. By means of the new K'_{eq}, a more accurate approximation may be made for the equilibrium concentration of phenol. A plot of k_{obs} vs $(k_2 - k_{obs}) \frac{[MeOH]}{[ArOH]_{app}}$ using the new values for $[ArOH]_{app}$ will have as slope a still more accurate approximation of K'_{eq}.

A computer program was written which carried this series of approximations out until two consecutive values of K_{eq} differ by one part in 10,000. Numerical values obtained for K_{eq} and k_1 were calculated by a least squares method.

The acidity of the phenol is related to the equilibrium constant by

$$pK_a = pK_{ap} - pK_{eq} \qquad (23)$$

where K_{ap} is the autoprotolysis constant of methanol at 35°. This constant, corrected for the concentration of solvent, is found to be 2.40×10^{-18}.[14]

Determination of Rate Constants in Methanol Solvent

The experimentally determined rate constants, k_{obs}, represent the rate of disappearance of total base from the reaction mixture. Solutions containing DNCB and the particular phenoxide under study are mixed at time zero. Aliquots of the reaction mixture are removed at convenient time intervals and quenched in 30-40 ml of cold, distilled water to stop the reaction.

The use of cold, distilled water as a quenching agent rather than a measured amount of standard acid simplifies the procedure and eliminates one possible source of error. The danger of hydroxide ion, formed by the reaction between methoxide or phenoxide ion and water, further reacting with DNCB was considered highly unlikely. The mixture containing phenol, DNCB, diphenylether, NaCl, methanol, and much water is a two phase system consisting of water-methanol as the predominant liquid phase, and an oil containing most of the aromatic compounds.

The amount of base present is determined by titration of the quenched solution with standard acid. The solutions are made up so that the concentration of base is somewhat greater than the concentration of DNCB. Since a mole of base reacts with a mole of DNCB, the reaction stops when all the DNCB is consumed. The difference between the amount of base found initially and at "infinity" -- after the reaction has had time to go to completion -- is an experimental determination of the concentration of DNCB present initially. If the validity of a particular experiment is questioned, a comparison of the calculated and found values of the initial concentration of DNCB will usually determine if any major mistakes were committed in setting up the experiment.

The halogen phenols reacted so slowly that the infinity method was not reliable and the calculated value for DNCB was used but for the others an infinity sample was employed.

The concentration of solvent was determined by weighing convenient volumes of reaction mixture and calculating the weight of solvent directly.

In a typical experiment, 0.7790 g DNCB was dissolved in 50 ml of MeOH at 35° ± 0.05° in a volumetric flask. o-methoxyphenol, 2.3241 g, and 7 ml of .768 N $NaOCH_3$ solution were dissolved in 50 ml of MeOH in another volumetric flask at 35°. A 5 ml aliquot of the phenoxide solution was quenched in 30 ml of distilled water and set aside as sample 1, time = zero. Twenty-five milliliters of each solution were then pipetted into a third volumetric flask and the clock started when the second pipette was half empty. As soon as the solution was pipetted into the flask, it was stoppered, removed from the bath, shaken, and replaced. A second 5 ml sample was removed and quenched as soon as possible after mixing the solutions and four more samples were removed and quenched at approximately 500 second intervals thereafter. The six samples were titrated to pH 7 with .0303 $\underline{N}$ $HClO_4$ using the Beckman pH meter. The following morning an "infinity" sample of 5 ml was taken, quenched, and titrated as was described for the other samples.

The amount of titrant used for the first sample was divided by two since it was taken before the phenoxide solution had been diluted by a factor of two. The rate of this reaction was determined as follows; the rate law for the reaction is

$$\log\left(\frac{[\text{base}]^{o} - X}{[\text{DNCB}]^{o} - X}\right) = \frac{[\text{base}]^{o} - [\text{DNCB}]^{o}}{2.303} kT + \log\left(\frac{[\text{base}]^{o}}{[\text{DNCB}]^{o}}\right) \qquad (24)$$

The data is expressed as millimoles per 5 ml aliquot.

The least squares slope of a plot of log $\frac{[\text{base}]}{[\text{DNCB}]}$ vs time is 9.787 x 10^{-5}. The rate constant which is given by

$$k_{obs} = \frac{\text{slope x } 2.303}{[\text{base}]^{o} - [\text{DNCB}]^{o}} \qquad (25)$$

is 6.619 x 10^{-3} $\underline{M}^{-1}$ sec^{-1}.

Eighteen milliliters of reaction mixture weighed 14.3484 g. It contained .4103 g of DNCB and .4182 g of o-methoxyphenol. Subtracting the weights of reagents gives 13.7904 g of MeOH per 18 ml of reaction mixture; thus [MeOH] = 23.9407 moles per liter for this particular experiment. If all the $NaOCH_3$ added had reacted with the o-methoxyphenol, the reaction mixture would be .1336 molar in free phenol. k_2, the rate constant for the reaction of methoxide ion with DNCB was found to be 7.63 x 10^{-2} $\underline{M}^{-1}$ sec^{-1}. The final factor $(k_2 - k_{obs}) \frac{[MeOH]}{[ArOH]}$ for this experiment is 12.4894 $\underline{M}^{-1}$ sec^{-1}.

The Rate of Reaction of Methoxide Ion

The rate constant for the reaction between methoxide ion and DNCB is determined by experiments identical to those just described except that no phenol is used in the reaction mixture.

The Rate of Reaction in t-Butanol Solvent

The rates of reaction in t-butanol were determined in a manner identical to that used for the reactions in methanol. The rates were so great in this solvent that a different technique was required to obtain the samples of reaction mixture for quenching.

A magnetic stirrer was placed in the constant temperature bath and held just beneath the surface of the water. A 100 ml beaker containing a magnetic stirring bar was clamped over the magnetic stirrer with the bottom about an inch below the surface. Five milliliters of the DNCB solution was pipetted into the beaker after it had reached thermal equilibrium with the bath. Five milliliters of phenoxide solution was then pipetted into the beaker with the stirrer operating. The timer was start-

Table 1. Workup for a Typical Kinetic Run

Sample	ml $HClO_4$	mm base	$X = [base]^o - [base]$	mm DNCB = $[DNCB]^o - X$	$\log \frac{[base]}{[DNCB]}$	time(sec)
1	8.85	.2685	0	.1946	.1399	0
2	8.56	.2594	.0091	.1855	.1455	120
3	7.71	.2336	.0349	.1597	.1652	592
4	7.04	.2133	.0552	.1394	.1847	1059
5	6.29	.1906	.0779	.1167	.2130	1727
6	5.90	.1788	.0897	.1049	.2317	2145
7	2.44	.0739	.1946	0	-----	----

ed when half the phenoxide was added. The reaction was quenched by quickly pouring 30 ml of distilled water into the beaker. The beaker was then removed from the bath and the solution titrated with standard $HClO_4$. A clean beaker would be put in the constant temperature bath and the procedure repeated for the next sample. The solutions were able to be quenched after as short as 3 to 5 seconds of reaction time by following this procedure. Although the experimental error involved in measuring the time was significant compared with the measured times, the resulting rate constants were good enough to allow the rates of the several phenols to be compared among themselves.

Purification of Materials

A Nestor-Faust 24 inch spinning band distillation column, NF-120, equipped with a stainless steel band was used for the distillation of liquid reagents, except solvents. These liquids were placed in small bottles, out gassed with dry N_2, and securely capped with rubber serum caps. When needed they were taken from the bottle with a syringe. Gas-liquid chromatographic analysis detected no noticeable deterioration and no observable impurities during the period each reagent was being used.

Solid reagents were stored in brown glass bottles. Melting points were taken periodically of those materials which were constantly in use over long periods of time to insure purity.

All melting points were taken with a Mel-Temp capillary melting point apparatus and are uncorrected.

Methanol

A commercial grade of methanol was distilled from magnesium turnings immediately before use. The methanol still was kept operating constantly, the methanol boiling under reflux when not being taken off. Each time methanol was distilled for use a forerun was taken and discarded.

t-Butanol

Reagent grade t-butanol, MC&B, was distilled immediately before use.

2,4-Dinitrochlorobenzene

Eastman white label product was recrystallized from ethanol and dried under vacuum (m.p., obs., 51.5°-52.5°; 50-51° literature value).[15]

Anisole

Eastman white label anisole was distilled on the spinning band distillation column (b.p., obs., 154°; 155° literature value).[16]

2,4-Dinitroanisole

Eastman white label product was recrystallized from ethanol and dried under vacuum (m.p., obs., 93.1°-93.8°; 94-95° literature value).[16]

m-Dinitrobenzene

Eastman white label product was recrystallized from ethanol and dried under vacuum (m.p., obs., 88.5°-89.5°; 89.5° literature value).[16]

Phenols

The liquid phenols were distilled on the spinning band distillation column.

o-Iodophenol

The Pfaltz and Bauer product was sublimed in the absence of light (m.p., obs., 42°-43°; 42°, literature value).[18]

Table 2. Boiling Points of Liquid Phenols

Ortho-Substituent	Observed Boiling Point	Reported Boiling Point	Source
H	30° @ 3.0mm	85° @ 20 mm[17]	J. T. Baker
CH_3	28° @ 2.5mm	90° @ 20 mm[17]	Aldrich
C_2H_5	31° @ 3.5mm	102° @ 20 mm[17]	Aldrich
$\underline{i}$-C_3H_7	33° @ 3.0mm	112° @ 20.5mm[19]	Aldrich
$\underline{t}$-C_4H_9	32° @ 2.9mm	114° @ 20 mm[17]	Eastman
OCH_3	31° @ 2.9mm	82° @ 10 mm[18]	Eastman
F	27° @ 2.5mm	152° @ 760 mm[18]	Aldrich
Cl	33° @ 2.7mm	176° @ 760 mm[18]	Eastman
Br	42° @ 3.0mm	185° @ 760 mm[18]	City Chemical

Preparation of Solutions

0.1 N NaOH

Approximately 4 g of J. T. Baker reagent grade NaOH was quickly washed with distilled water and dissolved in approximately one liter of distilled water. The solution was standardized by titrating a sample of primary standard potassium acid phthalate to the phenolphthalein end point. The average of at least two titrations was taken for the normality. It was stored in a one liter polyethylene bottle.

0.1 and 0.025 N $HClO_4$

Solutions were made up containing approximately 12 and 4 g respectively of J. T. Baker reagent grade 70 percent $HClO_4$ per liter of distilled water. These solutions were standardized by titrating samples of the standard NaOH to pH 7 using a Beckman Zeromatic II pH meter. The average of at least two titrations was taken for the normality. These solutions were stored in one liter polyethylene bottles.

Sodium Methoxide Solution

Approximately 9 g of sodium were washed in dry methanol to remove the skin of NaOH and then added to approximately 500 ml of dry methanol which had been outgassed with dry nitrogen. The solution was allowed to boil under reflux with a $CaSO_4$/KOH drying tube being used to exclude moisture and CO_2 until all the sodium was reacted. When the solution had cooled, its normality was determined by titrating a sample with .1 N $HClO_4$ to a pH of 7 using the pH meter. The solution was then diluted with dry methanol to bring the normality close to .75 and restandardized to confirm the desired normality. The solution was further outgassed with dry nitrogen and placed in a series of bottles which were sealed with rubber serum caps. Samples of the $NaOCH_3$ solution were removed via syringe when needed.

Potassium t-Butoxide Solution

Approximately 15 g of potassium was added to about 500 ml of t-butanol and the solution treated in a manner identical to that of the sodium methoxide solution.

Identification of Products

The products of the reaction between phenol (and o-methoxyphenol) and DNCB were isolated in small yield from the reaction mixtures used in determining the respective overall rate constants. The respective products of the reaction between phenol, o-methylphenol, o-methoxyphenol, and o-fluorophenol and DNCB were obtained in somewhat better yield by preparing reaction mixtures under conditions similar to those used in the actual kinetic runs but two to five times more concentrated in each reagent. In the case of the other phenols the product of the side reaction between $NaOCH_3$ and DNCB, 2,4-dinitroanisole, was present in appreciable quantity and could not be separated from the desired diphenylether. For this reason and the fact that the dinitroanisole was also produced in the other reactions to some extent, it was decided to synthesize all the substituted diphenylethers in a solvent in which no side reaction could take place. The solvent of choice was t-butanol, a solution of potassium t-butoxide in t-butanol being used to ionize the phenol for the reaction. All the substituted diphenylethers were synthesized and purified under similar conditions; to a solution of 3.0 g (1.48 mm) of DNCB in approximately 25 ml of t-butanol was added a mixture containing 12 ml (13.8 mm) of K-t-butoxide solution and approximately 1.5 mm of the particular phenol plus 15 ml of t-butanol. The resulting soluton was quickly outgassed by blowing dry nitrogen over the surface, capped with a rubber serum cap, and placed in the 35° constant temperature bath until the deep red color (presumably caused by formation of the Meisenheimer complex) which appeared immediately upon mixing was observed to disappear - a period of from four to twelve hours. At this point the solution was poured into about 500 ml of water contained in a 1 liter separatory funnel and the product extracted with two 100 ml portions of ethyl ether. It was found that a negligible amount of product was obtained by extracting with a third 100 ml portion of ether. The ether extract was dried with $MgSO_4$ and the ether allowed to evaporate. The resulting oil was first recrystallized from a smaller amount of ethel ether except that the products resulting from the reaction of ethyl-, chloro-, and iodophenol were first recrystallized from methanol-water. The crude diphenyl ethers were then recrystallized to constant melting point from ethyl ether.

The weights of phenol used in each synthesis, the yield of product after purification, and the melting point of the product are reported in Table 3.

The diphenyl ethers were identified by melting point (when known), Nuclear Magnetic Resonance Spectrum, and Mass Spectrum. The diphenyl ethers were sparingly soluble in CCl_4, $CDCl_3$, CS_2 and other available aprotic solvents. Consequently the NMR spectra were not of high quality and these solvents were only used for the products derived from o-methyl, ethyl, i-propyl, and t-butyl phenol. As the diphenyl ethers were readily

Table 3. Data for Synthesis of Products of Kinetic Runs

Phenol	Weight of Phenol Used, Grams	Weight of Purified Product/ Percent Yield	Melting Point	
			Found	Reported
Unsubstituted	1.4	1.81/46.5	71.0-71.5	70.0-71.5[21]
o-CH_3	1.6	1.78/43.4	89.5-90.0	88.0-89.0[21]
o-C_2H_5	1.8	1.13/26.3	37.0-38.0	*
o-*i*-C_3H_7	2.0	1.97/43.7	102-103.0	*
o-*t*-C_4H_9	2.2	2.35/50.0	94.5-95.0	*
o-OCH_3	1.9	2.40/55.8	86.5-87.5	92.5-94.0[21]
o-F	1.7	2.69/65.6	87.0-88.0	*
o-Cl	1.9	1.64/37.3	97.0-98.0	99.0-100[21]
o-Br	2.6	2.86/56.1	79.0-80.0	84.0-85.5[20]
o-I	3.3	2.02/34.9	93.0-94.0	93.5-94.0[21]

*No melting point available.

soluble in acetone, it was used as a solvent for the diphenyl ethers whose spectra would not be interfered with by the absorptions due to its methyl groups.

The presence of the parent ion of appropriate m/e in the mass spectrum was confirmed for each of the diphenyl ethers.

Table 4. NMR Data for Products of Kinetic Runs

Substituent	Solvent	NMR Spectrum*
H	CH_3COCH_3	τ = 1.86,d,1; τ = 2.25,dd,1; τ = 3.19-3.60,m,6
o-CH_3	$CDCl_3$	τ = 1.13,d,1; τ = 1.66,dd,1; τ = 2.34-3.14,m,5; τ = 7.78,s,3
o-C_2H_5	$CDCl_3$	τ = 0.91,d,1; τ = 1.41,dd,1; τ = 2.19-2.80,m,5; τ = 7.13,q,2; τ = 8.52,t,3
o-*i*-C_3H_7	CCl_4	τ = 1.21,d,1; τ = 1.68,dd,1; τ = 2.49-3.12,m,5; τ = 6.51, sepTet,1; τ 8.75, d,6
o-*t*-C_4H_9	CCl_4	τ = 1.23,d,1; τ = 1.71,dd,1; τ = 2.38-3.19,m,5; τ = 8.60,s,9
o-OCH_3	CH_3COCH_3	τ = 1.86,d,1; τ = 2.31,dd,1; τ = 3.26-3.78,m,5; τ = 6.93,s,3
o-F	CH_3COCH_3	τ = 1.80,d,1; τ = 2.19,dd,1; τ = 3.12-3.56,m,5
o-Cl	CH_3COCH_3	τ = 1.30,d,1; τ = 1.73,dd,1; τ = 2.42-3.19,m,5
o-Br	CH_3COCH_3	τ = 1.29,d,1; τ = 1.72,dd,1; τ = 2.48-3.19,m,5
o-I	CH_3COCH_3	τ = 1.30,d,1; τ = 1.72,dd,1; τ = 2.19, dd,1; τ = 2.53-3.20,m,4
2,4-Dinitroanisole	$CDCl_3$	τ = 1.43,d,1; τ = 1.62,dd,1; τ = 2.76, d,1; τ = 5.95,s,3

*The spectral data are presented for each peak or multiplet in the order chemical shift versus TMS, splitting pattern (s = singlet, d = doublet, dd = doublet of doublets, t = triplet, q = quartet, m = complex multiplet), and number of protons absorbing.

CHAPTER III

RESULTS AND DISCUSSION

Overall Rate Constants

The overall second order rate constants, k_{obs}, for the reaction of each of the ortho substituted phenoxides with DNCB in methanol at 35° in the presence of various concentrations of excess phenol are summarized in Tables 5-14 and illustrated graphically in Figures 1 and 2. The equilibrium concentrations of phenol, [ArOH], and the factors $(k_2 - k_{obs}) \frac{[MeOH]}{[ArOH]}$ are those provided by the computer after the best numerical values of the constants, k_1 and K_{eq}, were determined by successive approximations.

The tolerances provided with the values given for k_{obs}, k_1, k_2, and K_{eq} are not intended to imply any knowledge of the true value of these constants. The tolerances given for each number calculated by the least squares procedure is an estimate of the uncertainty in that number caused by the scatter of the points which define the straight line whose slope or intercept was calculated. These tolerances are generated by a statistical procedure written into the computer program.[22]

These results are illustrated in Figures 1 and 2. Note that in the plot for the unsubstituted phenol, Figure 1, three points are not shown because they lie so far off scale. These three points do fall exactly on the line when a graph going to a value of $(k_2 - k_{obs})\frac{[MeOH]}{[ArOH]} = 50$ is utilized.

Table 5. Reactivity of Phenoxide-Methoxide Solutions Toward DNCB in Methanol

$k_{obs} \times 10^3$	[ArOH]	$(k_2 - k_{obs}) \frac{[MeOH]}{[ArOH]}$
5.49 ± .29	0.0362	47.002
5.24 ± .18	0.0471	36.202
4.86 ± .26	0.0492	34.798
4.81 ± .30	0.0704	24.281
4.71 ± .40	0.0642	26.664
4.15 ± .58	0.1022	16.798
3.97 ± .25	0.1157	14.879
3.64 ± .51	0.2117	8.047
2.81 ± .10*	0.5392	3.145
2.80 ± .22*	0.5327	3.186
2.78 ± .21*	0.5307	3.203
2.55 ± .14*	0.5894	2.879

*These runs were not used in computing the constants k_1 and K_{eq} because it was found that at these high concentrations of phenol, k_{obs} was depressed due to the formation of biphenoxide ion.[23] This was not observed for any substituted phenol in this study.

Table 6. Reactivity of o-Methylphenoxide-Methoxide Solutions Toward DNCB in Methanol

$k_{obs} \times 10^3$	[ArOH]	$(k_2 - k_{obs}) \frac{[MeOH]}{[ArOH]}$
6.98 ± .40	0.0835	19.819
5.89 ± .06	0.1036	16.202
5.20 ± .12	0.1283	13.133
4.74 ± .21	0.1347	12.578
4.19 ± .18	0.1750	9.695
3.66 ± .10	0.2181	7.807
3.65 ± .07	0.2357	7.189
2.73 ± .16	0.3575	4.724
2.56 ± .07	0.3819	4.402
2.23 ± .13	0.4985	3.342

Table 7. Reactivity of o-Ethylphenoxide-Methoxide Solutions Toward DNCB in Methanol

$k_{obs} \times 10^3$	[ArOH]	$(k_2 - k_{obs}) \frac{[MeOH]}{[ArOH]}$
12.65 ± .31	0.0757	20.092
11.54 ± .37	0.0874	17.604
9.97 ± .46	0.1053	14.998
8.64 ± .16	0.1293	12.434
7.68 ± .54	0.1641	9.857
6.31 ± .32	0.2191	7.471
5.07 ± .39	0.2902	5.680
4.61 ± .35	0.3613	4.540
4.38 ± .52	0.3970	4.118

Table 8. Reactivity of o-i-Propylphenoxide-Methoxide Solutions Toward DNCB in Methanol

$k_{obs} \times 10^3$	[ArOH]	$(k_2 - k_{obs}) \frac{[MeOH]}{[ArOH]}$
13.72 ± .45	0.1247	11.907
11.71 ± .06	0.1555	9.809
11.58 ± .67	0.1650	9.254
9.55 ± .40	0.2189	7.120
9.06 ± .56	0.2387	6.560
7.53 ± .61	0.3172	4.985
6.34 ± .18	0.4178	3.790
6.22 ± .27	0.4797	3.273

Table 9. Reactivity of o-t-Butylphenoxide-Methoxide Solutions Toward DNCB in Methanol

$k_{obs} \times 10^3$	[ArOH]	$(k_2 - k_{obs}) \frac{[MeOH]}{[ArOH]}$
42.39 ± 1.51	0.1630	4.915
38.03 ± 3.20	0.2052	4.375
35.46 ± 1.09	0.2302	4.145
34.43 ± 1.09	0.2450	3.984
31.76 ± 0.57	0.2812	3.662
25.94 ± 4.25	0.3878	2.957
20.79 ± 0.34	0.5460	2.256
20.14 ± 0.37	0.5370	2.324

Table 10. Reactivity of o-Methoxyphenoxide-Methoxide Solutions Toward DNCB in Methanol

$k_{obs} \times 10^3$	[ArOH]	$(k_2 - k_{obs})\frac{[MeOH]}{[ArOH]}$
6.62 ± .09	0.1027	16.243
6.09 ± .42	0.1405	11.895
5.65 ± .17	0.1522	11.006
5.63 ± .18	0.1932	8.644
5.35 ± .42	0.2341	7.119
5.10 ± .11	0.2986	5.560

Table 11. Reactivity of o-Fluorophenoxide-Methoxide Solutions Toward DNCB in Methanol

$k_{obs} \times 10^4$	[ArOH]	$(k_2 = k_{obs}) \frac{[MeOH]}{[ArOH]}$
9.36 ± .99	0.0965	16.548
8.83 ± .49	0.1045	15.404
8.77 ± .65	0.1159	14.020
8.38 ± .89	0.1692	9.597
7.84 ± .48	0.2507	6.463
7.56 ± .34	0.2582	6.235
7.54 ± .68	0.2819	5.688

Table 12. Reactivity of o-Chlorophenoxide-Methoxide Solutions Toward DNCB in Methanol

$k_{obs} \times 10^4$	[ArOH]	$(k_2 - k_{obs}) \frac{[MeOH]}{[ArOH]}$
3.82 ± .18	0.1395	12.352
3.75 ± .23	0.0908	19.085
3.60 ± .58	0.1098	15.750
3.46 ± .46	0.1135	15.312
3.46 ± .71	0.1366	12.645
3.40 ± .34	0.2740	6.225
3.30 ± .21	0.2867	5.924
3.13 ± .25	0.2818	6.076

Table 13. Reactivity of o-Bromophenoxide-Methoxide Solutions Toward DNCB in Methanol

$k_{obs} \times 10^4$	[ArOH]	$(k_2 - k_{obs}) \frac{[MeOH]}{[ArOH]}$
7.77 ± .39	0.1019	16.119
7.58 ± .21	0.1164	14.125
7.49 ± .57	0.1172	14.062
7.02 ± .24	0.1268	13.061
6.13 ± .36	0.1612	10.363
5.89 ± .62	0.1876	8.910
4.86 ± .50	0.2261	7.553
4.71 ± .25	0.2498	6.770

Table 14. Reactivity of o-Iodophenoxide-Methoxide Solutions Toward DNCB in Methanol

$k_{obs} \times 10^4$	[ArOH]	$(k_2 - k_{obs}) \frac{[MeOH]}{[ArOH]}$
6.50 ± .51	0.0914	18.392
5.50 ± .27	0.1347	12.593
5.14 ± .35	0.1548	11.008
4.96 ± .27	0.1835	9.286
4.43 ± .28	0.2401	7.118
4.40 ± .01	0.2220	7.718

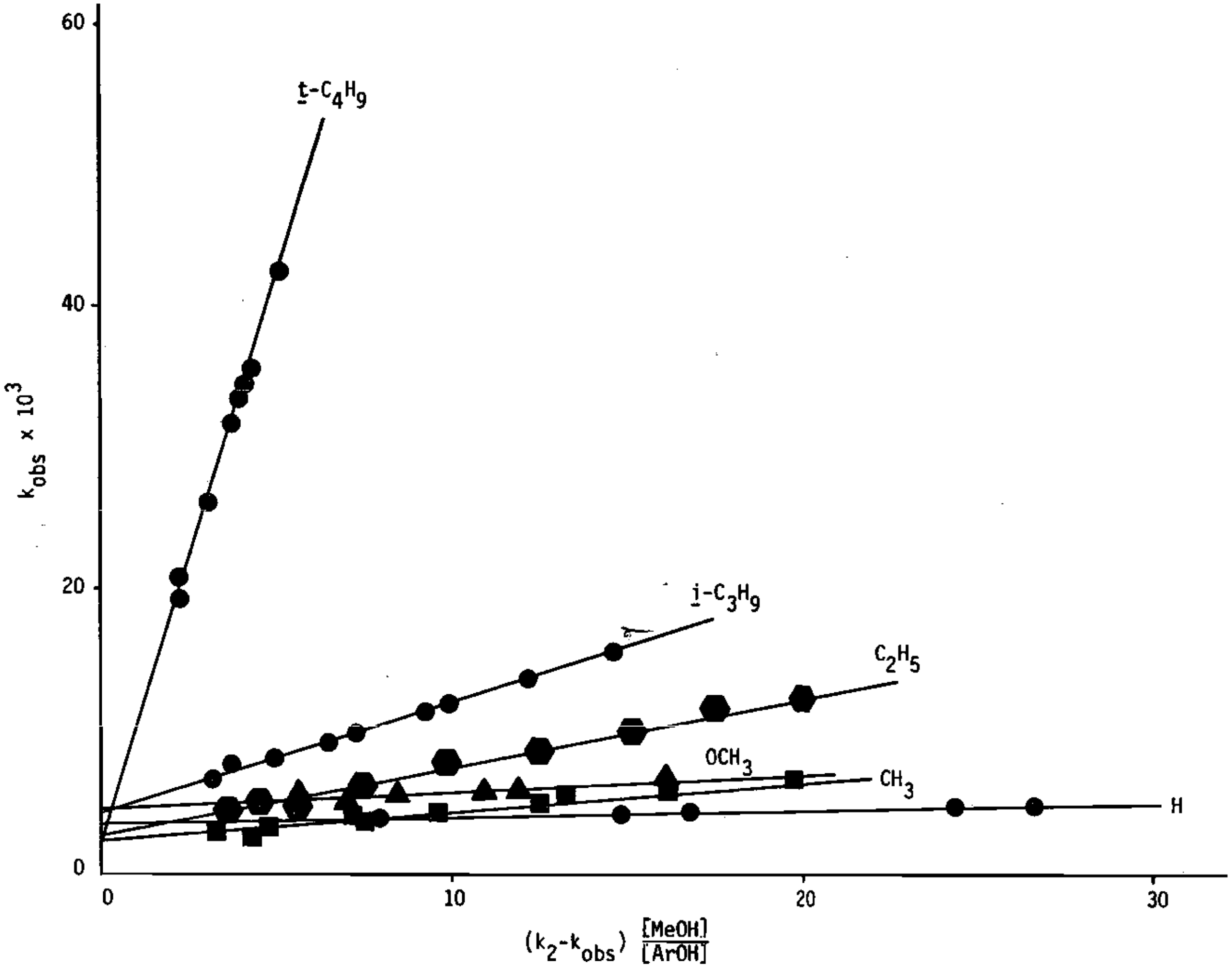


Figure 1. k_{obs} vs $(k_2 - k_{obs}) \frac{[MeOH]}{[ArOH]}$ for the Alkyl Substituted Phenols.

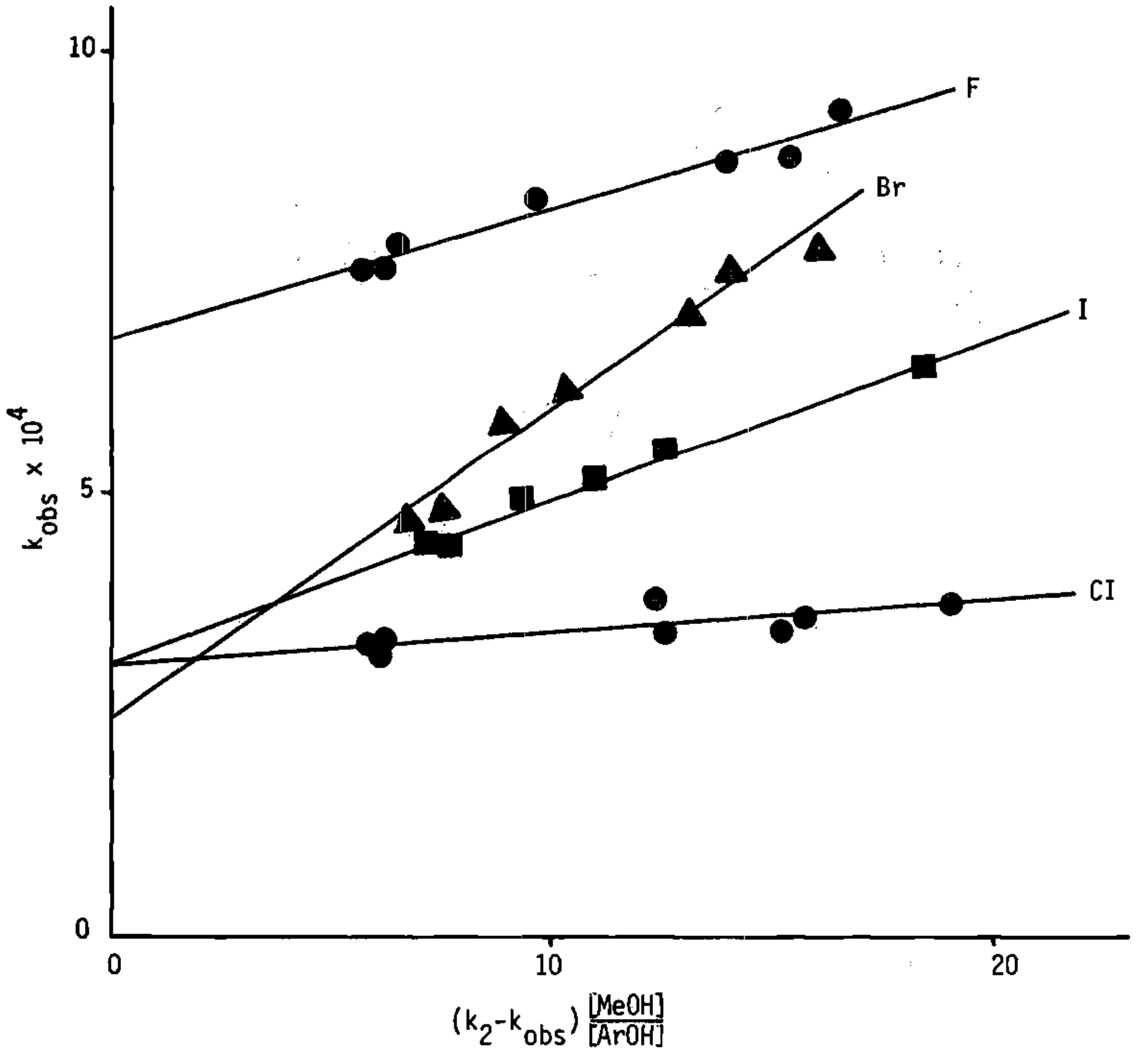


Figure 2. k_{obs} vs $(k_2 - k_{obs}) \frac{[MeOH]}{[ArOH]}$ for Halogen Substituted Phenols.

The slope and intercept of a plot of k_{obs} vs $(k_2 - k_{obs}) \frac{[MeOH]}{[ArOH]}$ were evaluated by the previously described method of successive approximations by means of a computer program written by this author and executed by a Burroughs B-5500 computer in the Rich Electronic Computer Center, Georgia Tech, for each of the ten phenols. K_{eq}, the equilibrium constant for the equilibrium between phenoxide ion and methanol, k_1, the second order rate constant for the reaction between phenoxide ion and DNCB, corresponding to the slope and intercept, respectively, and the pK_a which is calculated from K_{eq} and the autoprotolysis constant, K_{ap}, of methanol are presented for each phenol in Table 15.

The only available literature values for the acidities of phenols in pure methanol are 14.1[24] for phenol itself and 16.25[25] for o-t-butylphenol, both at 25°. Neither of these values are thermodyanmic pK_a's.

The data in Table 15 are presented in the form of a plot of pK_a vs log k_1 for nine of the phenols in Figure 3.

The appearance of two seemingly parallel lines in Figure 3 suggests that the substituents involved belong to two steric classes; one made up to OCH_3, H, F, and Cl and the other containing CH_3, C_2H_5, i-C_3H_7, and Br. In Table 16 is a comparison of the relative sizes of the substituents in the two classes, utilizing Taft's E_s values.[3]

The E_s values utilized in this, and subsequent, discussions are those for the particular substituent separated from the parent by a methylene group; e.g., for a substituent, X, the E_s value of the group CH_2-X is used. In these phenols and phenoxides the substituent is separated from the functional group by one rigid vinylene group. The

Table 15. k_1, K_{eq}, and pK_a in Methanol for Ten Phenols,

R	k_1	K_{eq}	pK_a
H	$3.35 \pm 0.33 \times 10^{-3}$	$4.81 \pm 0.12 \times 10^{-5}$	$13.30 \pm .01$
CH_3	$1.41 \pm 0.20 \times 10^{-3}$	$2.81 \pm 0.18 \times 10^{-4}$	$14.07 \pm .03$
C_2H_5	$2.28 \pm 0.25 \times 10^{-3}$	$5.20 \pm 0.21 \times 10^{-4}$	$14.34 \pm .08$
i-C_3H_7	$3.17 \pm 0.33 \times 10^{-3}$	$8.88 \pm 0.43 \times 10^{-4}$	$14.57 \pm .02$
t-C_4H_9*	$1.36 \pm 1.34 \times 10^{-3}$	$8.32 \pm 0.36 \times 10^{-3}$	$15.54 \pm .01$
OCH_3	$4.34 \pm 0.39 \times 10^{-3}$	$1.39 \pm 0.37 \times 10^{-4}$	$13.76 \pm .11$
F	$6.78 \pm 0.41 \times 10^{-4}$	$1.46 \pm 0.36 \times 10^{-5}$	$12.78 \pm .10$
Cl	$3.10 \pm 0.35 \times 10^{-4}$	$3.35 \pm 0.28 \times 10^{-6}$	$12.14 \pm .05$
Br	$2.47 \pm 0.70 \times 10^{-4}$	$3.48 \pm 0.59 \times 10^{-5}$	$13.16 \pm .06$
I	$3.08 \pm 0.30 \times 10^{-4}$	$1.88 \pm 0.26 \times 10^{-5}$	$12.89 \pm .11$

*Due to the very basic nature of the o-t-butylphenoxide ion, nearly all of it is converted to methoxide under equilibrium conditions, resulting in abnormally large values of k_{obs}. The degree of extrapolation necessary to reach the intercept from the available data points causes a corresponding large uncertainty in the numerical value of the intercept. Data from analogous sytems (for example 2-alkylpyridines, ref. 10a) suggest that the rate of reaction of o-t-butylphenoxide should probably be at least an order of magnitude less than that of phenoxide itself. k_1 for t-butylphenol will not be considered in the discussion due to the uncertainty in its position.

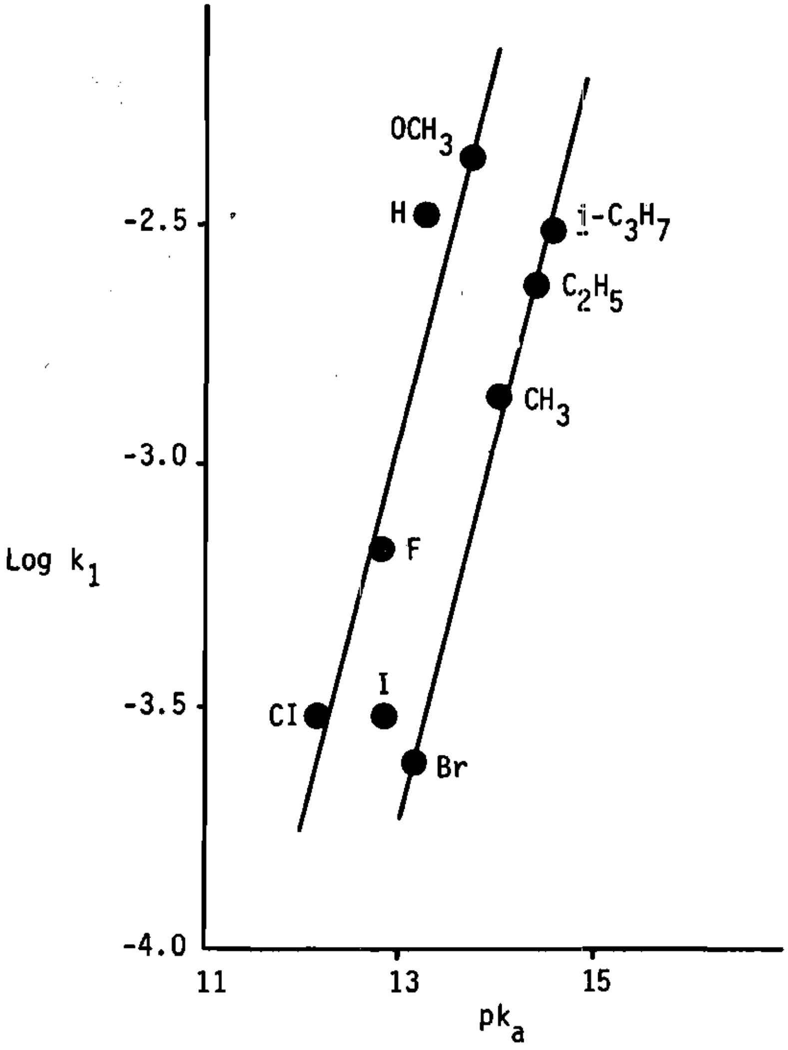
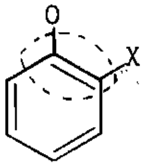


Figure 3. Log k_1 vs pK_a for <u>Ortho</u> Substituted Phenols in Methanol.

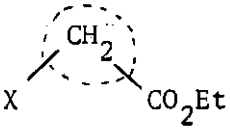
Table 16. Taft's Steric Parameters for the Substituents* of Figure 3

R	E_s	R	E_s
Br	-0.27	OCH_3	-0.19
CH_3	-0.07	H	0.00
C_2H_5	-0.36	F	-0.24
<u>i</u>-C_3H_7	-0.93	Cl	-0.24
Average	-0.41	Average	-0.17

*The iodo group, E_s = -0.20, is probably much more nucleophilic than its size would indicate due to its polarizability.



steric parameters were originally determined from esterification reactions involving substituted acetates. The substituent could be considered as being separated from the functional group by one rigid methylene group.



The choice of CH_2-X rather than X as a basis for the E_s values utilized in this study is intended to minimize differences in solvation and steric effects between the reference system and the compounds under study by making the geometry of the substituent with respect to the reaction center as similar as possible in the two systems.

Alkyl Substituted Phenols

There is some evidence that the effective sizes of the ethyl and i-propyl groups may be somewhat smaller than their E_s values would indicate in certain compounds having about the same steric requirement as a methyl group.[10a] In ortho alkyl phenols free rotation about the carbon-carbon single bond joining the substituent to the ring will result in the methyl group presenting a proton towards the phenolic oxygen all the time. The ethyl group will present a proton toward the oxygen two-thirds of the time and a methyl group one-third. The i-propyl group will present a proton toward the oxygen one-third of the time and a methyl group toward it two-thirds of the time. If the phenolic oxygen is heavily solvated, the solvent shell can conceivably interfere with this free rotation in the cases of ethyl and i-propyl groups, resulting in these two groups spending a considerable amount of time in energetically favored conformations which offer the least interference with the solvent shell. These favored conformations involve presenting a proton toward the phenolic oxygen and that implies a steric effect similar to that of the methyl group, Figure 4.

Referring to Figure 3, the nucleophilicity of the anions of ortho methoxy, hydrogen, fluoro, and chlorophenols are well correlated by their acidity, expressed in pK_a units. The presence of the second, apparently parallel, line formed by the points for the ortho bromo, methyl, ethyl, and i-propyl phenoxides suggests that the nucleophilicities of these compounds should be correlated by the same line that correlates the first four phenoxides, but the other ones have rather bulky substituents of about the same steric requirement which through steric inhibition of solvation reduce the acidity of their respective phenols by about one pK_a unit compared to phenoxides of the same nucleophilicity but with smaller substituents.

The acidity of the ortho alkyl phenols correlate reasonably well with the size of the substituent. The polar substituent constants of the alkyl groups are quite similar while the acidities of these

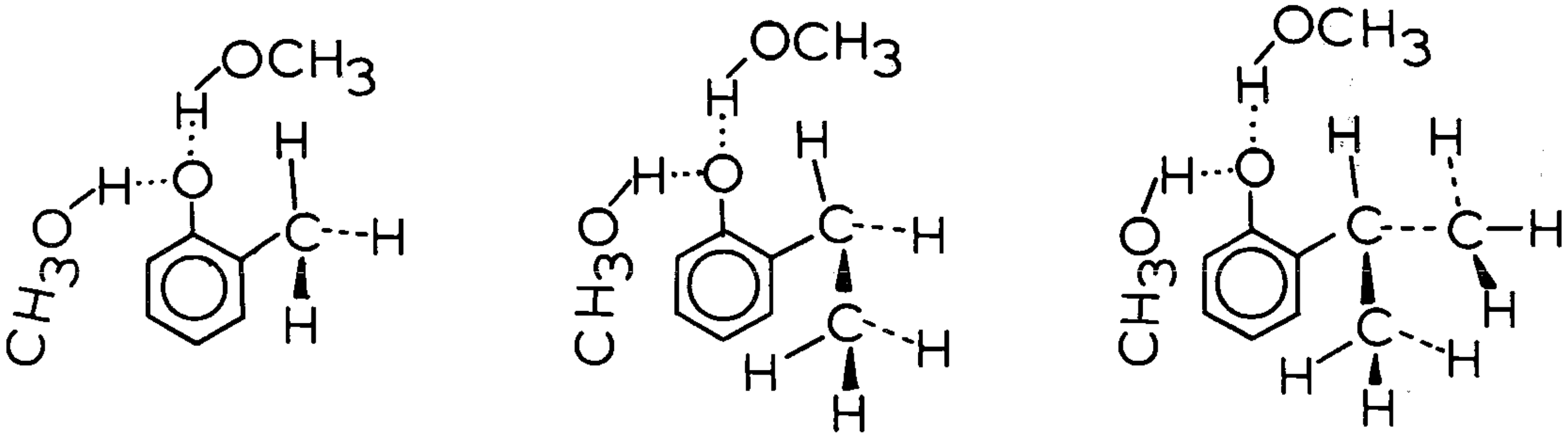


Figure 4. Ortho Methyl, Ethyl, and i-Propylphenol Showing the Alkyl Group in the Position of Least Steric Interference with the Solvent Shell.

phenols have a range of one and a half pK_a units. This requires a ρ value of approximately -5 which is unusually large. It is felt that steric inhibition of solvation of the phenoxide anion which destabilizes it relative to the unionized phenol is the dominating effect in changing the relative acidity of the ortho alkyl phenols. The effect of the alkyl substituents on the acidity of these phenols is illustrated in Figure 5. The large decrease in acidity on going from a hydrogen to a methyl substituent can be attributed to the polar effect of the methyl groups.

The situation with respect to the nucleophilicity of the ortho alkyl phenoxides is somewhat more complex (see Figure 6). It has been observed, especially in the 2-alkyl-pyridine system, that bulky alkyl groups normally cause a large reduction in the nucleophilicity of such compounds.[10a] In the series of compounds under study the ortho-t-butylphenoxide had too low a reactivity to measure accurately. The mildly surprising rate increase on going from ortho-methyl to ortho-i-propylphenoxide may be rationalized by considering the attack of these phenoxides on the substrate, DNCB, to occur in two almost indistinguishable stages. In the first stage, the heavily solvated phenoxide ion is attempting to break through its solvent shell so as to approach the substrate. This is facilitated by steric inhibition of solvation of the anion by the ortho substituent. The degree of disruption of the solvent shell increases with increasing substituent size; the larger alkyl groups ease the approach to the transition stage, as the denuded phenoxide ion approaches the immediate vicinity of the substrate prior to entering the transition state, the primary steric effect of the ortho alkyl group

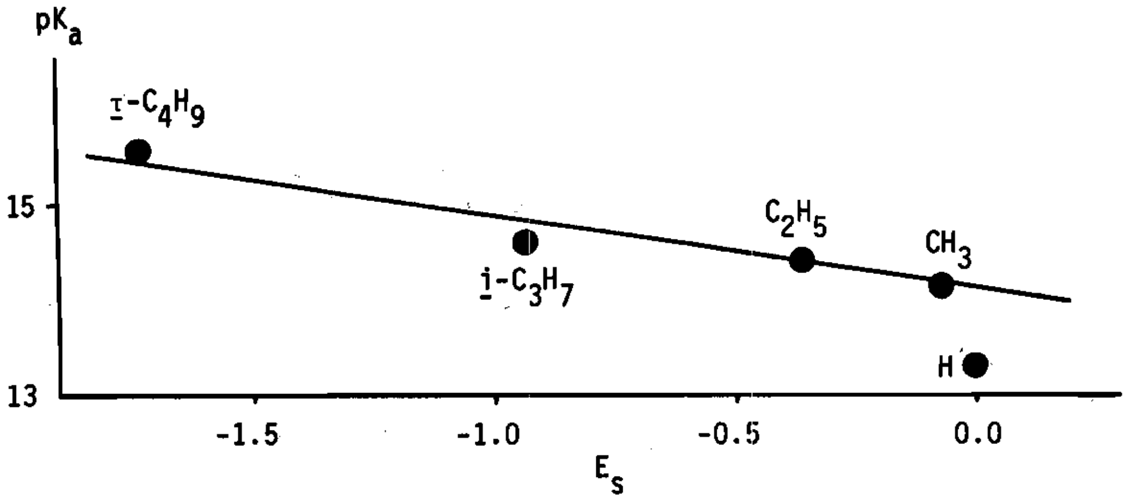


Figure 5. A Plot of pK_a vs E_s for <u>Ortho</u> Alkylphenols in Methanol.

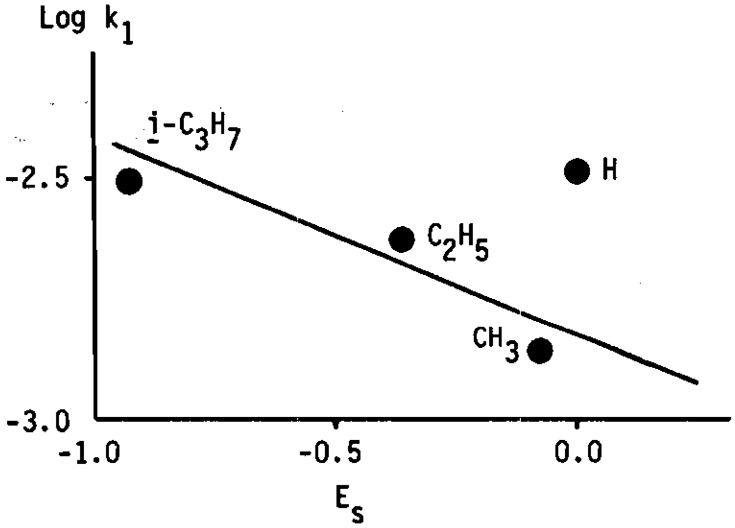


Figure 6. A Plot of Log k_1 vs E_s for the Ortho Alkylphenoxides.

becomes the dominant influence in determining the rate of reaction. Phenol itself, having no primary steric effect, is the most reactive of the alkyl phenoxides even though it receives no aid from any substituents in breaking through its solvent shell. Ortho-t-butyl phenoxide, while having the most powerful solvation reducing substituent, is extremely unreactive because the t-butyl group saddles it with a nearly insurmountable primary steric effect. An intermediate position is held by the methyl, ethyl, and i-propyl groups. These three groups, in the approach to the transition state, are able to assume similar conformations which minimize their primary steric effect by presenting a proton rather than a methyl group toward the phenolic oxygen. Considering the amount of steric inhibition of solvation evidenced by the sharply decreasing acidities of these compounds it seems that there is still considerable rotation about the carbon-carbon single bond in the ethyl and i-propyl groups which sweeps the substrate away from the phenolic oxygen to some extent; otherwise the rate increase might possibly be even greater on going from methyl to ethyl to i-propyl. The polar effects of these alkyl groups certainly increase in a direction to cause the observed rate increases but it has been pointed out that their polar effects are normally outweighed by their steric effects.

It was decided to compare the rates of reaction of these ortho alkyl phenoxides towards DNCB in t-butanol with those in methanol. The purpose in this change of solvent was two-fold. 1) Due to the relatively greater basicity of t-butoxide compared to methoxide it was hoped that the nucleophilicities of the alkyl phenoxides could be determined directly, without interference from the equilibrium between phenoxide ion and solvent. 2) The much greater bulk of t-butanol would allow some conclusion to be drawn concerning the importance of solvation of the anion on the rate of reaction.

Unfortunately the rate of reaction of phenoxide with DNCB was so rapid that the rate constants were extremely difficult to obtain accurately. It was found, however, that with the exception of the extremely basic o-t-butyl phenoxide ion the reaction with the solvent to form 2-butoxide was negligible as expected. In such cases $k_{obs} = k_1$ and the results are listed in Table 17.

Due to the difficulty in obtaining accurate rate constants in t-butanol solvent no attempt was made to determine the rate of the reaction of t-butoxide ion with DNCB. Instead of making use of equation 22 to get k_1 for o-t-butylphenoxide ion, the average of the observed rate constants, k_{obs}, was used to provide an approximate value of k_1.

The rates in methanol and t-butanol are compared in Table 18. Two things are evident upon inspection of this table. First, substitution of an alkyl group for ortho hydrogen has qualitatively the same effect in either solvent and second, the phenoxides react about one hundred times faster in t-butanol than in methanol. The greater rate of reaction in t-butanol is interpreted as being due to the greater size of the solvent molecules and the decreased dielectric constant (11.24[26] compared to 33.0[29] for methanol), resulting in considerably less solvation of the phenoxide ion. The arguments presented earlier concerning the secondary steric effects of the alkyl groups appear to hold in this solvent.

Table 17. Rate of Reactions of Alkyl Phenoxides With DNCB in t-Butanol

R	H	CH_3	C_2H_5	i-C_3H_7	t-C_4H_9
$k_1 \times 10^1$	2.34 ± .37	2.92 ± .23	2.89 ± .36	4.32 ± .51	8.44 ± 1.42
	1.22 ± .53	2.28 ± .16	3.85 ± .75	3.94 ± .86	11.29 ± 2.84
	1.45 ± .20	2.50 ± .48	3.13 ± .60	3.28 ± .68	9.70 ± 2.22
	2.50 ± .48		3.82 ± .29		11.26 ± 1.02
					10.09 ± 0.62
Average	1.88 ± .40	2.57 ± .29	3.42 ± .50	3.85 ± .68	10.16 ± 1.62

Table 18. Comparison of the Rates of Reaction, k_1, of o-Alkyl Phenoxides Toward DNCB in t-Butanol and Methanol

Substituent	k_1(t-Butanol) x 10^1	k_1(Methanol) x 10^3
H	1.88 ± 0.40	3.35 ± 0.33
CH_3	2.57 ± 0.29	1.41 ± 0.20
C_2H_5	3.42 ± 0.50	2.28 ± 0.25
i-C_3H_7	3.85 ± 0.68	3.17 ± 0.33
t-C_4H_9*	(1.0)	(> .1)

*The rate constants for o-t-butylphenoxide are not known with accuracy for reasons discussed in the text.

As a further confirmation of the importance of solvation in determining the reactivity of these phenoxide ions, an attempt was made to determine their rates of reaction toward DNCB in tetrahydrofuran solvent. This solvent is expected to solvate the metal cation exclusively, making it very easy for the nucleophilic center to reach the substrate. The reaction of sodium o-ethylphenoxide with DNCB was attempted in a manner similar to those reactions done in methanol. It was found that the reaction went to completion in approximately 15 seconds. No other experiments in tetrahydrofuran were attempted. The very great reactivity of o-ethylphenoxide in this solvent should further illustrate the importance of solvation effects in determining the reactivities of ortho alkyl substituted phenoxides toward DNCB.

Halogen Substituted Phenols

The effect of the size of the halogen substituents on the rate of reaction of ortho substituted phenoxides is illustrated in Figure 7.

The points for the unsubstituted and methyl substituted phenoxides are included in Figure 7 for reference. The polar effect of these halogens is illustrated in Figure 8.

The points for the unsubstituted and methyl substituted phenoxides are included in Figure 8 for reference. In the halogen series the polar effect of the substituent seems to be more important than the steric effect in determining the reactivity of the compound.

While a bromine atom is the same size as a methyl group, its inductive effect reduces the nucleophilicity of the respective phenoxide ion by a factor of ten. With the exception of o-iodophenoxide, the re-

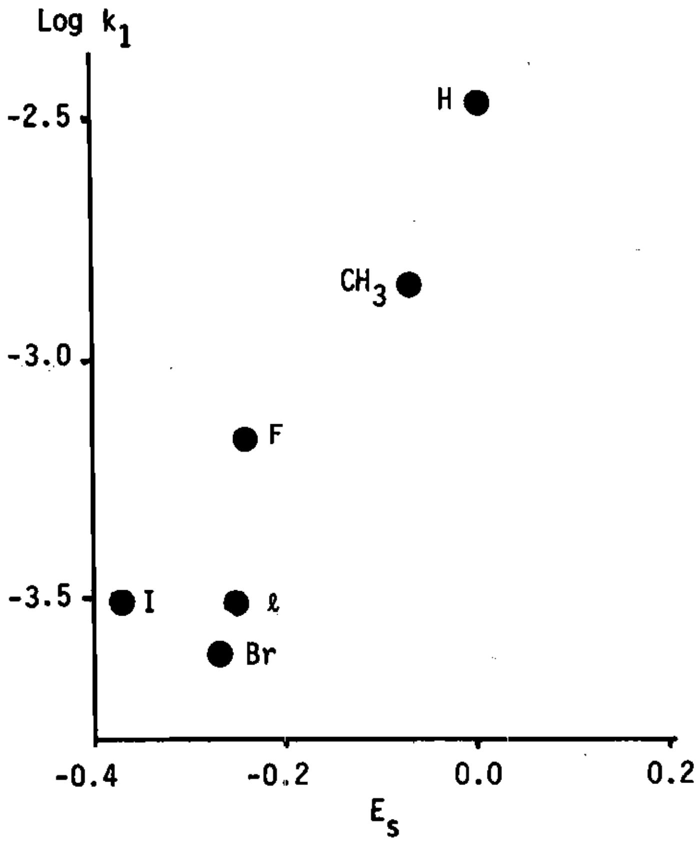


Figure 7. Log k_1 (Methanol) vs E_s for Ortho-Halogen Substituted Phenoxides.

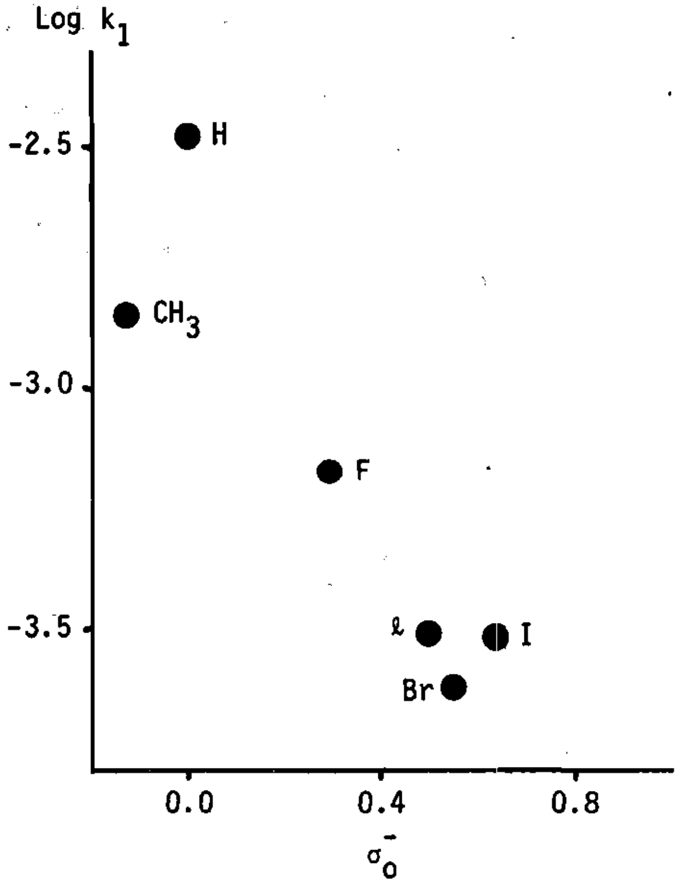


Figure 8. Log k_1 (Methanol) vs σ_o^- for Ortho-Halogen Substituted Phenoxides.

activities of the halogen compounds are correlated quite well by σ_o^-. The enhanced reactivity of the iodo compound could be attributed to the high polarizability of iodine which results in London Forces lowering the transition state energy for this compound.[28] Of course steric inhibition of solvation may also be at work due to the large size of the iodine atom.

The relatively large reactivity of o-fluorophenoxide compared to the other o-halogen compounds, which is consistent with the smaller σ_o^- value, is attributable to resonance donation of electrons to the benzene ring. Both oxygen and halogen, particularly fluorine, donate electrons to the benzene ring through resonance structures of the type illustrated in Figure 9.[29]

In the case of a phenoxide ion, resonance of this type decreases the nucleophilicity and increases the acidity by reducing the electron density at the oxygen atom. This resonance donation of electrons by oxygen is inhibited by the presence of a fluorine atom, especially ortho to it, due to electrostatic repulsion from the electrons the fluorine is attempting to donate.

The increasing size of the halogen substituent, traversing the series fluoro to iodo, is expected to decrease the acidity of the respective substituted phenols by steric inhibition of solvation. The inductive effect of this series increases in a direction which should increase the acidity of the substituted phenol as the series is traversed. It is fortuitous in this case that the two opposing effects almost cancel each other, resulting in the acidity of the ortho halogen phenols being almost independent of the particular halogen substituent.

The relatively large acidity of the chlorophenol, see Figures 10

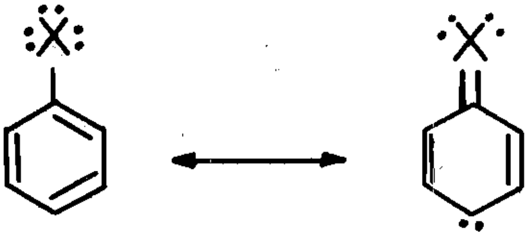


Figure 9. Resonance Donation of Electrons to the Benzene Ring.

and 11, is the result of a unique combination of opposing effects which in this case is unevely weighed in favor of the acid strengthening effect. The chlorine atom is smaller than the bromine or iodine atoms and it has much less of the acid weakening resonance ability of the fluorine atom. Points corresponding to the unsubstituted and methyl substituted phenols are included for reference.

While it may be possible to devise other qualitative explanations for the observed acidities of these ortho-halophenols, the rationalization presented above seems to be the most workable. In Figure 10, it is observed that although bromine is the same size as and iodine is larger than the methyl group, the bromo and iodophenols are more acidic than o-methylphenol by one pK_a unit presumably due to the inductive effect of these halogens. On the other hand the bromo and iodophenols are about one pK_a unit less acidic than would be expected from a consideration of their inductive effect alone (see Figure 11).

The effect of the o-methoxy group is to increase the nucleophilicity of the phenoxide and decrease the acidity of the phenol. The methoxy group is less electro-negative than fluorine but it donates electrons to the benzene ring in the same manner as fluorine, with the overall effect being acid weakening. Its relatively small size also enhances the nucleophilicity of the anion.

Other Factors Affecting the Reactivity of the Phenoxides

The reaction between methoxide ion and DNCB was briefly examined to determine whether or not changes in the ionic strength or the presence of agents capable of forming charge transfer complexes had any sig-

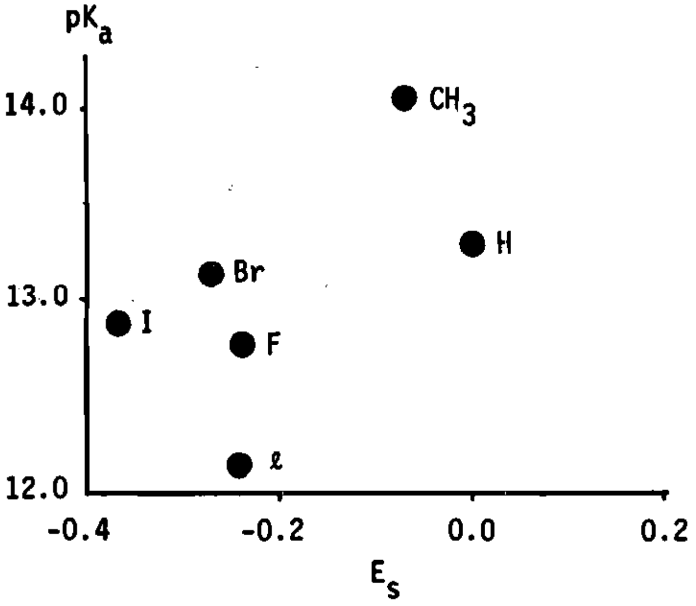


Figure 10. pK$_a$ of Ortho-Halogen Substituted Phenols vs E$_s$.

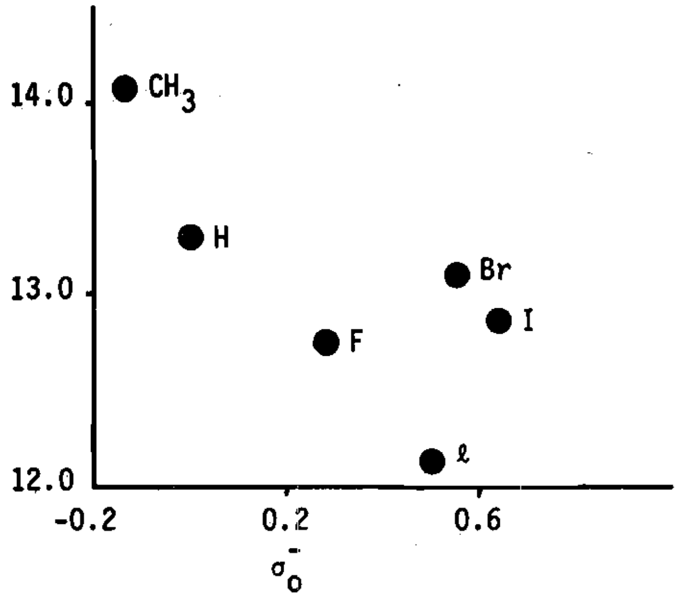


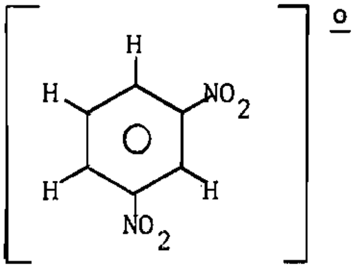
Figure 11. pK_a of <u>Ortho</u>-Halogen Substituted Phenols vs σ_o^- .

nificant effects upon the system under study. The rate of reaction of methoxide ion with DNCB, k_2, was determined at ionic strengths varying from .030 to .0750 (the ionic strength of the solutions used for all phenoxide kinetic runs was held at approximately .05). These results are listed in Table 19.

It was found from these results that within the range of ionic strengths used in this study a two-fold increase in ionic strength causes approximately a two percent increase in the rate of reaction. The rate of reaction of a phenoxide ion with DNCB was expected to be affected by about the same amount or less and the ionic strength is thus not a critical factor in this study.

The reaction of methoxide ion with DNCB in the presence of <u>meta</u>-dinitrobenzene, DNB, was briefly examined. This substance is capable of tying up the nucleophilic ions by forming charge transfer complexes with them. It has also been shown to react with strongly basic ions such as methoxide to form the radical anion I.[30,31]

I.



The results of a series of experiments in which DNB was added to the reaction mixture are presented in Table 20. The results of these preliminary experiments are inconclusive but it appears that DNB causes a slight rate increase. Since the substrate in all reactions (DNCB) is a deriva-

Table 19. Reaction Between Sodium Methoxide and DNCB

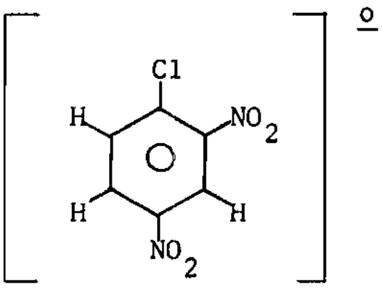
I	$k_2 \times 10^2$
.0300	7.48 ± .43
.0423	7.59 ± .39
.0523	7.50 ± .32
.0526	7.77 ± .30
.0750	7.80 ± .54

Table 20. The Rate of Reaction of Methoxide Ion Toward DNCB in the Presence of DNB

[DNB]	$k_2 \times 10^2$
0	7.63 ± 0.15
0.0115	8.33 ± 0.52
0.0211	8.38 ± 0.57
0.0269	6.98 ± 0.11
0.0316	8.50 ± 0.26
0.0515	7.50 ± 0.29
0.6380	7.22 ± 0.34
1.1647	8.19 ± 0.40

tive of DNB, the importance of the possible side reaction between DNCB and methoxide ion to form the radical anion II warrants further investigation.

II.



The rate of the reaction between DNCB and aniline was found to vary inversely with the initial concentration of aniline.[32] Formation of a charge transfer complex between aniline and DNCB was suggested as being responsible for this decrease in rate. It was decided to investigate the possibility of charge transfer complexes being a significant factor in the reactions of phenoxide with DNCB. The effect of phenol or phenoxide as charge transfer complexing agents could not be ascertained due to the nucleophilic reactivity of phenoxide toward DNCB but the similar compound anisole was expected to have about the same ability to form charge transfer complexes while not being directly involved in the reaction. A series of experiments was performed in which methoxide ion was reacted with DNCB in the presence of added anisole. The results are depicted in Table 21 and in Figure 12. The results of these experiments indicate that the formation of charge-transfer complexes between anisole and DNCB is a significant, but not necessarily major, factor in this reaction.

Table 21. The Effect of Added Anisole on the Rate of Reaction of Methoxide Ion and DNCB

[Anisole]	$k_2 \times 10^2$
0	7.63 ± .15
.0758	7.03 ± .21
.0957	6.96 ± .29
.1260	6.96 ± .24
.1867	6.96 ± .20
.2562	6.52 ± .38

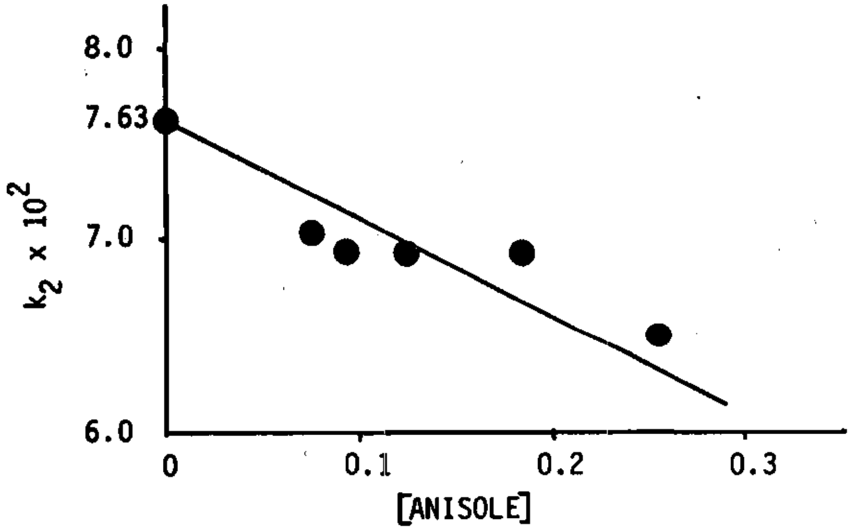


Figure 12. Depencence of the Rate of Reaction of Methoxide Ion with DNCB on Added Anisole.

CHAPTER IV

CONCLUSIONS

It is concluded that solvation effects play an important part in determining the magnitude and direction of the effect of <u>ortho</u> substituents on the reactivity of phenols and phenoxides. In strongly solvating solvents the ethyl and iso-propyl groups tend to assume a conformation of minimum steric interference of about the same steric requirement as the methyl group as the phenoxide ion approaches the transition state in aromatic nucleophilic substitution. The polar effect of the alkyl groups in this reaction series is minimal compared to the steric effect. In the halogen series the polar and steric effects have about equal importance.

CHAPTER V

RECOMMENDATIONS

This study should be extended to cover the para substituted phenols in order to obtain further information about the polar effect of these substituents on phenols. If a suitable technique could be worked out for determining the reaction rates between phenoxide and DNCB in THF, this data for the ortho alkylphenoxides would provide valuable information about the relative primary steric effect of the methyl, ethyl, and i-propyl groups.

The effect of m-dinitrobenzene on the rate of reaction of these nucleophiles needs to be determined. There is a possibility that the rates of reaction of nucleophiles with DNCB may depend upon the initial concentration of DNCB.

It is conceivable that the method presented herein for the determination of the acidity of strongly nucleophilic bases in solvents other than pure water might be of value in its own right in cases where the usual methods can not be applied.

LITERATURE CITED*

1. J. Hine, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, New York (1962), Chapter 4.

2. E. S. Gould, "Mechanism and Structure in Organic Chemistry," Holt, Rinehart, and Winston, New York, New York (1959), Chapter 7.

3. R. W. Taft in "Steric Effects in Organic Chemistry," Melvin S. Newman, Editor, John Wiley and Sons, New York, New York (1956), Chapter 13.

4. D. A. K. Jones and G. G. Smith, J. Org. Chem., 29, 3531 (1964).

5. M. M. Davis and H. B. Hetzer, J. Res. Nat. Bur. Stand. U. S. A., 60, 569 (1958).

6. C. L. Liotta, Chem. Com., 338 (1968).

7. M. T. Tribble and J. G. Traynham, private communication.

8. J. E. Seffler and E. Greenwald, "Rates and Equilibria of Organic Reactions," John Wiley and Sons, Inc., New York, New York (1963), p. 211.

9. N. B. Chapman, J. Shorter, and J. H. P. Utley, J. Chem. Soc., 1824 (1962).

10. a. H. C. Brown and A. Cahn, J. Am. Chem. Soc., 77, 1715 (1955).
    b. H. C. Brown and X. R. Mihm, ibid., p. 1723.
    c. H. C. Brown and R. R. Holmes, ibid., p. 1727.
    d. H. C. Brown and R. H. Horowitz, ibid., p. 1730.
    e. H. C. Brown and R. H. Horowitz, ibid., p. 1733.
    f. H. C. Brown and D. H. McDaniel, ibid., p. 3752.
    g. D. H. McDaniel and H. C. Brown, ibid., p. 3756.

11. J. F. Bunnett, Quart. Rev., 12, 1 (1958).

12. J. F. Bunnett and J. J. Randall, J. Am. Chem. Soc., 80, 6020 (1958).

13. L. K. Dyall, J. Chem. Soc., 5160 (1960).

---

*Abbreviations herein follow the form found in Chemical Abstracts, 50, 1J (1956).