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**NUCLEOPHILIC DISPLACEMENT REACTIONS
OF
BENZYL CHLORIDES**

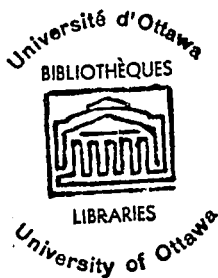
**A Thesis submitted in Partial Fulfillment of the Requirements
of the Degree of
Doctor of Philosophy**

**Department of Chemistry
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August, 1968

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PREFACE

This work is concerned with the nucleophilic displacement reactions of substituted benzyl chlorides. The effects of ortho substituents in the S_N2 reactions of benzyl chlorides were investigated. For the better understanding of the problem, the ground state structures of substituted benzyl chlorides (substrates) and substituted thiophenoxides (nucleophiles) were also examined.

Some anomalous results have been found in the reactions of 3,5-dinitrothiophenoxide and m-nitrothiophenoxide with benzyl chlorides. 3,5-Dinitrothiophenoxide and m-nitrothiophenoxide exhibit abnormally high reactivities towards benzyl chlorides. An effort was made to examine the factors which affect the rates of these reactions.

ACKNOWLEDGMENTS

The author wishes to express her appreciation to Dr. D.H. Paskovich, under whose guidance and supervision the work was carried out. She would also like to thank Dr. K.J. Laidler and Dr. R.R. Fraser for reading the manuscript and for their valuable suggestions.

The author is especially grateful to her husband for his understanding and useful discussion throughout the course of this work. To her mother the author owes a special debt for her encouragement to pursue a higher education.

The author would like to acknowledge the receipt of a Province of Ontario Fellowship and the typing of this thesis by Mrs. A. Eriksen is gratefully appreciated.

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ABSTRACT

The rates of reactions of methoxide and a series of substituted thiophenoxides with 2-methyl, 2,6-dimethyl, 4-methyl, 3-nitro and unsubstituted benzyl chloride have been measured. The pK_a values of nine substituted thiophenols were determined in methanol. The magnitude of the London interaction energy in the transition state for 2,6-dimethylbenzyl chloride was found to be approximately twice that of the observed value for 2-methylbenzyl chloride. This suggests that the effect of London interaction may be additive.

The chemical shifts of the CH_2 -groups of benzyl chloride, 2-methylbenzyl chloride and 2,6-dimethylbenzyl chloride measured in various mixed solvents indicate that ground-state solvation of the reaction center is similar for the first two chlorides. The transition-state activity coefficients for reactions of 2-methyl, 2,6-dimethyl and unsubstituted benzyl chloride with methoxide were obtained from treatment of the rate constants measured in MeOH and DMF. The results indicate that differences in transition-state solvation are small. Bunnett's adjusted rate ratio for the evaluation of London energy between the ortho substituent and the approaching nucleophile at the transition-state remains constant in various solvents and is discussed in terms of the ground state and the transition-state solvation of reactions.

The modified reaction constants, ρ_N , are estimated by plotting the logarithms of the rate constants for substituted benzyl chlorides against the corresponding values for unsubstituted chloride. The similarity of the reaction constants between o-methylbenzyl chloride and p-methylbenzyl chloride can be attributed to the polar influence which predominates over the steric effect for the ortho substituent. However, systematic deviations for the nucleophiles of m-nitrothiophenoxide and 3,5-dinitrothiophenoxide were observed in the plots mentioned above. The reactivities for these two nucleophiles increase as the electron-donating ability of the substituent of benzyl chloride increases.

The kinetic parameters were determined. Charge-transfer complex stabilization at the transition-state is proposed for the accelerating effect of m-nitro and 3,5-dinitrothiophenoxide with benzyl chlorides.

A linear relation between substituent effects and the degradation of the molecular ion $(RSSR)^{\cdot+}$ for five substituted aryl disulfides has been found.

INTRODUCTION

I. SOLVENT EFFECT ON THE NUCLEOPHILIC DISPLACEMENT REACTION

Interpretation of the change in rate of a reaction with a change in solvent remains one of the most complex problems in physical-organic chemistry. The effect of a solvent change is generally predicted by considering the extent of solvation of the initial and transition state of a chemical reaction. A convenient way of expressing these changes is provided by the Brønsted-Bjerrum equation¹:

$$k = k_0 f_A f_B / f_{\ddagger} \quad (I-1)$$

where k and k_0 are the rate constants in any solvent and the gas phase respectively, and f_A and f_B are the activity coefficients of the reagents, while f_{\ddagger} is the activity coefficient of the transition state.

A quantitative theory was developed by Hughes, Ingold and co-workers². It was assumed that solvation is essentially an electrostatic phenomenon and the energy change will be more important than the entropy change. The prediction of the change of the reaction rate caused by a solvent change was based on the charge type of the reaction. A reaction involving an increase in polarity from the initial state to the transition state should be faster in a more polar solvent. The opposite situation is also true, namely that the rate of a reaction involving a decrease in polarity in the transition state compared to the ground state will decrease as the polarity of the solvent increases. If the charges on the transition state are dispersed relative to the initial state, the rate should decrease as the solvent becomes more polar.

Many authors have attempted to correlate solvent effects with such physical properties of the solvent as dipole moment, dielectric constant and refractive index. Amongst these, dielectric constant is most commonly used.

A relationship between the dielectric constant and the rate constant is given in the equation³:

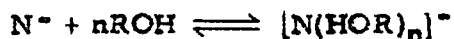
$$\ln k_2 = \ln k_0 - \frac{1}{kT} \left[\frac{(\epsilon - 1)}{(2\epsilon + 1)} \left(\frac{w_A^2}{r_A^3} + \frac{w_B^2}{r_B^3} - \frac{w^{*2}}{r^{*3}} \right) \right] + \sum \frac{\phi}{kT} \quad (I-2)$$

where k_2 is the rate constant in any solvent; k_0 is the rate constant at $\epsilon = 1$; ϵ is the dielectric constant; w_A , w_B and w^* are the dipole moments of the reagents A and B and the transition state; r_A , r_B and r^* are the radii of the reagents and the transition state; ϕ is the contribution of non-electrostatic forces; k is the Boltzmann constant and T the temperature. The change of free energy of activation was proposed⁴ as a function proportional to $(\epsilon - 1)/(2\epsilon + 1)$. In the Menschutkin reaction, the logarithm of the rate gives an excellent linear plot against $(\epsilon - 1)/(2\epsilon + 1)$ for many systems⁴. If, however, benzene derivatives such as chlorobenzene are used as the solvent, the resulting displacement rate is higher than that obtained by using aliphatic derivatives such as propyl chloride, although both have approximately the same dielectric constant. It appears that this relationship breaks down even qualitatively in some cases^{5,6}. The rate enhancement in benzenoid solvents is probably due to the further stabilization of the transition state by the high polarisability of the π -electrons of the aromatic ring.

Solvents are not continuous media with a bulk dielectric constant⁷. In the vicinity of the reacting species, individual solvent molecules play an important specific role⁸. Application of equation (1-2) is limited by the fact that ϕ is assumed to be small or constant. The deviation is essentially due to selective solvation as a result of greater interaction between the molecules of the solute and the solvent.

Solvent effects on the reaction rate vary in a very complex manner from reaction to reaction and it is not possible to correlate the solvent effects with any single property of the solvent. The effect of a solvent can be classified on the basis of its effects on certain parts of the reactant, e.g. the leaving group, anion and macroscopic properties of the solvent. The classifications are rather arbitrary but useful for discussion. For example, a solvent can affect the bond rupture of the leaving group and it may also affect the nucleophilicity of the nucleophile.

(a) Solvation of the anion: Anionic reactions are much faster in dipolar aprotic solvents than in the protic solvents⁸. When an anion is dissolved in a protic solvent, it may act as a hydrogen-bond acceptor for the solvent molecules:



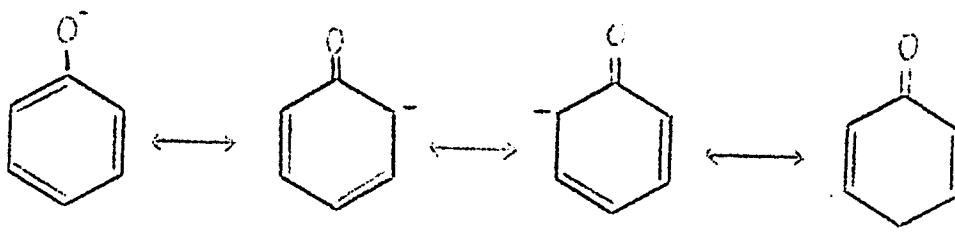
It has been proposed that this hydrogen-bonded anion $[N(HOR)]^-$ exerts rate-diminishing influences which increase as the hydrogen-bonding ability of the anion increases⁹. Rate constants for aromatic nucleophilic substitution reactions in dipolar aprotic solvents are 10^5 times greater than for reactions in protic solvents⁹. Similarly, substitution reactions of anions at saturated carbon centers such as methyl iodide¹⁰ increase by a factor up to 10^7 as the hydrogen bond capacity of

the solvent decreases from water to dimethyl formamide (DMF). The corresponding solvolysis rates are little influenced by this same solvent change. The susceptibility of the anion to solvent change is in the order $F^- > Cl^- > CN^- > Br^- > N_3^- > I^- > SCN^- > \text{picrate}^-$. This corresponds roughly with their increasing size and polarizability and decreasing tendency to form hydrogen bonds with protic solvents¹⁰. Parker also investigated the effects of changing from protic to aprotic solvents for nucleophiles containing group VI elements. He found that the nucleophilic tendencies decrease in the series $SeCN^- > SCN^-$ and $PhS^- > PhO^-$ in both protic and aprotic solvents. This behaviour is attributed in part to the so-called nucleophilicity of the nucleophile, rather than to differential solvation of the nucleophile.

Tommila and co-workers have studied the alkaline hydrolysis of ethyl acetate¹¹ and benzoic ester¹² in mixed solvents of dimethyl sulfoxide-water. The rate of the reaction increases as the water composition of the solvent decreases. The rate enhancement is especially pronounced at high dimethyl sulfoxide concentration when the mole fraction of DMSO exceeds about 0.3. The rate increase was attributed to an increase in the activity of the hydroxide caused by its reduced solvation in the presence of DMSO. In the case of alkaline hydrolysis of substituted benzoic ester in acetone-water¹³, the rate decreases at first with decreasing water concentration, but then increases when the mole fraction of acetone exceeds 0.5. No corresponding increase is evident in the rate in a dioxane-water solvent system. Tommila proposed that the ratio of water molecules to acetone

molecules becomes greater than about 0.5; probably most of the water molecules are bound (by hydrogen bond) to acetone in a 1:1 complex. A further increase of the mole fraction of acetone causes partial desolvation of the hydroxide anion.

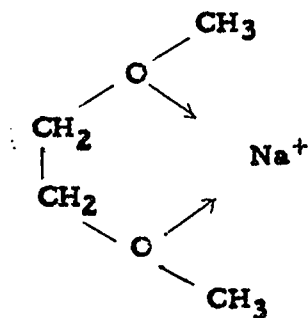
Further experimental evidence indicating the importance of solvation on the reactivity of anions comes from the work of Kornblum¹⁴. He reported that the reaction of phenoxide or p-alkylated phenoxide in a wide variety of solvents with benzyl chloride gives aryl ether as the sole product. When these reactions are conducted in water, phenol or fluorinated alcohol, a substantial amount of o- and p-alkylated products results. Thus, the phenoxide ion is capable of bond formation at oxygen or at ortho- and para- ring carbon atoms.



When phenoxide is dissolved in water, phenol, fluorinated alcohol or other substances which form strong hydrogen bonds, the oxygen of the phenoxide is so intensely solvated that the availability of the oxygen anion for nucleophilic displacement is greatly decreased. As a consequence, displacement takes place at the otherwise unfavored ortho and para carbon atoms.

(b) Solvation of the cation: Anions and cations require different solvating characteristics of the solvents⁸. Whereas hydrogen bonding solvents are good anion solvators, solvents containing atoms having unshared electron pairs such as oxygen and nitrogen are generally good cation solvators.

Zaugg and co-workers have shown specific solvent effects on the cation of the enolate nucleophile in the alkylation by an alkyl halide^{15, 16, 17}. The pseudo first-order rate constant for the alkylation of sodio-n-butyl malonic ester with n-butyl halide in benzene solution is greatly accelerated by adding small amounts of many polar additives such as di-substituted amides. The striking rate acceleration is thought to be produced by specific solvation of the sodium ion by polar additives which tend to dissociate the high-molecular-weight ion-pair aggregates of the sodio-derivatives that exist in benzene solution¹⁵. Further evidence of a specific solvent effect is the six-fold rate difference between the alkylation reaction run with tetrahydrofuran (THF) and ethylene glycol dimethyl ether as the additive. Both additives are, of course, aprotic and, further, possess nearly identical dielectric constants (7.3 D for THF and 6.8 D for glyme). The marked difference in the rates observed in these solvents was ascribed to the increasing ability of monoglyme to solvate sodium ion by a bidentate donor mechanism:



Although 1,4-dioxane and 1,3-dioxolane are diethers like monoglyme, their ring structure prevents them from having a conformation as shown above. Lacking this ability, they behave more like THF as cation solvators and have little catalytic activity. The alkylations of potassium and sodium phenoxide with butyl halide have been studied in THF, dimethyl ether of ethylene glycol and polyethylene glycol dimethyl ether¹⁷. In tetraethylene glycol dimethyl ether the reaction rate is about 150 times higher than in the monoglyme. The rate in THF is only 1/8 of that in the monoglyme. The rates of the reactions increase markedly with the increasing chain length of the glycol ethers, as shown in the following table:



| Solvent | Dielectric Const. | Relative Rates |
|-------------|-------------------|----------------|
| Mono-EGDME | 6.99 | 1 |
| Di-EGDME | 7.27 | 12 |
| Tri-EGDME | 7.51 | 117 |
| Tetra-EGDME | 7.68 | 154 |

The dielectric constants of the various polyethylene glycol dimethyl ethers are all very similar. Hence the great variation in rates of reaction observed in different ethers cannot be explained from the small change in dielectric constants. These striking rate

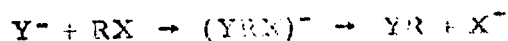
changes were attributed to the short range interaction between ether oxygen atoms and alkali ions in the solvation process. The increase of rate with increasing chain length of the glymes was thought to arise from the ability of several oxygens in one molecule to act as ligands for the cation.

(c) Solvation of the transition state: Miller and Parker proposed that large polarizable charged transition states are more solvated in aprotic solvents than in protic solvents⁹. When solvation is made by the small unshielded proton of the protic solvents, steric resistance is negligible, so that small anions are highly solvated by the close fitting of the dipoles of the solvents.

Roberts and co-workers studied the influence of aqueous dimethyl sulfoxide on various saponification reactions^{18, 19}. It was found that the rate constants in all cases increased with increasing dimethyl sulfoxide content. The rate constant increases for the branched ester are proportional to the DMSO content over the entire solvent composition range. In the case of alkaline hydrolysis of ethyl esters (RCOOC_2H_5 , R groups vary), the rate constant increase for the straight chain esters are also sensitive to the DMSO content of the solvent¹⁸. A similar situation was found in the hydrolysis of alkyl benzoate ($\text{C}_6\text{H}_5\text{COOR}$, R groups vary). The branched alkyl benzoates fail to exhibit deviations from linearity in plots of $\log k$ vs. M_{DMSO} (mole fractions of DMSO) for the effect of DMSO concentration on reaction rates. It appeared that a major portion of the solvent was associated with the dramatic influence of DMSO upon the solvation shell geometry. The larger solvation shell of DMSO is better able to accommodate the loose, polarizable transition state and

is sterically insensitive to specific solvation for the branched chain ester, i. e. the rate is linearly related to dielectric constants and the solvent sensitivity values are nearly constant for large steric variations in the branched chain esters.

The relative hydrogen-bonding solvation of the transition state has been estimated by Parker²⁰ on the basis of a proposed relation to the activity coefficient of the transition state complex. The specific rate constant k_s of the general reaction in a solvent s is given by the equation:



$$k_s = k_0 \frac{\gamma[Y] \gamma[RX]}{\gamma[YRX]^-} \quad [I-3]$$

where k_0 is the specific rate in a standard solvent and γ is an activity coefficient referred to this standard state. The activity coefficient as defined, referred to this standard state of 1M-solute in dimethyl formamide. Equation [I-3] then becomes:

$$k_m = k_d \frac{\gamma^*[Y] \gamma^*[RX]}{\gamma^*[YRX]^-} \cdot \frac{\gamma^{II}[Y] \gamma^{II}[RX]}{\gamma^{II}[YRX]^-} \quad [I-4]$$

where k_m and k_d are specific rates in methanol and in dimethyl formamide respectively. The activity coefficient γ, γ^{II} accounts for all interactions between nucleophile and methanol other than the hydrogen bond donation of the two reactants and the transition state respectively. Because methanol and DMF have similar bulk dielectric constants,

it is assumed that the non-hydrogen bonding interactions would be the same in both solvents, hence:

$$\frac{[\gamma_{[Y]}^* - \gamma_{[RX]}^*]}{\gamma_{[YRX]}^*} \approx 1$$

Since RX is a neutral molecule, it would not have a hydrogen-bonding interaction with methanol comparable in strength to that between Y⁻ and methanol:

$$\gamma_{[RX]}^H \approx 1$$

Equation (I-4) may then be simplified to:

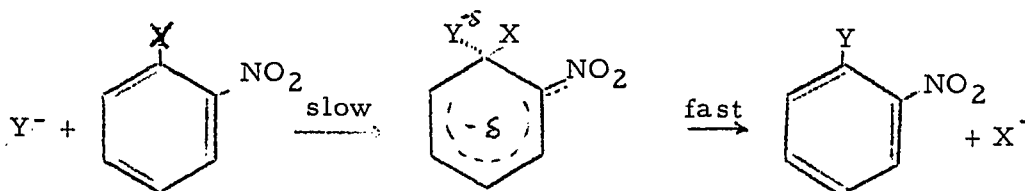
$$k_m/k_d = \gamma_{[Y]}^H / \gamma_{[YRX]}^H$$

A comparison between specific rates, k_d , of reactions of methyl chloride with nucleophile Y⁻ and specific rates, k_I , of methyl iodide with the same nucleophile Y⁻ give the hydrogen-bonding activity coefficient of the transition state complex $\gamma_{[YCH_3I]}^H$ (for the transition state complex of Y⁻ with methyl iodide).

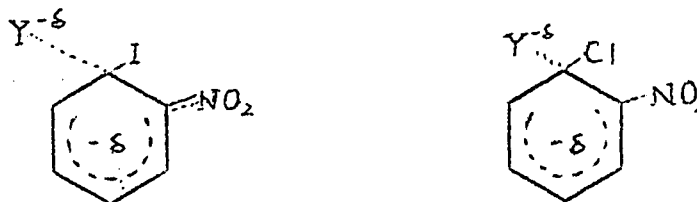
$$\frac{k_I^m}{k_I^d} \frac{k_{Cl}^d}{k_{Cl}^m} = \frac{\gamma_{[Y]}^H}{\gamma_{[Y]}^H} \frac{\gamma_{[YCH_3Cl]}^H}{\gamma_{[YCH_3I]}^H} = \frac{\gamma_{[YCH_3Cl]}^H}{\gamma_{[YCH_3I]}^H}$$

It was found that the transition state solvations are in the order $(YCH_3Cl)^- > (YCH_3Br)^- > (YCH_3I)^-$ by methanol relative to dimethyl formamide. The chlorine-containing transition state

$(YCH_3Cl)^-$ has a stronger hydrogen-bonding interaction with methanol than does the corresponding larger, more polarizable, iodo-containing transition state $(YCH_3I)^-$. Thus, other things being equal, nucleophilic displacement reactions of alkyl chlorides tend to be relatively faster in methanol than the corresponding reactions of alkyl iodides. For S_NAr reactions, such as the nucleophilic displacement reaction of 2-nitro halobenzenes, the bond forming is considered to be the rate limiting step.



It appears that the transition state of $(YArCl)^-$ is less solvated than $(YArI)^-$ by methanol. This is attributed to the negative charge on Y^- being more localized in $(YArI)^-$ than $(YArCl)^-$, as shown in the following structures:



(d) Solvation of the leaving group: The presence of some complexing agents in nucleophilic reaction mixtures is known to facilitate the rate if the agent forms a complex with the leaving group. The rate of the reaction between methyl bromide and pyridine is enhanced by the addition of a small amount of not only halogen-complexing agents such as HgBr , AlBr_3 , but also of such hydrogen bonding agents as methanol, phenol and p-nitrophenol²¹. Miller and Parker¹⁹ reported that the reaction of sodium azide in DMF with 4-fluoronitrobenzene proceeded until a mole of azide per mole of 4-fluoronitrobenzene was consumed. A deep red colour was produced, but no sodium fluoride was precipitated. The addition of 5 ml of water per 100 ml of DMF caused the precipitation of sodium fluoride. It was concluded that a stable intermediate sigma complex is first formed which only liberates fluoride when a protic solvent is available to "solvate off" the fluoride ion.

The second type of interaction between the solvent and the leaving group is the London interaction. Reinheimer²² observed that the polarizability of the solvent has a significant influence on the reaction rate in the Menschutkin reaction. The rate of the reaction of pyridine with ethyl bromide in monosubstituted benzene as solvent was shown to increase with the increasing polarizability of the substituent group on the benzene ring of the solvent²². The rate increase was attributed to the London energy of interaction between the polarizable solvent molecules and the leaving halogen atom. Rate constants plotted against the polarizability of the substituent on the benzene ring gave a linear relationship. Calculation of the London energy based on theoretical models was compared with the experimental

value obtained from the rate. These comparisons indicate that the London energies of interaction are of the correct order of magnitude to account for the observed rate changes.

(e) The effect of ion-pairing: When dissociation of the reacting salt in the solvent is incomplete, ion pairs and more complex aggregates are present. The rate of displacement reactions for such ion paired nucleophiles increases as the dielectric constant of the solvent increases²³⁻²⁴. For such solvents the equilibrium between the ion-pairs and the separated ions



is thought not to be displaced completely to the right. The existence of this phenomenon is also manifested by an increase in the second order rate constant with a decrease in the total concentration of the ionic reactant. The reactivity of the ion-pairing species remains a controversial problem. Early studies made by Acree^{23,24} reported that the ion-pairs have comparable reactivity. Hughes, Ingold and co-workers, however, considered the increase in rate at lower salt concentrations as a salt effect^{25,26}.

The importance of ion-pair association in controlling apparent nucleophilicity becomes experimentally observable²⁷ when the reactivity of lithium halide and tetrabutyl ammonium halide with n-butyl p-bromobenzene sulfonate in acetone is compared. With lithium halide the order $I^- > Br^- > Cl^-$ is observed, while the reverse order is obtained for the tetrabutyl ammonium halides. These results are explainable by considering that the tetrabutyl ammonium salt is dissociated to a greater extent than the lithium salt, and that

the relative reactivity of the latter is controlled by the degree of ion pairing. This suggests that the nucleophilicity order of the non-ion paired anion in acetone is actually $\text{Cl}^- > \text{Br}^- > \text{I}^-$.

Lichtin²⁸ analyzed the rate constant for free ions (k_f) and associated species (k_p) for the exchange reactions of p-nitrobenzene bromide with Br^{32} . The salts used to study this exchange were lithium bromide and tetraethyl ammonium bromide. The data was analyzed and was consistent with the rate law $R_e = k_f(\text{RBr})(\text{Br}^-) + k_p(\text{RBr})(\text{M}^+\text{Br}^-)$. It appears that k_f is independent of the nature of the cation.

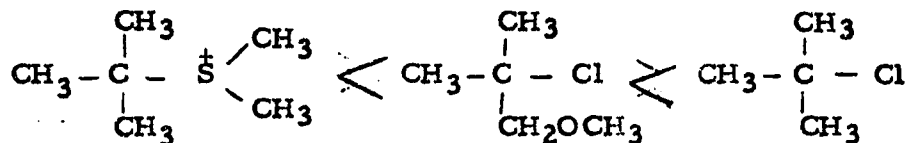
Weaver and Hutchison²⁹ considered that ion pairs are kinetically unreactive. The rate order for the reaction of halide with methyl toluenesulfonate in DMF is $\text{I}^- < \text{Br}^- < \text{Cl}^-$. This is the reverse of the order in aqueous solution. In Weaver and Hutchinson's opinion³⁰, the polarizability seems unnecessary as an explanation for the nucleophilic order usually observed in protic solvents for the halide anions. The view that protic solvents have a retarding effect seems to be much more consistent. They argued that their assumption concerning the kinetic unreactivity of ion pairs can be justified by the fact that alkyl iodides can be prepared by the reaction of alkyl chloride with lithium iodide in acetone³⁰. Even though the reactivity of chloride ion is greater than that of iodide ion and the reactivity of alkyl iodides is greater than alkyl chlorides, in acetone the equilibrium is displaced toward the formation of alkyl iodide. This must result from the ion pairs of the predominantly associated lithium chloride being kinetically unreactive.

(f) The effect of solvent sorting: Both the ionic and dipolar types of solute will tend to be solvated by the more polar component of the binary mixture. As a less polar component of the solvent is added, the composition of the immediate environment of the solute species will be unaware of the change in the bulk composition until a sufficient amount of the less polar component has been added to overcome the selectivity of the solute for the more polar component. It was proposed that the activation energy will pass through a maximum or a minimum value with change in solvent composition³¹. Hyne has studied the variations in activation energy of reactions with various mixed solvents. The solvolyses in ethanol-water mixture of sulfonium salts and alkyl halides represents the two kinetic cases of ion to "dipole" and dipole to "ion" in moving from initial to transition state. The former shows a maximum in the activation energy and the latter a minimum. The greater the difference in charge density between the initial and transition state, the greater will be the minimum or maximum.

Hyne and co-worker³² also reported the temperature dependence of the energy minimum in the solvolysis of benzyl chloride in ethanol-water mixture. As the temperature is raised, the additional thermal energy in the system will render it increasingly difficult for the solute in both the initial and transition state to maintain the specificity of solvation as the mole fraction of non-aqueous component is increased. As a consequence, the solvent independent ranges of energies of both states will be diminished and the difference between the activation energies will decrease.

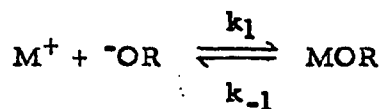
The effect of solvent sorting on the activation energy of nucleophilic displacement reactions has also been reported. When an attack of an anion upon a neutral molecule results in a dispersal of charge in the transition state, the activation parameters of such reactions pass, in general, through a maximum when the relative amounts of the component in a binary solvent mixture are continuously varied^{31, 33, 34}. A qualitative relationship between the substituents of p-substituted benzyl chloride in solvolysis and the depth of the activation minimum $\Delta\Delta E^\ddagger$ was made. The value of $\Delta\Delta E^\ddagger$ increases as σ^+ decreases, indicating the effect of the various substituents in enhancing charge development in the transition state and so favoring the specificity of solvation.

(g) Effect of solvent structure: Robertson³⁵ proposed that part of the energy requirement in the activation process is the work required to break down the initial state solvation shell. This hypothesis is supported not only by the existence of large negative heat capacity changes, but also by the difference in the kinetic solvent isotope effect. In the solvolyses of some tertiary butyl compounds which weakly interact with the initial state water shell, less work will have to be done in disorganization of this shell in the activation process and ΔC_p^\ddagger will be reduced accordingly. The negative value for the hydrolysis of the following compounds increases in the order



The ratios $k_{\text{D}_2\text{O}}/k_{\text{H}_2\text{O}}$ also decrease as the negative ΔC_p^\ddagger values increase.

Other evidence for this effect was found in the nucleophilic displacement reactions by Ritchie and co-workers³⁶⁻³⁷. The rate constant for the reaction of malachite green [4,4'-bis-(dimethylamino)triphenylmethyl tetrafluoroborate] with base was shown to increase by a factor of 6×10^2 on going from water to methanol.³⁶ In water solution, hydroxide was used as the nucleophile, while in methanol methoxide was used instead of hydroxide. The corresponding rate increase for p-nitromalachite green was 10^3 for the change of solvent from water to methanol. The nucleophilicity of hydroxide and methoxide are known to be quite similar. The change in the rate observed must be ascribed to a solvent effect. The change of the solvent from water to methanol also causes an increase by a factor of 63 in the rate of dissociation of product for malachite green and 24 for p-nitromalachite green. The rate of dissociation of the product was calculated from the equilibrium constants of the reactions:



M^+ = carbonium ion of malachite green derivatives

$$K_d = k_{-1}/k_1$$

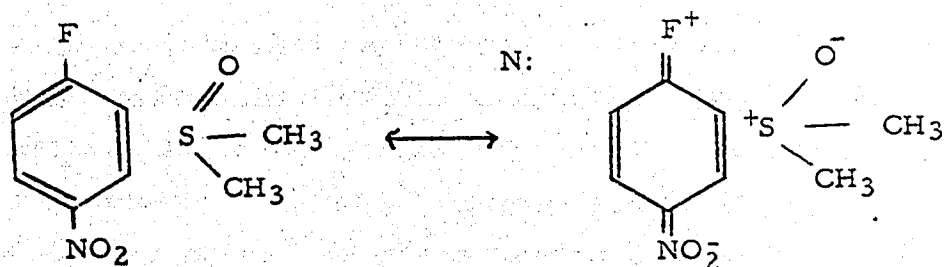
$\text{}^-\text{OR} = \text{}^-\text{OCH}_3 \text{ or } \text{}^-\text{OH}$

Both the forward and reverse reaction rates are found to change in the same direction. It was postulated that solvent reorganization is a significant contribution to the reaction process. The solvent molecules which are hydrogen bonded or otherwise associated with ions in the reactant state, and which are associated with other solvent molecules in the final covalent state, are at least partially free and in the process of reorganization at the transition state. The ground state nucleophile desolvation may be one of the factors in the rate increase of the forward reaction. Since both forward and reverse rates are affected in the same direction, it cannot be explained on this basis alone.

Kingsbury's catalytic effect of dimethyl sulfoxide has a similar significance although he did not emphasize the term "solvent structure" at that time³⁸. In the nucleophilic aromatic substitution reactions in dimethyl sulfoxide-water mixtures, a significant rate increase occurs even at low DMSO concentration. The rate increase is associated with a decrease in ΔH^\ddagger . The change in ΔS^\ddagger is small. An excellent linear plot of $\log(k_{obs} - k_0)$ vs. (DMSO) was observed:

$$\log(k_{obs} - k_0) = r(\text{DMSO}) + C$$

The DMSO catalysis is independent of the charge which the nucleophile bears. This argues against any mechanism in which DMSO alters the solvation of the ion in the ground state. Two possibilities were proposed for the DMSO mechanism of catalysis. The first proposal suggested that the substrate is polarized by a random DMSO molecule and that the polarized dipole substrate is more readily attacked than the unpolarized species.



The other possibility considered is that the hydrogen bond acceptor ability of the DMSO component breaks up the pseudo-polymerized structure of the methanol into smaller aggregates. This solvent cage may be able to accommodate the charge dispersal more easily than the methyl alcohol cage. Upon the addition of a tetraethyl ammonium salt, which is considered to be "order destroying", there is an enhancement of the rate, while an "order producing" lithium salt decreases the rate.

II. EMPIRICAL CORRELATIONS

Since the efforts to correlate the reaction rate with the physical properties of the solvent such as dielectric constant or refractive index³⁹ can only be applied with limited success, attempts have been made to obtain such relationships by experiment. Various workers sought to draw conclusions about the polarity of a solvent by working backward from the effect of a solvent on a solvent-dependent standard process, and to derive empirical parameters of the solvent from the rate constant or absorption maxima determined in solvents. Reichardt offered a review⁴⁰ on empirical parameters of the polarity of solvent.

(a) The Winstein-Grunwald equation: Grunwald and Winstein⁴¹ investigated the solvolysis of aliphatic compounds. A quantitative measure of the ionizing power of a solvent and the solvolysis is given by:

$$\log k_A/k_B = m (Y_A - Y_B) \quad (I-5)$$

where k_A and k_B are the rate constants of an S_N1 solvolysis in solvent A and B, m is a constant at a given temperature and is characteristic of the substrate. The standard state was defined as the solvolysis of *t*-butyl chloride at 25° in 80% by volume of aqueous ethanol. $Y = \log k^t\text{-BuCl} - \log k_o^t\text{-BuCl}$.

By definition, the Y value for 80% aqueous ethanol is zero and m for *t*-butyl chloride is 1.00. This equation can be applied satisfactorily to the rate of solvolysis of certain tertiary halides and primary derivatives which react by S_N2 mechanisms. If Y is plotted

against $\log k$ for the solvolysis of benzhydryl or neophyl chloride in various binary mixtures, each mixture gives a different straight line. Ion pair return which depresses the observed solvolysis rate below the ionization rate by various amounts depending on the nature of the solvent, contributes to the observed dispersion in some cases^{43, 42}. Thus the parameter m which is supposed to be independent of the solvent must contain another factor which is a measure of the nucleophilic character of the solvent.

(b) Swain has proposed a four parameter equation⁴⁴ that correlates the rate of solvolysis with both ionizing power and nucleophilic participation of the solvent:

$$\log k/k_0 = c_1d_1 + c_2d_2 \quad (I-6)$$

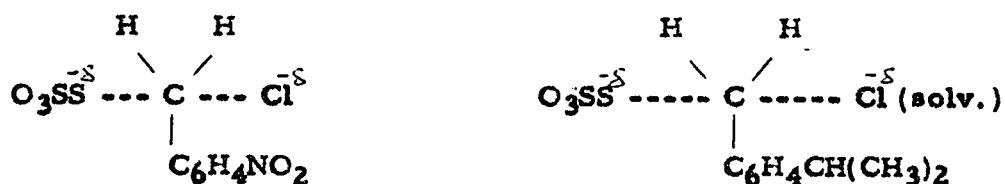
The parameters d_1 and d_2 are the measures of solvent nucleophilic and electrophilic character, respectively, and c_1 and c_2 are the measures of substrate sensitivity to those solvent characteristics. k is the first-order rate constant for solvolysis of any compound in any solvent, and k_0 is the corresponding rate constant in a standard solvent 80% ethanol. The application of Swain's equation, which includes the nucleophilic character of the solvent, is broader than Winstein's $m Y$ equation. Because of the fundamental difficulties associated with the numerical treatment, a value of $c_1/c_2 = 300$ was arbitrarily assigned for the substrate methyl bromide; hence the derived c_1 parameters must be regarded as completely empirical⁴³ and as having no mechanistic significance as measures of the substrate sensitivity to the nucleophilic character of the solvent.

(c) Miscellaneous parameters: Other parameters derived from various sources such as X-values from electrophilic aliphatic substitution on a saturated carbon atom, Ω -values from the rates of Diels-Alder reactions, Z-values from the charge transfer absorption of 1-alkylpyridinium iodides and E_t -values from the solvatochromic band of pyridinium N-phenolbetaine have been discussed by Reichardt⁴⁰.

III. SOLVENT EFFECT ON NUCLEOPHILIC DISPLACEMENT REACTION OF BENZYL HALIDE

Early studies on the kinetics of displacement reactions between p-nitrobenzyl halides and lithium halides in an acetone-water mixture⁴⁵ and in dioxane-water solutions⁴⁶ were known to be greatly influenced by the nature of the solvent in which they took place. In a plot of $\log k_2$ vs. $1/D$ (reciprocal dielectric constant of the solvent) there was a maximum at approximately 1:1 composition of the above solvent mixtures. The result was explained as follows. In dioxane-rich solvents, the reactant lithium chloride is present for the most part as associated ion pairs. As the water content of the solution increases, the dissociation of the ion pairs increases, and the dissociation is complete in a 1:1 water-dioxane mixture. When the water content of the mixed solvent is increased, two factors are operating in this system: (a) the dissociation of the ion-pair which will increase the rate, and (b) the increase of the dielectric constant of the solvent will decrease the rate. These competing effects are apparent from the existence of the maxima of the curves.

The solvent effect on reactions of benzyl halides has been shown to be a function of its substituents. Fuchs⁴⁷ reported the rate of reaction of p-substituted benzyl chloride with sodium thiosulfate measured in 60% bis(2-methoxyethyl)ether - 40% water and 60% ethanol - 40% water mixtures. The rate ratio in the two solvents (k_d/k_E) varies from 2.71 for the nitro compound to 0.95 for the isopropyl compound, and appears to be a linear function of the σ -values of the substituents. The transition state for the nitro compound was said to be relatively tight, with considerable S-C and S-Cl covalent bonding and little solvation. At the other extreme, the transition state involving the isopropyl compound has relatively weak S-C and S-Cl bonding with rather long bond distances:



In the case of the isopropyl compound, there is relatively little loss of solvation energy accompanying the formation of the transition state. Fuchs and co-worker⁴⁸ also studied the solvent effect on the change of reaction constant (ρ) of benzyl chlorides. The reactions of p-substituted benzyl chlorides with thiosulfate were measured in 40% water - 60% organic solvent in order to keep the concentration of the solvating solvent constant. There is no simple relationship between absolute rates and dielectric constants of the solvents, nor is there any particular tendency for the reaction to proceed faster in solvents of

relatively low dielectric constants or of low water content, but the Hammett ρ -values are found to be a linear function of $1/D$ for the majority of the solvents (a plot of $\log k_{\text{NO}_2}/k_{\text{H}}$ vs. $1/D$ is linear).

Tommila and co-workers reported the influence of the solvent on the rates of reactions of benzyl chlorides with methoxide⁴⁹ and hydroxide ion³³ in dimethylsulfoxide-methanol mixtures. Addition of DMSO to the solvent results in an increase in the reaction rate. The rate enhancement is considerable at low DMSO concentration and very great at high DMSO concentration when the mole fraction reaches 0.5. Tommila suggested that most of the methanol is bound to DMSO in a 1:1 complex. On further addition of DMSO, the methoxide nucleophile is deprived of its solvating shell of methanol. At high DMSO concentration, a plot of $\log k$ vs. $\log (\text{MeOH})$ is a good straight line with slope -2.0 when the methanol concentration is less than 200 ml per liter:

$$dx/dt = k_0(a-x)^2 + k_1(\text{MeOH})^n(a-x)^2$$

$$= k_{\text{obs}}(a-x)^2$$

$$\log (k_{\text{obs}} - k_0) = n \log (\text{MeOH}) + \text{constant}$$

where k_{obs} is the rate constant in the mixed solvent and k_0 is the rate constant in 100% DMSO.

At low concentration of DMSO in the range from pure methanol to a mole fraction of about 0.5 of DMSO, dimethyl sulfoxide was found to have catalytic activity:

$$\log (k - k_0) = r(\text{DMSO}) + \text{const.}$$

where k and k_0 are the rate constants in mixed solvent and pure methanol respectively, and r is a measure of the sensitivity of a given system to the catalysis by DMSO. The value of r was found to be relatively independent of the system involved.

IV. NUCLEOPHILIC REACTIVITY

The term "nucleophilic" was defined by Ingold⁵⁰ as "nucleus seeking" or "positive center seeking". A nucleophile is a reagent which supplies a pair of electrons to form a bond between itself and another atom. This is similar to the Lewis definition of a base. To avoid confusion basicity is defined as thermodynamic affinity for a proton while nucleophilicity pertains to kinetics (rates). This discussion will be restricted to the affinity of the nucleophiles for carbon only or, in Parker's term, "carbon basicity".

The factors determining nucleophilic reactivity have been discussed by several authors. Edwards and Pearson⁵¹, Edwards^{52, 53} and Bunnett offer excellent reviews⁵⁴ on this topic. The general factors can be summarized as follows:

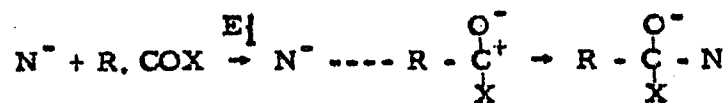
(a) Correlation with base dissociation constant: The rates of certain displacement reactions sometimes parallel the affinities of the nucleophiles (N^-) for protons. The more basic a nucleophile toward a proton, the better it acts as a nucleophilic reagent. The pK_a values of nucleophiles are correlated with rate constants by the equation:

$$\log k = \beta \text{p}K_a + \text{const.}$$

where k is the rate constant of the nucleophile, and $\text{p}K_a$ is the dissociation constant of the nucleophile. The slope of the plot, β , is a measure of the degree of bond formation in the transition state. This parameter is similar to the Hammett rho value, but opposite in sign. For the purposes of better defining β , let us consider that the reaction of N^- with a proton to form a full bond represents the maximum degree of electron supply by N^- . For displacement reactions on carbon atoms, however, the formation of $\text{N} \cdots \text{C}$ partial bonds in the transition state is considered to have less demand for electrons than if a full bond were formed. Hence, the lesser degree of $\text{N} \cdots \text{C}$ bond formation in the transition state, the less sensitive the reaction rate would be to the electron density at N^- . Consequently, a higher β value implies a greater degree of bond formation in the transition state. Hudson and Loveday⁵⁵ have shown that the Brønsted relation holds for the alkylation of 3-bromopropanol with para-substituted phenol and the acylation with ethyl chloroformate. The low exponents observed for alkylations ($\beta = 0.22$) and high exponents for acylation ($\beta = 0.78$) were interpreted in terms of the above electrostatic treatment. It was assumed that the $\text{S}_{\text{N}}2$ transition state was formed by stretching the C-X bond, which requires energy E_1 , followed by interaction with the nucleophile:



The transition state for acylation is assumed to be similar to that of the sp^3 -hybridized intermediate:



If the charge on the nucleophile N is z and that on the carbon atom is δ , then

$$\Delta E^* = E_1 + z\delta / r_1 \epsilon \quad (I-6)$$

where ΔE^* is the activation energy; E_1 is the energy for the polarization of the C-X bond; r_1 is the N-C bond length, and ϵ is the dielectric constant of the medium. For the combination of a proton with N^- , the heat of the reaction ΔH is given by the equation:

$$\Delta H = z/r_0 \epsilon \quad (I-7)$$

Combination of equations (I-6) and (I-7) gives

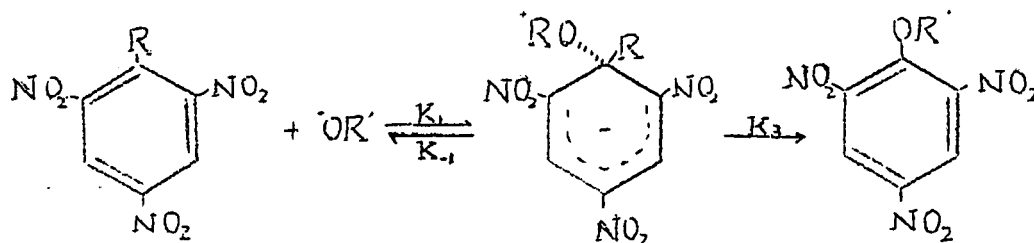
$$\Delta E^* = (r_0/r_1) \cdot \Delta H + \text{const.}$$

or

$$\log k = (r_0/r_1) pK_a + \text{const.} \quad (I-8)$$

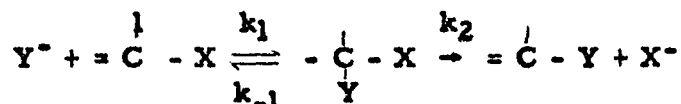
From equation (I-8) one could expect a higher slope for the acylation in the Brønsted plots, because it involves a tetrahedral transition state with a greater degree of bond formation than in the case of alkylation. In his review, Bender⁵⁶ gives several reactions involving carboxylic acid derivatives and various nucleophiles to which the Brønsted relation is applicable. It appears that if only limited structural changes of the nucleophiles are made in the families of substituted phenoxide, pyridines, imidazoles, amino acids or aniline, then a plot of the $\log k$ vs. pK_a of the nucleophiles should give a straight line.

Murto has presented examples^{57, 58, 59} for the application of the Brønsted equation to the S_NAr reactions. Specifically, the reactions of 1-substituted 2,4-dinitrobenzene or picrylic compounds with nucleophiles were studied.



The slopes of the Brønsted equation for the reactions of 2,4-dinitrophenyl compounds are similar to those of the reactions of picryl compounds, although the latter are 10^3 - 10^4 times faster than the former. The low β values found were interpreted as an indication that the extent of bond formation in the first transition state is small. The constancy of the β value for two reactions, despite a decrease in nitro group activation, implied that at least the initial stages of the reaction are very similar, irrespective of the extent of nitro activation. The view that the bond formation of the first transition state is small is also supported by the positive curvature of the plot $\log k$ vs. pressure for alkaline hydrolysis and methanolysis of dinitrofluorobenzene. These data implied that the compressibility of the rate determining transition state is greater than that of the initial state, i. e. the transition state is a loose complex.

Bunnett and co-worker⁶⁰ discussed the effect of carbon basicity of the nucleophiles on the rate of substitution at an unsaturated center:



when $k_{-1} \gg k_2$, $k_{\text{obs.}} = (k_1/k_{-1})k_2 = K_{\text{eq.}}k_2$. The overall rate coefficient is the product of an equilibrium constant times k_2 . It appeared that the overall rate of displacement of a constant substituent X by various nucleophiles is dependent principally on their thermodynamic affinities for carbon. The fluoride ions, alone among halogen anions, displace p-nitrophenoxide ion from p-nitrophenyl acetate.

(b) Polarizability: The extraordinarily high reactivity of sulfur bases RS^- as compared to RO^- of the same basicity indicates that the process of base dissociation is not a sufficiently complete model for nucleophilic reactivity. The polarizable molecules or ions are more reactive than one would expect from their basicity. How the polarizability affects the reaction rate was discussed by Edwards and Pearson⁵¹. If one examines the process of binding a proton to a base, the proton will seek out the position in the molecule which has the greatest electron density. This density will be partly the result of the original charge distribution and partly the result of the redistribution caused by the electric field of the proton. It has been calculated by quantum mechanical perturbation methods that the perturbation of the original electron density by a proton is not great. The proton is unique as it can be placed in the most favorable region almost without restriction. Where any other substrate reacts with N,

N will be seriously restricted by the electrons which the substrate (S) possesses. Repulsion between the electrons of N and the electrons of S will raise the energy rapidly as N and S are brought together. This is brought about by the operation of the Pauli exclusion principle. Two factors must be considered when one is attempting to explain the increase of rate in a displacement reaction, when a less basic, but more polarizable nucleophile is used.

The first factor is the polarization of bonding electrons occurring in the direction from N towards S. This permits better electrostatic interaction without bringing in Pauli exclusion effects due to the rest of the N molecule, as explained. The second factor to be considered is the polarization of non-bonding electrons on N away from S. Certain highly reactive nucleophiles are characterized by having empty orbitals available which are relatively low in energy. These empty orbitals can be used to accommodate some of the non-bonding electrons of the atom N in the transition state. The additional possibility exists that in some cases these empty orbitals can be used to hold some of the electrons on the substrate S⁵¹.

Since nucleophilicity cannot be correlated with a single property of the nucleophile, Swain and Scott⁶¹ derived a nucleophilic parameter from the empirical treatment in which the reaction of methyl bromide with water at 25° was used as the standard:

$$n = \log k_n/k_o$$

where k_n and k_o are the rate constants for the reaction of MeBr with nucleophile and water respectively. If the reactions for other substrates were made, the equation would become:

$$\log k_n/k_o = sn$$

where s is the susceptibility of the substrate. This equation can be applied for the reactions of mustard ion with various nucleophiles and also for several other systems⁶². The fit to this equation is poor in some cases. In order to justify these facts, it was concluded that the interaction of a nucleophile with a substrate in a displacement process involves at least two independent mechanisms.

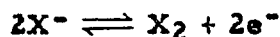
Edwards derived a two parameter equation⁵²:

$$\log k/k_o = \alpha E_n + \beta H \quad (I-9)$$

where k/k_o is the rate relative to water.

$$E_n = E_o + 2.6$$

where E_o is the oxidation potential for the oxidative dimerization



The value of -2.6 is the oxidation-reduction potential for water. The H scale is the acidity of the nucleophile relative to water.

$$H = pK_a + 1.47$$

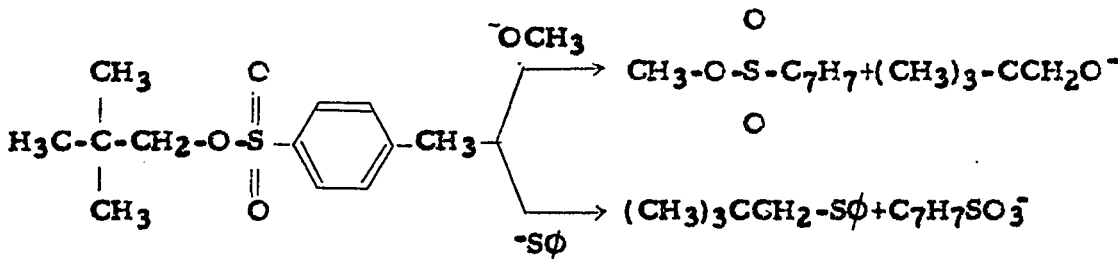
where α and β are the empirical constants. Equation I-9 gives much better correlation than does Swain and Scott's and can be applied to the equilibrium. Later Edwards devised a new equation to correlate the basicity and the polarizability with the reaction rate. It was assumed that E_n of the donors are dependent both on their polarizability and on their basicity:

$$E_n = aP + bH \quad (I-10)$$

where P is the polarizability of the donor relative to water. It was obtained from the molar refraction $P = \log (R_\alpha/R_{H_2O})$. If equation (I-10) is substituted into equation (I-9), it gives a new double scale equation,

$$\log k/k_0 = AP + BH$$

The relative importance of the basicity and the polarizability of a nucleophile to the influence of the reaction rate depends strongly upon the properties of a substrate. The polarizability of the nucleophile becomes less important as the polarizability of the electrophilic atom in the substrate increases. For example, the nucleophilic substitution in neopentyl *p*-toluene sulfonate can take place either on the carbon atom or on the more polarizable sulfur atom⁶³.

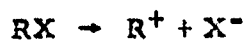


It appears that polarizable reagents like the thiophenoxide ion react preferentially at the carbon atom, whereas the less polarizable but more strongly basic methoxide ion attacks at the polarizable sulfur atom.

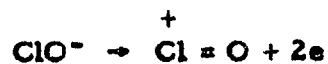
Bunnett and Bassett⁶⁴ reported that the relative rate of C-O/S-O scission of 2,4-dinitrophenyl p-toluenesulfonate varies according to the reagent used (1: with sodium thiophenoxide to 0.12: with sodium methoxide).

Davis⁶⁵ renamed equation I-9 an oxibase scale rather than referring to "double basicity". Since a β H term measures the sensitivity of the substrate to the basicity of the nucleophile, it is reasonable to assume that β is a measure of acidity of the substrate. The trend of the β value can be predicted. The more positive the centre being attacked, the larger is β . The α E term measures the sensitivity of the substrate to the oxidation potential of the nucleophile. It is suggested that α measures the ease of reduction of the substrate. The oxibase scale was then used to predict the ease of the displacement of the leaving group in S_N2 reactions^{66,67}. A leaving group was considered as a nucleophile leaving the reaction centre rather than one approaching the electrophilic center. The leaving group can then be correlated with the nucleophilic constant of oxidation and basicity. The α -value for various carbon substrates has been shown to be linearly related to the electrode potential⁶⁶ of the leaving group. The relationship gives a positively sloped correlation. The β values are controlled by the difference in electronegativity between the leaving group and the reaction center. The β value of methyl iodide is low (nearly zero) because carbon and iodide have nearly the same electronegativity. The quantitative prediction of C-alkylation, O-alkylation, C-acylation and O-acylation of the displacement reaction of enolate ions was made on the basis of this oxibase scale. C-methylation is favored with methyl iodide, but very little O-methylation is observed. O-acylation is generally favored kinetically over C-acylation. The prediction is based on the values of α , β , E and H⁶⁸.

(c) The alpha effect: Certain groups of nucleophiles are found⁵¹ to react more rapidly than expected if one considers only nucleophilicity. This group is composed of nucleophiles such as hydroxylamine, hypochlorite ion, etc. The common feature that can be distinguished in these nucleophiles is the presence of an electronegative atom containing one or more pairs of unshared electrons adjacent to the nucleophilic atom. This "excess" reactivity is called the "alpha effect"⁵¹. A pair of electrons leaving the nucleophile for a substrate resembles to some extent the ionization of a halide ion from an organic halide to form a carbonium ion.



Any factor which would stabilize the carbonium ion R^+ should also stabilize the nucleophile N^{m+e} by the sharing of an unshared pair of electrons on the adjacent atom:



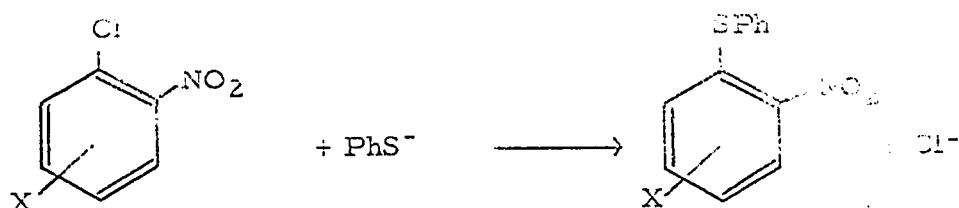
To the extent to which the transition state represents some removal of an electron pair from the reactive atom, an unshared pair of electrons may contribute to the stability of the transition state.

IV. ORTHO EFFECTS ON NUCLEOPHILIC DISPLACEMENT REACTIONS

The effect of meta- and para-substituents on the reaction rates has been correlated successfully by means of the Hammett and related equations. A statistical method of analysis of this type of data has been recommended by Jaffe⁶⁹. Similar methods have also been suggested by Webster⁷⁰ and by Taft⁷¹. For ortho substituents, steric and other effects vary with the reaction as well as the inductive and resonance effects and so make it impossible to correlate the reaction rate with any single parameter. Effects peculiar to ortho-substituents are often referred to as "ortho effects".

(a) Polar effect: The ortho or proximity effect which produces deviation from the sigma-rho linear relationship was suggested by Hammett⁷² to be caused by the ortho substituents altering the entropy of activation. If the ortho substituent does not alter the entropy of activation in a non-linear manner, the ortho effect is nearly parallel to that of a para substituent.

Briex and co-worker⁷³ studied the effects of substituents in aromatic substitution reactions of 4-, 5- and 6-substituted 1-chloro-2-nitrobenzenes with sodium thiophenoxide:



In the case of 6-substituted (ortho) derivatives, a plot of $\log k_{\text{ortho}}$ vs. σ_{para} values gave a ρ value of -3.46. This correlation of the rate constant for the ortho compounds with the σ constant of para substituents showed that the polar effect predominates for the reaction of o-derivatives. However, a lower ρ value for the ortho derivative than for the corresponding ρ value for the 4-substituted compound shows either that the polar effects are not transmitted with nearly the same intensity from ortho and para positions, or that some other influential ortho effect is operative.

Sharbati⁷⁴ reported the ortho effect on the reactions of 6-substituted-2-nitrochlorobenzene with piperidine. The reactions follow the Hammett relationship, $\log(k/k_0) = \rho\sigma$, except for the bromo and methyl compounds. The differences in rate are mainly determined by the polar effect.

(b) Primary steric effect: The ortho substituent can influence the rate by hindering the entrance of the nucleophile. This effect should be rate retarding. This will make ΔS^\ddagger more negative and will increase ΔH^\ddagger . The deviation of methyl and bromo compounds described above⁷⁴ may involve the primary steric effect. Piperidine is a relatively large reagent, and steric hindrance to its approach will be important when the steric requirements of the ortho substituents are large. In the case of steric effects related to the van der Waals radii, the methyl group ($r = 2\text{\AA}$) was the largest substituent they studied, and it showed the greatest deviation from the line. Bromine ($r = 1.95\text{\AA}$) also diverges from the line, in spite of its different polar effect. It was proposed that an approximate van der Waals radius of 1.9\AA is the lower limit in this reaction above which a steric effect becomes important.

The alkaline hydrolysis of substituted ethyl benzoates has been widely studied⁷⁵. Hydrolysis of the ortho-substituted esters (except o-fluoro) were markedly slower than the para isomers, and the low rates were associated with low values of the pre-exponential factor. The differences in the activation energies between ortho and para compounds were small. The dominant factor in this case is the steric interaction in the transition state between the ortho-substituent and the groups attached to the carbonyl-carbon atom. This would restrict the conformational freedom of the transition state and thus explain why, in the ethyl benzoate series, the ortho effects are associated with reduction in the pre-exponential factor of the Arrhenius equation.

Chapman and co-workers⁷⁶ discussed the ortho effect on alkaline hydrolysis of substituted methyl benzoates in terms of thermodynamic parameters. The values of ΔS^\ddagger are lowered by o-alkyl substituents (o-Me, o-Et) and by o-halogen substituents (except fluorine) and the activation entropy decrease is associated with the increase in activation enthalpy.

Yoshida⁷⁷ reported that the ortho effect of alkaline hydrolysis of ethyl benzoate is not affected by change of solvent. The logarithms of the rate constants for ortho and para compounds in 3% and 85% (wt.) of aqueous ethanol were plotted against the substituent constants respectively. Each line represents the regression line of the Hammett plot. Ortho compounds fall below the line, and the ortho effect was estimated as the difference in reactivities of ortho and para compounds ($\log k_p - \log k_o$), being represented as the vertical length deviated from the regression line. It was found that ortho effects are indifferent to the solvent change. The constancy of the ortho effect was extended to various aqueous dimethyl sulfoxide solvent mixtures⁷⁸. Similar results were obtained. These results indicate that the hydrolysis of ortho-substituted ethyl benzoate does not involve the steric inhibition of solvation in the transition state.

(c) Secondary steric effect: Bunnett has shown that in the reactions of o-halogen nitrobenzene with alkoxide⁷⁹, steric interference with attainment of coplanarity of the nitro group decreases the reactivity of the ortho isomer compared to that of the para isomer in which the nitro group is unhindered. The interference causing an ortho substituent to be non-coplanar with the aromatic ring has been termed the secondary steric effect.

In the reactions of 4-, 5- and 6-substituted 1-chloro-2-nitrobenzene with thiophenoxide⁷³, the rate ratio for 4-(para) and 6-(ortho) substituted compounds (k_p/k_o) is 26 for the NO_2 substituent. Similarly, the effect of steric hindrance with resonance may also be seen for the $-\text{COOCH}_3$ substituent; $k_p/k_o = 43$. The rates for meta and ortho isomers are similar. It is therefore likely that the contribution of 6-COOMe substituent is mainly inductive.

Another interesting set of data is available from the comparison of introducing the OCH_3 group into the ortho, meta and para positions of 1-chloro-2-nitrobenzene respectively. In the para position the methoxyl group has a deactivating effect :

$k_{p-\text{OCH}_3}/k_H = 0.43$ (k_H is the rate constant of the unsubstituted compound). This is as expected from the electronic effect (an electron-donating substituent reduces the rate, and electron-withdrawing group enhances the rate), whereas for the meta position, $k_{m-\text{OCH}_3}/k_H = 5.7$, indicating that the methoxy substituent is interacting inductively with the reaction centre.

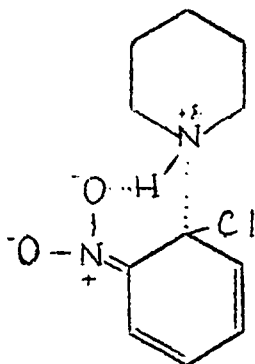
The ratio $k_{o-\text{OCH}_3}/k_{p-\text{OCH}_3} > 1$ is consistent with a larger, favorable inductive effect and a smaller unfavorable mesomeric effect for the ortho substituent. This cannot be the primary steric effect, in which all the rates for the ortho compound should be slower than the para isomer. Rather, it is attributed to the decreased delocalisation of the π -electrons in the ortho compared to the para isomer, and is explained by steric inhibition of resonance of the ortho OCH_3 substituent with the ring. Assumptions attributed to the distortion of the ortho-nitro group out of the plane of the benzene ring have been found to be justified by X-ray diffraction structure analysis of 1-halo-2-4-dinitrobenzene⁸⁰.

(d) Steric interference with solvation of the transition state: Watkinson⁸¹ examined the effects of ortho-substituents on the alkaline hydrolysis of substituted ethyl phenylacetate. All ortho substituents examined exert a retarding influence on the hydrolysis, as reflected by an increase in activation energy. The entropy of activation does not vary with substituents beyond the limit of experimental error. Log k/k_0 values for the hydrolysis in 80%, 70% and 60% ethanol-water respectively were plotted against the corresponding log k/k_0 values in 85.4% ethanol-water. Three straight lines were obtained except in the case of the ortho isomers.

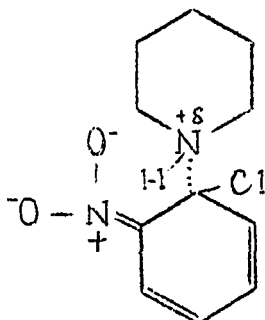
The deviation of the ortho compounds increases as the water content of the solvent increases. Correlation between the deviation observed with ortho-substituents and their size is in the direction $F < Cl < Br < I$. The o-methyl shows a similar effect to that of Br (which is of similar size). All the ortho-substituted esters are hydrolysed more slowly in solvents of higher water content. In other words, ortho effects increase as the water content of the solvent increases.

It was suggested that ortho substituents interfere with solvation of the transition state. As the water content of the solvent increases, this solvation becomes increasingly important: any interference with it will therefore become increasingly significant. The alkaline hydrolysis of ortho t-butyl⁷⁶ and 2,6-dimethyl substituted methyl benzoate was also proposed to have steric inhibition of solvation in the transition state.

(e) Built-in solvation: It has been established that o-nitrohalogenbenzenes react with primary and secondary amines more rapidly than do p-nitrohalogen benzenes but that para isomers react faster than o-isomers with methoxide or thiophenoxide ions. Chapman and co-workers⁸² suggested that a hydrogen bond is formed in the transition state of the former reaction:



Hawthorne⁸³ supplied evidence against this proposal by showing that piperidine and N-deuteropiperidine react at identical rates with both o- and p-chloronitrobenzene. He showed that the N-H bond of piperidine is not broken during the rate-determining steps of these reactions. Bunnett⁸⁴ therefore proposed a transition state structure:

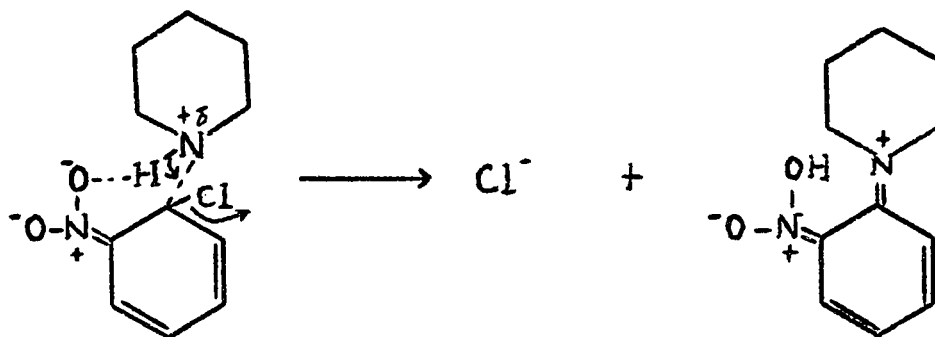


in which the sites of positive charge in the piperidine nitrogen atom and the nitro oxygen atom are ideally located for direct electrostatic interaction. This interaction can be considered as "build-in solvation", decreasing the need for participation of the solvent molecules in the transition complex.

It was observed that the ortho-para ratios for this displacement decrease as the solvents become more polar. The change in ratios is caused largely by an increase in rates in the para series, as expected for reactions of an ion with the neutral molecule. In the ortho series there is little change either in rate, or in ΔH^\ddagger and ΔS^\ddagger . Brioux and co-workers⁸⁵ had made a similar observation, namely that the ratio k_o/k_p is 30 times greater for the same reaction in benzene than in methanol, but only a small decrease of the rate of the ortho compound was found.

Ross and Finkelstein⁸⁶ argued that the failure to observe the deuterium isotope effect is not sufficient basis for discarding the Chapman hydrogen-bonding proposal. They proposed that the isotope effects are either absent or very small. Therefore, the reactions of o- and p-nitrobenzene with the tertiary amine 1,4-diazabicyclo[2,2,2]-octane, which is not able to form a hydrogen bond, were

studied in benzyl chloride. The k_o/k_p ratio is only 0.004 at 150°. The k_o/k_p ratio for the reaction with piperidine in the same solvent at 120° is 5.6. The ortho-para ratio observed is characteristic of the reaction with alkoxides and phenoxides which are not the hydrogen bond donor. This result leads support to Chapman's proposal. In order to explain the failure to observe a deuterium isotope effect in the reactions of o-nitrochlorobenzene with piperidine, the possibility that the rate-determining step is a concerted process, including breaking or partial breaking of the N-H bond, together with breaking of the C-Cl bond, was proposed.



(f) Effect of London interaction: This effect was proposed and developed by Bunnett. He noted that the ease of displacement of halide from 1-halo-2,4-dinitrobenzene increases as the polarizability of the halogen increases⁸⁷. The rate ratios of the nucleophiles thiophenoxide and methoxide in the reaction have been found to vary in a systematic fashion. The order of these ratios for the halogens is $I > Br > Cl > F$.

In order to examine whether or not this characteristic is fundamentally concerned with the bond breaking of the halide in the rate-limiting step, data were collected for reactions of halide ions with alkyl halides, in which bond breaking of the halogen being displaced is involved in the transition state⁸⁸. Again, these data showed that a more polarizable leaving group is displaced more rapidly by a more polarizable nucleophile than are the corresponding reactions of less polarizable leaving groups with less polarizable nucleophiles. Thus, the observed substrate characteristic has to do with the presence of certain halogens at or near the site of substitution and not with their being displaced in a rate-determining step. London dispersion forces are considered to be responsible.

Bunnett proposed that the rate-accelerating effect arises from a lowering of the transition state energy barrier by virtue of a favorable London interaction. This led to the expectation that o-substituents of high polarizability would in general, after allowance had been made for their electronic and steric effects, accelerate reaction with nucleophiles of high polarizability.

The reactions of nucleophiles of various polarizabilities with 1-fluoro-4-nitrobenzene and its 2-bromo and 2-methyl derivatives⁸⁹ were studied by Reinheimer and Bunnett. London forces were estimated by comparison of the rate ratio k_Y/k_{HO^-} , where k_Y

is the rate constant of the reaction of nucleophile Y with the substrate, and k_{HO^-} is the rate constant of hydroxide ion with the same substrate. Hydroxide was chosen as the basis for comparison because of its low polarizability and small size. The ratio k_Y/k_{HO^-} reflects differences in inherent nucleophilic reactivity of reagents and difference in local interaction. Allowance was made for the difference in inherent nucleophilic reactivity of the reagents by adjusting such ratios to the scale of 1.0 for p-fluoronitrobenzene for each reagent. The adjusted ratio is defined by:

$$(k_Y/k_{\text{HO}^-})_{\text{o-R}} / (k_Y/k_{\text{HO}^-})_{\text{H}}$$

where the numerator is the reaction with o-substituted p-fluoro-nitrobenzene and the denominator is the reaction with p-fluoronitrobenzene. The adjusted ratios represent only the difference between the reagent under consideration and hydroxide ion with respect to their interactions with the o-substituents. The adjusted rate ratio is increased by o-methyl substitution and increased to an even greater extent by an o-bromine. Electronically, the reaction is assisted by the electron withdrawing substituent. Therefore, bromine should accelerate and methyl should decelerate the reaction, i. e.

$k_{\text{CH}_3} < k_{\text{H}} < k_{\text{Br}}$. Sterically, each group hindered the reaction in the order $k_{\text{H}} > k_{\text{CH}_3} \succ k_{\text{Br}}$. Neither of these factors can be used to interpret the order observed - $k_{\text{Br}} > k_{\text{CH}_3} > k_{\text{H}}$. London interactions were again postulated.

The reaction rate order observed is, however, explicable if one considers London interactions between the ortho substituent and the attacking nucleophile.

Semi-quantitative comparisons between calculated London energies for reactions of o-substituted benzyl chloride with nucleophile Y and the energies estimated from the rates were made by Bunnett and Reinheimer⁹⁰. The London forces acting between the attacking nucleophile and nearby substituents should be proportional to the polarizability of the reagent and the substituent, and inversely proportional to the sixth power of their distance of separation. This factor should be negligible in the initial state where the reagent and the substrate are widely separated. The equation for the energy is:

$$-W_{YR} = 2.1 \frac{3\alpha_Y \alpha_R}{2r^6} \left(\frac{I_Y I_R}{I_Y + I_R} \right) \quad (I-11)$$

where $-W_{YR}$ is the energy of attraction between atoms Y and R; α_Y , α_R are the polarizabilities; r is the distance of separation, and I_Y and I_R are the ionization potentials of the substrate nucleophile. An empirical factor of 2.1 was introduced to obtain a better fit between calculated and experimental data.

For the calculation of transition states, the following characteristics were assumed:

- (1) The Y -----C-----Cl bond is linear and perpendicular to a plane in which the ring carbon and methylene hydrogens lie:
- (2) The C-----Y distance is 1.15 times the normal covalent C-Y distance.

(3) The polarizability and ionization potential of Y in the transition state is half way between the values for the Y⁻ ion and Y atom:

(4) A constant value of 225 kcal per mole for the I_R of the o-substituent was used throughout the calculation.

The empirical interaction energies were also estimated from the adjusted rate ratios:

$$(k_Y/k_{\text{CH}_3\text{O}^-})_R / (k_Y/k_{\text{CH}_3\text{O}^-})_H$$

Methoxide was used as the reference nucleophile. The calculated values do not agree precisely with those from the experiment, but the relative order for the London interactions between ortho substituents and polarizable nucleophile Y being o-bromo higher than o-methyl was expected.

Sisti and Lowell⁹¹ suggested the use of para substituted benzyl chloride as the reference rather than benzyl chloride. The ortho and para-methyl or ortho and para bromo-substituted benzyl chloride afford a better opportunity to observe indications of London forces in rate ratios with minimum considerations for electrical effects. The polar effect will be cancelled in the ratio k_o/k_p if the susceptibility constants ρ and ρ^* are nearly identical for both compounds. In order to cancel the differences in nucleophilicities, the adjusted rate ratio was again used:

$$\left(\frac{k_{o-R}}{k_{p-R}}\right)_Y / \left(\frac{k_{o-R}}{k_{p-R}}\right)_{MeO^-}$$

Inspection of the adjusted values illustrates, as shown in the following table, that the trend for London interaction is correct only if a given substituent is considered; the energies increase as the polarizability of the nucleophile increase: $I^- > PhS^- > MeO^-$.

| Nucleophile | Solvent | $(k_{o-R}/k_{p-R})_Y / (k_{o-R}/k_{p-R})_H$ | | |
|-------------|----------|---|------|------|
| | | -H | -Me | -Br |
| MeO^- | Methanol | 1.00 | 1.00 | 1.00 |
| $C_6H_5S^-$ | Methanol | 1.00 | 1.60 | 1.61 |
| I^- | Acetone | 1.00 | 3.11 | 2.30 |

However, on examination of the substituted methyl and bromine benzyl chloride with a given nucleophile, the adjusted ratios do not show the trends expected from London interactions, i. e. a nucleophile of relatively high polarizability does not give values for the most polarizable substituent (bromo compound). It was suggested that the trend of energies for a nucleophile with a given substituent is also consistent with decreasing steric interaction between the coming nucleophiles, $MeO^- > PhS^- > I^-$, and the given ortho substituent, since highly polarizable nucleophiles can easily distort their bonding electrons while bringing the rest of the molecule close enough to avoid excess repulsive forces.

The reason that the o-bromo compound does not give a higher value than the o-methyl compound with the same nucleophile is also thought to be due to possible steric dissimilarities, the variation of distance between a given nucleophile and ortho substituents, and conformational differences.

About the same time as Sisti, Reinheimer and co-workers⁹² published their work on the London force interactions in reactions of benzyl chlorides with various nucleophiles by applying the theory of the extrathermodynamic relationship described by Leffler and Grunwald. The substituent effects may be considered as a linear combination of independent effects while the total relative activation energy is a sum of effects due to polar (pol), steric (st) and London (L) force interactions:

$$\Delta\Delta F_{\text{total}}^{\ddagger} = \Delta\Delta F_{\text{pol}}^{\ddagger} + \Delta\Delta F_{\text{st}}^{\ddagger} + \Delta\Delta F_{\text{L}}^{\ddagger} = 2.3RT \log \frac{k_x}{k_H}$$

where k_x and k_H are the specific rates of substituted benzyl chloride and benzyl chloride respectively. It was assumed that polar effects are equal for the ortho and para isomers, and that the energy difference between the reaction of o-methyl and p-methyl benzyl chloride may then be expressed as:

$$\begin{aligned} \Delta\Delta\Delta F_{\text{total}}^{\ddagger} &= \Delta\Delta\Delta F_{\text{st}}^{\ddagger} + \Delta\Delta\Delta F_{\text{L}}^{\ddagger} = 2.3RT \left(\log \frac{k_{\text{o-R}}}{k_H} - \log \frac{k_{\text{p-R}}}{k_H} \right) \\ &= 2.3 RT \log \frac{k_{\text{o-R}}}{k_{\text{p-R}}} \end{aligned}$$

To eliminate steric effects from the rate ratio, a final comparison is made between $\Delta\Delta\Delta F^\ddagger$ using Y as a nucleophile and $\Delta\Delta\Delta F^\ddagger$ using methoxide as a nucleophile:

$$\Delta\Delta\Delta\Delta F^\ddagger_{\text{total}} = \Delta\Delta\Delta\Delta F^\ddagger_{\text{L}} = 2.3RT \left[\log\left(\frac{k_{\text{O-R}}}{k_{\text{P-R}}}\right)_Y - \log\left(\frac{k_{\text{O-R}}}{k_{\text{P-R}}}\right)_{\text{CH}_3\text{O}^-} \right]$$

$$\Delta\Delta\Delta\Delta F^\ddagger_{\text{L}} = 2.3RT \left[\log\left(\frac{k_{\text{O-R}}}{k_{\text{P-R}}}\right)_Y / \left(\frac{k_{\text{O-R}}}{k_{\text{P-R}}}\right)_{\text{CH}_3\text{O}^-} \right] \quad (I-12)$$

The adjusted rate ratio derived is exactly the same as Sisti's adjusted ratio. The difference between this term and Bunnett's rate ratio is that the p-substituted benzyl chloride is used for comparison rather than benzyl chloride as the reference standard. There is a linear relationship between the London energy estimated from the rate ratio (eq. I-12) and the energies calculated from equation (I-11) with various polarisable nucleophiles, but the slopes for the o-methyl compound and for the o-bromo compound are different.

This difference in slope was interpreted to be the result of the rather gross approximations and assumptions made for the derivation of the equation for $\Delta\Delta\Delta\Delta F^\ddagger$. No other treatment has yet explained the rate ratios as satisfactorily as the London force interaction theory.

V. NUCLEOPHILIC REACTIVITIES OF BENZYL HALIDES

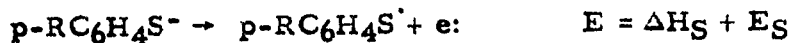
The variations of velocities for reactions of substituted benzyl bromides with sodium hydroxide were first pointed out by Lapworth and Shoesmith⁹³, and the rate of reaction of benzyl bromide with potassium iodide in acetone solution was measured by Conant et al⁹⁴. Bennett and Jones⁹⁵ have made systematic studies on the reactions of ortho-, meta- and para-substituted benzyl chlorides with potassium iodide. The activation energies for ortho isomers were found to be lower than for para or meta isomers. No explanation was offered. Swain and Langsdorf⁹⁶ observed that a smooth curve with positive curvature (concave up) was obtained when the Hammett equation of $\log k/k_0$ was plotted against substituent constants for the reactions of meta and para substituted benzyl chloride with the same nucleophile. Two different curves for meta and para compounds were observed in these plots.

These results were explained on the basis of the direct interaction of the substituent with the reaction center, which caused a change in mechanistic character of the displacement reaction for that substrate. A strong electron-donating substituent such as p-CH₃ should not only stabilize the transition state, by inducing a high positive charge on the reacting center of the methylene group of benzyl chloride by resonance, but should also increase the capacity of the reacting center for the positive charge, and therefore favour more completion of bond breaking relative to bond making at the transition state, which would lead to a more negative ρ relative to the unsubstituted substrate. A strongly electron-withdrawing substituent (p-NO₂) should increase the capacity of the reacting center for negative charge, and favour bond making (making a more positive ρ). This reasoning would predict a positive curvature in the Hammett plot.

Displacement reactions have often been grouped into sharply differentiated mechanistic categories such as the S_N1 mechanism in which the transition state is depicted as the breaking of the leaving group bond without new bond formation occurring. The S_N2 mechanism is considered as a fundamentally different mechanism with synchronous bond making and breaking. Accordingly, one might expect ρ to be strongly negative, close to zero for the S_N1 and S_N2 reactions respectively. Since there is no clear dividing line to distinguish between these "mechanisms", there seem to be all degrees of intermediate behaviour. Swain⁹⁶ preferred to use the magnitude of ρ rather than such rigid mechanistic formalities as S_N1 or S_N2 to designate the mechanism.

Hudson and Klopman⁹⁷ have put forward a qualitative scheme to account for the variation of the bond-making in the transition state with the changing of the p-substituents of benzyl bromide in a nucleophilic displacement reaction. Similar to Swain's observation, they noted that rates increase on the introduction of electron releasing and electron attracting substituents in the reaction series of p-substituted benzyl bromides with p-substituted thiophenoxide or methoxide.

The plots of $\log k$ against the pK_a values of the corresponding nucleophiles (p-substituted thiophenols) showed systematic deviation⁹⁸ from the Brønsted relation. The deviations were explained as follows. Consider the neutralization to proceed by the following series of processes:



The overall energy of the process is:

$$\Delta H = \Delta H_S + E_S - D_{SH} - I + \Delta H_H \quad (\text{I-13})$$

Suppose that substitution proceeds by a stretching of the R-Br bond to the critical separation distance characteristic of the transition state, which requires an energy E_1 followed by a transfer ze from the nucleophile to R^{+z} . Then the energy required, ΔE^* , is given by:

$$\Delta E^* = \alpha \Delta H_S + \beta E_S - \gamma D_{NR} + E_1 \quad (\text{I-14})$$

In this equation, the energy of polarization of the nucleophile is introduced in the βE_S term as a fraction of the electron affinity, and the repulsion energy between the electrons in the p-orbital forming the reaction coordinate is included in the bond energy term D_{NR} . Substitution in the nucleophile will generally change the terms ΔH_S , E_S and D_{NR} in a regular way, but not necessarily proportionally.

Comparison of equations I-13 and I-14 shows that ΔE^* is linear in ΔH (the Brønsted relation holds) only when:

(a) $E_S = E + E_c$ [the electron affinity in the present case may be assumed to be given by the sum of constant E for the atom S , and the conjugation energy E_c in the ion] :

(b) $\Delta H_S = -K_1 E_c + \text{constant}$:

(c) $D_{NR} = -K_2 E_c + \text{constant}$.

Deviation from these linear relations will produce the deviations frequently observed in the Brønsted relation.

Reaction constants, however, were obtained by plotting the $\log k_2$ values for the reaction of each substituted benzyl bromide against the $\log k_2$ values for the corresponding reaction of benzyl bromide. The slope of this plot gives a reaction parameter ρ_N , which has a similar significance to the Brønsted coefficient, since it is a measure of the sensitivity of the rate to changes in the charge distribution in the nucleophile. The reaction parameter ρ_N increases regularly with the decrease in electron density at the reaction center. This conclusion was supported by the linear increase in ρ_N with the increase of the substituent constants⁹⁸.

EXPERIMENTAL

The melting points (uncorrected) were taken by the capillary technique on a "Thomas Hoover" capillary melting-point apparatus.

The infrared spectra were measured on liquid films, solutions, or nujol mulls on a Perkin-Elmer "Infrared" Model 137, and a Beckman Infrared Spectrophotometer, I. R. - 8.

The nuclear magnetic resonance (NMR) spectra were taken on a Varian Model V-4302 NMR spectrometer at 60 Mc/sec.

The mass spectra were recorded using the RMU-6D mass spectrometer, manufactured by Hitachi, Tokyo, Japan.

The ultraviolet spectra were taken on a Perkin-Elmer "Ultraviolet-Visible Spectrophotometer", Model 202.

The vapour-phase chromatography (VPC) was performed on a Beckman GC-2.

I. PREPARATION AND PURIFICATION OF THE SUBSTRATE

In order to study the reactions of substituted benzyl chlorides with substituted thiophenoxides, the following substrates and nucleophiles were prepared:

(1) Benzyl chloride: A commercial product (Fisher Scientific Co.) was redistilled. (B.p. 61.9° at 12 mm); lit.⁹⁹ b.p. 63° (8mm).

(2) o-Xylyl chloride: This material was prepared by the method of Kharasch and Brown¹⁰⁰. The yield of the product was 55% with b.p. $87-88^{\circ}$ (13 mm.); lit.¹⁰¹ b.p. $197-9^{\circ}$.

(3) p-Xylyl chloride: The procedure to prepare this compound was the same as that for o-xylyl chloride. From redistillation the fraction b.p. $90-91^{\circ}$ at 20 mm. was collected; lit.¹⁰² b.p. 90° (20 mm.). The rate constants for reactions of this compound with methoxide and thiophenoxide do not agree with the values of Reinheimer and co-workers (see Results and Discussion, p. 143). A blank test was made to check whether the starting material p-xylene contaminated the p-xylyl chloride. From vapour-phase chromatography with apiezon column at 70° , the product showed only one peak, and the peak for p-xylene under the same conditions appeared at a different position. The spectrum for the mixture of the product and the starting material was shown to have two peaks.

(4) m-Nitrobenzyl chloride: A commercial product (Eastman Kodak) was recrystallized twice from benzene to a constant melting point of $45-46^{\circ}$; lit.¹⁰³ m.p. $45-47^{\circ}$.

(5) 2,6-Dimethylbenzyl chloride:

(a) 2-Bromo-m-xylene from 2,6-dimethylaniline:

A mixture of 181.2 g (1.5 moles) of 2,6-dimethylaniline in 880 ml (6 moles) 48% HBr was diazotized¹⁰⁴ with 11.73 g (1.7 moles) of NaNO₂. The addition of NaNO₂ was controlled and the temperature kept below 5°. When the diazotization was complete, 5 g. of copper powder were added and the mixture was heated very cautiously. If nitrogen was evolved vigorously, the flask was cooled with ice. The mixture was heated for 2 hrs. on a steam bath. One liter of H₂O was added to the mixture which was then steam distilled. The distillate was made alkaline with 10 g of NaOH and the lower red layer of crude 2-bromo-m-xylene was separated. The crude product was dissolved in ether and washed with dilute acid and water. The ether solution was treated with anhydrous Na₂SO₄ before evaporation of the solvent. Purification was effected by distillation under reduced pressure. A 40% yield of product was collected with b. p. 100-102° (20 mm); lit.¹⁰⁵ b. p. 93° (20 mm).

Another method for the preparation of 2-bromo-m-xylene was tried, by the decomposition of [C₆H₃(CH₃)₂N₂Br]₂HgBr₂ complex¹⁰⁶, but the yield was poor. A mixture of 108.9 g (0.9 mole) of 2-aniline-m-xylene in 1720 ml of water and 360 ml of conc. HCl was diazotized with 360 ml of 20% NaNO₂ solution, according to the method described in Organic Synthesis¹⁰⁴. The diazonium salt was added to a cold suspension of HgBr₂, formed by treating 0.45 mole of Hg(NO₂)₂ and 213.3 g of NaBr in a total volume of 642 ml of water. The yellow insoluble complex [C₆H₃(CH₃)₂N₂Br]₂HgBr₂ was separated immediately and collected by filtration. It was then washed with water

and acetone, and air dried. The air dry complex was well mixed with 772 g of finely ground NaBr. The mixture was then added in a small portion through a wide rubber tube to a flask heated in an oil bath at 90°. After each addition of the mixture, a vigorous gas evolution occurred. After the decomposition was complete, the mixture was extracted with benzene. The solid lumps were broken with a stirring rod. The benzene solution was washed with dilute acid and alkali. The 2-bromo-m-xylene was vacuum distilled. The fraction b.p. 88° (15 mm) was collected; lit.¹⁰⁵ b.p. 90-93° (20 mm).

(b) 2,6-Dimethyl benzoic acid from 2-bromo-m-xylene:

The bromide was converted to carboxylic acid by the Grignard method¹⁰⁷. A solution of 185 g (1 mole) of 2-bromo-m-xylene and 218 g (2 moles) of ethyl bromide in 1 l. of dry ether was added with stirring from a funnel to 85 g (3.5 g-atom) of Mg turnings in 150 ml of dry ether. (All the glassware was oven dry before use). After completion of the addition (about 1.5 hrs.), the reaction was heated under reflux for 30 mins. The reaction mixture was then cooled, and the solution of alkyl magnesium bromides was decanted slowly from the excess of Mg on to 600 g of dry ice which was stirred manually. When most of the dry ice had evaporated, an additional portion was added, along with 250 ml of dry ether. The 800 ml of 20% HCl and enough ice to keep the mixture cold were added with stirring. The organic products were extracted with ether, and the ethereal layer was washed with water to remove HCl and most of the propionic acid. The benzoic acid was extracted by shaking with 10% alkaline solution. The aqueous solution was acidified, and the solid collected by filtration in 80% yield. The product was purified by recrystallization from MeOH to give a solid of m.p. 115-116°C; lit.¹⁰⁵ m.p. 116°.

(c) 2,6-Dimethylbenzyl alcohol from 2,6-dimethylbenzoic acid: A solution of 91 g (0.6 mole) of 2,6-dimethylbenzoic acid in 500 ml of dry tetrahydrofuran (if dry ether was used as solvent, the yield was very poor) was added drop by drop over a period of 3 hrs. to a slurry of 40 g of LiAlH_4 (purity over 95%) in 1400 ml of dry THF under nitrogen atmosphere. The mixture was heated under reflux for 18 hrs. After cooling the reaction mixture, cold water was slowly added from a dropping funnel to decompose the unreacted hydride. The THF layer was separated, and the solvent was removed under reduced pressure. The crude product was obtained in a yield of 70%. It was then purified by recrystallization from 20% aqueous methanol to give a solid of m.p. 81° ; lit.¹⁰⁵ m.p. 91° .

(d) 2,6-Dimethylbenzyl chloride from 2,6-dimethylbenzyl alcohol: The alcohol was converted to chloride by reaction with thionyl chloride¹⁰⁸. 2,6-Dimethylbenzyl alcohol, 54.4 g (0.4 mole) was dissolved in 34.8 g (0.4 mole) of pyridine. To the rapidly stirred mixture, which was cooled in an ice bath, 50 g (0.42 mole) of freshly distilled thionyl chloride was added from a dropping funnel at a rate of 3-5 drops per sec., the temperature of the mixture not being allowed to go above 60° . When the addition was complete, the mixture was stirred for 3-4 hrs. The mixture was extracted with ether, and the ethereal layer was washed with water. (The yield would be low if the extraction was incomplete). After recrystallization from acetone, a solid of m.p. $31-32^\circ$ was obtained in a yield of 65%; lit.¹⁰⁵ m.p. 31° .

II. PREPARATION AND PURIFICATION OF THE NUCLEOPHILES

(1) Thiophenol. Commercial product (Eastman Company) purified by vacuum distillation.

(2) m-Thiocresol. Commercial product (Eastman Company) purified by vacuum distillation.

(3) p-Nitrothiophenol. Following the method of Price and Stacy¹⁰⁹, 78.7 g (0.5 mole) of p-chloronitrobenzene was dissolved in 125 ml of alcohol. A solution of sodium disulfide prepared from 94.3 g (0.36 mole) of sodium sulfide pentahydrate and 11.7 g (0.365 mole) of sulfur was then added over a period of about 10 min. An alcoholic solution of 20 g (0.5 mole) of NaOH was added drop by drop from the dropping funnel over a period of about 20 min. as the reaction mixture was boiled under reflux. The mixture was cooled and poured on to 1 kg of ice and 750 ml of water. The residue was removed by filtration, and the filtrate was acidified with HCl. p-Nitrothiophenol precipitated and was collected by filtration and washed with 250 ml of water. The crude thiophenol was dissolved in 75 ml of alcohol. After addition of a solution containing 40 g of NaOH in 750 ml of water, the solution was filtered. The product was reprecipitated with HCl and collected by filtration in a yield of 55%; m.p. 75°C; lit.¹⁰⁹ m.p. 75°C.

(4) p-Methyl thiophenol; This compound was synthesized by the method described in Vogel¹¹⁰.

The mixture of 720 g of crushed ice and 240 g of conc. H₂SO₄ was cooled to 0° in a freezing mixture of ice and salt and 60 g. of p-toluenesulfonyl chloride was added gradually to the rapidly stirred mixture. Zinc powder, 120 g (90-100% purity), was added slowly without the temperature rising above 0°C (about 30 min.). The mixture was stirred for a further one and one-half hours. The ice-salt bath was then removed

and the mixture was allowed to warm up. The reaction began with the evolution of hydrogen. The mixture was cooled occasionally when the reaction became vigorous. When the energetic reaction subsided, the mixture was heated under reflux until the solution became clear (4-6 hrs.). It was then steam distilled. The p-thiocresol crystallized in the steam distillate. The crude product was recrystallized twice from methanol to give a solid of m. p. 44°C ; lit.¹¹⁰ m. p. 43° .

(5) p-Bromothiophenol: The procedure for the synthesis of this compound was similar to that of the synthesis of p-methylthiophenol. A mixture of 360 g of crushed ice and 120 g of conc. H_2SO_4 was cooled to 0° and 47.5 g of p-bromobenzene sulfonyl chloride was added to the cooled mixture. The compound was reduced by adding 60 g of zinc powder. The mixture was warmed and stirred overnight after the vigorous evolution of the hydrogen subsided. A white crystalline solid was obtained from the steam distillate of the mixture. It was purified by recrystallization from petroleum ether (b. p. $60-80^{\circ}$) to give a solid of m. p. 75° ; lit.⁹⁸ m. p. $74-75^{\circ}$.

(6) p-Methoxythiophenol: The compound was prepared by the reaction of potassium ethyl xanthate with diazotized p-anisidine. The procedure followed was similar to that described in Organic Synthesis¹¹².

(a) Preparation of potassium ethyl xanthate¹¹¹: With heating, 300 g (5.36 moles) of KOH was dissolved in 3 l. of ethanol. The solution was then cooled in an ice bath and the temperature was kept below 10° . To the rapidly stirred mixture, carbon disulfide was added gradually until the solution was no longer alkaline: about 456 g (360 ml, 5.95 moles) of CS_2 was required. The potassium ethyl xanthate was collected by filtration and air dried.

(b) Reaction of ethyl xanthate and p-anisidine:

p-Anisidine (123 g) was dissolved in 200 ml of conc. HCl and 200 g of crushed ice. The mixture was diazotized with a solution containing 80 g of sodium nitrite and 170 ml of water below 5°. The diazotized p-anisidine was treated with enough sodium acetate to neutralize the free acid. The cold filtrate of this diazotized solution was then added slowly to a solution (the temperature of the solution was kept at 70-80°) of 300 g (1.9 moles) of potassium ethyl xanthate in 700 ml of water. Stirring and heating were continued for about two hrs. to complete the decomposition of the intermediate of diazonium ethyl xanthate. The mixture was cooled to room temperature and extracted with ether. The ethereal layer was separated and a dark brown oil was obtained after the ether was removed. This oil was heated under reflux under nitrogen for 3 hrs. with a solution containing 115 g of potassium hydroxide in 2 l. of 95% ethanol and 20 g of glucose. At the end of the reaction, the volume of the mixture was reduced to about 300 ml by reduced pressure evaporation. The solution was acidified with cold dilute H₂SO₄. A few grams of zinc dust were then added, and the mixture was steam distilled. The distillate was extracted with ether. The ethereal solution was dried over CaCl₂. The crude product obtained after the removal of the solvent was purified by fractional distillation to give a 52% yield of liquid of b. p. 41° (0.25 mm); lit. 112 - 88-90° (5 mm).

(7) m-Methoxythiophenol: The procedure was similar to that for the preparation of p-methoxythiophenol. m-Anisidine, 12.35 g (0.1 mole), in 20 ml of conc. HCl and 20 g of crushed ice was diazotized with 8 g of NaNO₂ in 20 ml of water. The neutralized diazonium solution was added to 18.8 g of potassium ethyl xanthate in 20 ml of water at 70-80°.

Stirring and heating were continued for about 1 hr. after the addition of the diazonium solution. The dark oil obtained was then hydrolyzed with 17 g of NaOH in 67 ml of 95% ethanol. The product was separated from the reaction mixture by steam distillation. It was then purified by fractionate distillation to give a 55% yield of liquid of b. p. 65° (0.25 mm); lit.¹¹³ - $148-151^{\circ}$ (14 mm).

Anal. Calculated for C_7H_8OS : C, 59.96; H, 5.75; S, 22.87.

Found: C, 59.80; H, 6.13; S, 22.64.

(8) m-Nitrothiophenol: This compound has been reported in the literature as a brown oil¹¹⁴ or a straw coloured oil¹¹⁵ with 1% less carbon in the elementary analysis than the calculated value. Several attempts to synthesize it by the method of Bordwell and Anderson¹¹⁵ were unsuccessful. The product obtained was a golden orange oil and contained an extra band at 3400 cm^{-1} in the infrared spectrum, even after being twice distilled. Another method, similar to the preparation of p-nitrochlorophenol, was tried by adding the sodium disulfide to the m-nitrochlorobenzene. This was also unsuccessful. It was finally synthesized by the reduction of the appropriate disulfide as follows:

(a) Preparation of m-nitrophenyl disulfide from m-nitrobenzene sulfonyl chloride: The method described in Organic Synthesis¹¹⁶ was followed. m-Nitrobenzenesulfonyl chloride (33.5 g) was placed in a three necked flask and 103.3 ml (0.75 mole) of 47% hydriodic acid was added dropwise with stirring over a period of 30-45 min. Iodine crystals precipitated as the reaction proceeded. After the addition was complete, the reaction was stirred and refluxed on a steam bath for 3 hrs. It was necessary to change the air condenser several times during the reaction because the sublimation of iodine blocked the condenser. The reaction mixture was then cooled to room temperature.

About 135 g of sodium bisulfide was required to reduce the iodine. The addition of NaHSO_3 should be slow, since the evolution of SO_2 can cause excessive foaming. When all the iodine was reduced, the pale yellow m-nitrophenyl disulfide suspended in the solution. The disulfide was purified by recrystallization from acetone to give a solid of m.p. $82-83^\circ$ in a yield of 72%; lit.¹¹⁶ m.p. $81-83^\circ$.

(b) Preparation of 3-nitrothiophenol from m-nitrophenyl disulfide. A mixture of 7.6 g of 3-nitrophenyl disulfide, 4.4 g of NaOH and 50 ml of ethanol was heated under reflux and 6.3 g of $\text{Na}_2\text{S}_2\text{O}_4 \cdot 2\text{H}_2\text{O}$ in 35 ml of water was added dropwise over a period of 20 min. After the addition was complete, the heating was continued for 15 min. The warm solution was then poured into 250 ml of ice water. The mixture was filtered, and the filtrate was acidified with dilute HCl . The oil remained suspended in the aqueous solution, and was extracted with ether. A brown oil (5.7 g) was obtained after the evaporation of the ether under reduced pressure.

(c) The disulfide can also be reduced by glucose¹¹⁷. Glucose (4 g) was mixed with 5.7 g of pulverized bis(3-nitrophenyl)-disulfide and left overnight in 150 ml ethanol. The mixture was then heated at 50°C . After being treated with 4 g NaOH in 10 ml H_2O the mixture was poured into 100 ml cold water and filtered. The filtrate was added dropwise to 20 ml concentrate H_2SO_4 in 150 g of crushed ice. The brown oil suspended in aqueous solution and the crude product was extracted with ether.

(d) Purification of m-nitrothiophenol by column chromatography: The condition for the separation of the crude product was tried first by thin-layer chromatography. It was found that a thin-layer of silica gel with chloroform as the solvent for elution would give a clear separation of the three spots. If other solvents such as methanol, methylene dichloride, benzene or mixed solvents of different polarity were used, a long tail was developed in the thin layer. This was also the case if alumina was used instead of silica gel. A column was then packed with silica gel in chloroform. Four g of the crude product were put in the column and the column was washed with chloroform. m-Thiophenol was found in the first fraction. Some of the thiol was also found in the second fraction (probably due to the overload of the column). A 1.8 g yield of m-nitrothiophenol was obtained: it was a viscous clear yellow oil which crystallized when cooled with ice water. The oil was then purified by molecular distillation. Its identity was characterized by spectroscopy. Some characteristic peaks which appeared in the nuclear magnetic spectrum and the infrared spectrum are shown as follows:

I.R.: 3050 cm^{-1} , 2540 cm^{-1} , 1550 cm^{-1} , 1500 cm^{-1} , 1325 cm^{-1} ,
 780 cm^{-1} and 710 cm^{-1} .

N.M.R.: 3.7 p.p.m. and the aromatic protons are spread between
7.3 p.p.m. → 8.3 p.p.m.

It also showed the molecular peak $m/e = 150$ in mass spectrum.

$n_D^{25.7} = 1.6271$.

Anal. Calc. for $C_6H_5NO_2S$; C, 46.43; H, 3.25; N, 9.03; S, 20.69.

Found: C, 46.51; H, 3.41; N, 9.23; S, 20.73.

(9) 3,5-Dinitrothiophenol: This is a new compound and was synthesized by the reduction of the appropriate disulfide.

(a) Preparation of potassium 3,5-dinitrobenzene sulfonate from m-dinitrobenzene. The sulfonate was prepared by direct sulfonation of the benzene derivative with fuming sulfuric acid¹¹⁸. A mixture of 50 g of meta-dinitrobenzene and 150 ml of fuming sulfuric acid (15.18%) and 4.5 g of Hg as catalyst was heated at 150-160° for 9 hrs. The mixture was then cooled and poured on to ice, and the acid was neutralized with milk of lime (excess of lime or $Ba(OH)_2$ cannot be used, as the product is sensitive to alkali and appears to change readily into nitrohydroxyl-sulfonic acid). The deep purple colour of the filtrate changed to orange as the liquid was evaporated by heating in atmospheric pressure. The potassium salt of 3,5-dinitrosulfonate was obtained by adding a calculated quantity of potassium carbonate (excess of carbonate cannot be used, for the reason explained above). The solution was evaporated until crystallization began; yield 35%. Major peaks in nmr using D_2O as solvent are: 1.13 (doublet, $J = 2$ cps), 0.85 (triplet, $J = 2$ cps).

(b) Preparation of 3,5-dinitrobenzene sulfonyl chloride from potassium 3,5-dinitrobenzene sulfonate: The first attempt to synthesize this compound by treatment with chlorosulfonic acid¹¹⁹ did not succeed. Dry 3,5-dinitrobenzene sulfonate (7 g) was dissolved in 10.5 ml of chlorosulfonic acid, and the mixture was heated on a steam bath for 2 hrs. On standing in air, the product did not crystallize on the wall of the flask as was reported¹¹⁹. The mixture was then poured on to ice. A white solid substance, m.p. 195°, was obtained. It was not the starting material, nor the 3,5-dinitrobenzene sulfonyl chloride.

The method described in Organic Synthesis¹²⁰ was then followed, and the product was obtained with good yield. A mixture of 11.44 g (0.04 mole) of dry potassium 3,5-dinitrobenzene sulfonate (which had previously been dried under vacuum and heated under an infrared lamp for at least 15 hrs.) and 10.4 g (0.05 mole) of finely divided PCl_5 was placed in a flask equipped with an air condenser and fitted at the top with a CaCl_2 drying tube. The solid mixture was mixed thoroughly and then placed in an oil bath which was heated to 110° . Heating was continued at this temperature for 1 hr. The condenser was removed for brief intervals now and then during the heating period, and the reactants were stirred by means of a glass rod. At the end of the heating period, the product was a thick paste. In order to remove the POCl_3 formed in this process, as well as most of the unreacted PCl_5 , the mixture was heated on a steam bath for 2 hrs. under vacuum produced by a water aspirator. Two traps between the receiver and the aspirator were necessary to assure that there was no contact between phosphorous chloride and water. The dry cake was pulverized, and transferred to a beaker, then 75 ml of water and 200 ml of chloroform were added to the beaker. The mixture was placed on a steam bath and stirred until most of the solid dissolved. The chloroform layer was separated and the volume of the solution was reduced by evaporation. The solution was then cooled and the product crystallized. Filtration gave 7 g of the pale yellow 3,5-dinitrothiophenol¹¹⁹ in a yield of 70%. It was then recrystallized from chloroform, m.p. 101° ; lit.¹¹⁹ m.p. $100-101^\circ$.

(c) Preparation of 3,5-dinitrophenyl disulfide from 3,5-dinitrophenyl sulfonyl chloride. The procedure was similar to that described under the preparation of 3-nitrophenyl disulfide. 3,5-Dinitrobenzene sulfonyl chloride (40 g, 0.15 mole) was placed in a flask. The stirrer was started and 103.3 ml (0.75 mole) of 55% HI was added dropwise to the flask. After the addition was complete, the mixture was stirred for another 3 hrs. It was then cooled to room temperature. Sodium bisulfite was added slowly to reduce the iodine. Pale yellow crystals of 3,5-dinitrophenyl disulfide remained suspended on the colorless solution. The crude product was purified by recrystallization twice from benzene to give 18.7 g (64% yield) of 3,5-dinitrophenyl disulfide of m.p. 178°; lit.¹²¹ m.p. 176°.

(d) Preparation of 3,5-dinitrothiophenol from 3,5-dinitrophenyl disulfide: Glucose (6.28 g) was mixed with 8.8 g of pulverized disulfide and left overnight in 75 ml of ethanol. The mixture was then treated slowly with 4 g of sodium hydroxide in 10 ml of water. Several temperatures for this reaction were tried in order to get the maximum yield. It was observed that if the temperature exceeded 50°C, the brown viscous tar deposited in the bottom of the flask. The higher the temperature, the more tar was formed. The mixture was stirred for 1 hr. and was then poured into 130 ml of cold water. The filtrate was added drop by drop to 21 ml of concentrated H₂SO₄ in 160 g of crushed ice. The pale yellow 3,5-dinitrothiophenol precipitated from the acidic solution. The crude product, 4.5 g, was purified twice by recrystallization from benzene to give a solid of m.p. 90-91° in a yield of 52%. This yellow rod-like crystalline solid slowly turns opaque when dry. The

structure was characterized by spectroscopy. Major bands in I.R. appeared at 3100 cm^{-1} , 2590 cm^{-1} , 1580 cm^{-1} , 1350 cm^{-1} , 780 cm^{-1} , 650 cm^{-1} . The peaks appearing in n.m.r. are at 4.1δ , 8.5δ , 8.8δ ; the maximum absorption in U.V. (taken in 95% ethanol) is $276\text{ m}\mu$ with $\epsilon = 2.4 \times 10^4$. The molecular weight was determined by mass spectroscopy and showed the molecular peak $m/e = 200$.
Anal. calc. for $\text{C}_6\text{H}_4\text{N}_2\text{O}_4\text{S}$: C, 36; H, 2.14; N, 13.99; S, 16.02.
Found: C, 36.12; H, 2.19; N, 13.83; S, 16.11.

III. PREPARATION OF DISULFIDES

(1) Diphenyl disulfide: Five g of thiophenol was dissolved in 10 ml of methanol and 2.7 g of 30% hydrogen peroxide was added drop by drop to the flask with stirring. The mixture was heated under reflux for 4 hrs. on a steam bath. [One way to judge whether the reaction is complete or not for these oxidation reactions of substituted thiophenols is by their odor. All the thiol compounds studied are characterized by their irritating smells, whereas the corresponding disulfides are odorless]. After the reaction was complete, the volume of the reaction mixture was reduced. The crude product crystallized as white needles. It was recrystallized from ethanol: m.p. $59.5\text{-}60^\circ\text{C}$; lit.¹²² m.p. $60\text{-}61^\circ$.

(2) Bis-(p-nitrophenyl)disulfide: Two g of p-nitrothiophenol was dissolved in acetic acid. To this rapidly stirred solution, 0.5 g of hydrogen peroxide was added dropwise. The mixture was refluxed on a steam bath for 5 hrs. The solid substance was removed by filtration and the product recrystallized in acetic acid. It was a light yellow solid of m.p. 182°C ; lit.¹²² m.p. 181° .

(3) Di-m-methylphenyl disulfide: Ten g of m-thiocresol was dissolved in 20 ml of methanol and 4 g of 30% H_2O_2 was added. The mixture was refluxed for 3 hrs. and then stirring was continued in the open air until the irritating smell disappeared. The reaction mixture was cooled with dry ice acetone solution and di-methylphenyl disulfide solidified at $-22^\circ C$. The liquid was discarded and the product was purified by vacuum distillation to give a liquid of b.p. 26° (0.25 mm); lit. ¹²³ b.p. 150° decomposition.

(4) Di-p-methylphenyl disulfide: Five g of p-methyl thiophenol was dissolved in 15 ml of methanol; 2 g of 30% H_2O_2 was added dropwise and the mixture stirred in the air at room temperature overnight. The product crystallized on cooling the mixture in ice water. The disulfide was recrystallized twice from ethanol to give a solid of m.p. $44.5-45.5^\circ$; lit. ¹²² $45-46^\circ C$.

(5) p-Methoxyphenyl disulfide: The procedure was the same as that for the preparation of diphenyl disulfide. p-Methoxyphenyl disulfide is a yellow oil of b.p. $40^\circ C$ (0.05 mm).

(6) p-Bromophenyl disulfide: The procedure was the same as that for diphenyl disulfide. The product is a yellow crystalline solid of m.p. $92^\circ C$.

IV. PURIFICATION OF THE SOLVENTS

(1) Methanol: Following the method described in Vogel¹²⁴ 10 g of dry magnesium turnings and 1 g of iodine were placed in a flask, 100 ml of methanol was added and the mixture was warmed until the iodine disappeared. Hydrogen was soon vigorously evolved. The heating was continued until all the magnesium converted into the methylate. Two liters of methanol were then added, and the mixture was heated under reflux for half an hour. The mixture was then distilled with exclusion of moisture, and the first 50 ml of distillate was discarded.

(2) Ethanol: The experimental procedure is the same as that for purification of methanol. In both cases, the purity of the starting material should not be lower than 99% in order to obtain the absolute alcohol.

(3) Dimethyl formamide: Dimethyl formamide (Baker Chemical Company) was shaken repeatedly with calcium oxide and the mixture was stored overnight. The liquid was decanted and treated with calcium hydride¹²⁵. The mixture was vacuum distilled; b.p. 45-46°C, (12-13 mm).

(4) Dimethyl sulphoxide: Dimethyl sulphoxide (Matheson Coleman and Bell) was treated with calcium hydride until it ceased bubbling and the mixture was then distilled under vacuum. The distilled dimethyl sulphoxide was kept in a bottle containing molecular sieves (1/16" pellets).

(5) Tetrahydrofuran (THF): THF (Fisher Scientific Co.) was treated with potassium hydroxide and allowed to stand overnight. The liquid was then decanted and treated with sodium metal for at least two days. The liquid was again removed from sodium and distilled over lithium aluminumhydride under reduced pressure.

(6) Dioxane: Dioxane was first treated with potassium hydroxide for 24 hrs. The liquid was then refluxed over an excess of sodium for 7 hrs. until the reaction ceased and the sodium remained bright. The liquid was fractionally distilled; b.p. 100°C.

(7) 2-Methoxyethanol (Fisher Scientific Co.): This was purified by fractional distillation; b.p. 124°C.

V. MEASUREMENT OF THE ACIDITY CONSTANTS FOR SUBSTITUTED THIOPHENOLS

Approximately 0.003N solution of the thiophenol was prepared by dissolving a weighed portion of thiol in freshly distilled methanol in a 25 ml volumetric flask. Five ml of this solution was then diluted to 50 ml with methanol and 25 ml of the diluted solution was allowed to reach the thermal equilibrium in the thermostat bath at 25°C ($\pm 0.05^\circ\text{C}$). The solution was titrated with 0.11 N of lithium methoxide in methanol. A small stream of nitrogen was passed through the reaction vessel to avoid the oxidation of the thiophenoxide by air. The pH values were measured by a "Radiometer" Type PHM26 with a glass electrode as the indicating electrode and a calomel electrode as the reference electrode. Commercial buffer solutions were used for standardisation; pH 7.00 (Corning glass work), pH 6.48 (Radiometer), pH 9.18 (Beckman). Before the titration was started, the pH meter was repeatedly standardized with these three buffers until the reading showed the correct values.

pK_a values were obtained from the points of half neutralization. End points determined from the experiment were compared with the stoichiometric end points; good agreement was observed. One of the typical titration curves is shown in Fig. E-1. Two measurements for the acidities constants have been taken in each case.

VI. KINETIC MEASUREMENTS

(1) Preparation of the reaction solution:

(a) Lithium methoxide: A 0.2N solution of $LiOCH_3$ was prepared by dissolving 1.4 g of high purity lithium wire (Foots Mineral Company) in 900 ml of freshly distilled methanol. The solution was filtered if there was a small amount of residue left after hydrogen evolution. The concentration of the solution was standardized three times with potassium hydrogen phthalate, which was dried previously in an oven at 80° . The reproducibilities were within 0.3%.

(b) Lithium thiophenoxide or substituted thiophenoxides: These reagents were prepared by adding 10% excess of thiol to the standardized lithium methoxide solution.

(2) Determination of the reaction rates:

(a) In the lithium methoxide run: A 20 ml of 0.1355N solution of lithium methoxide was diluted to 75 ml and the dilute solution was transferred to a 250 ml long neck flask. A weighed amount of substrate (benzyl chloride) was dissolved in methanol in a 25 ml volumetric flask. Both solutions were allowed to reach the thermal equilibrium in a

FIGURE E-1

Titration curve of p-CH₃-thiophenol for pKa
measurement

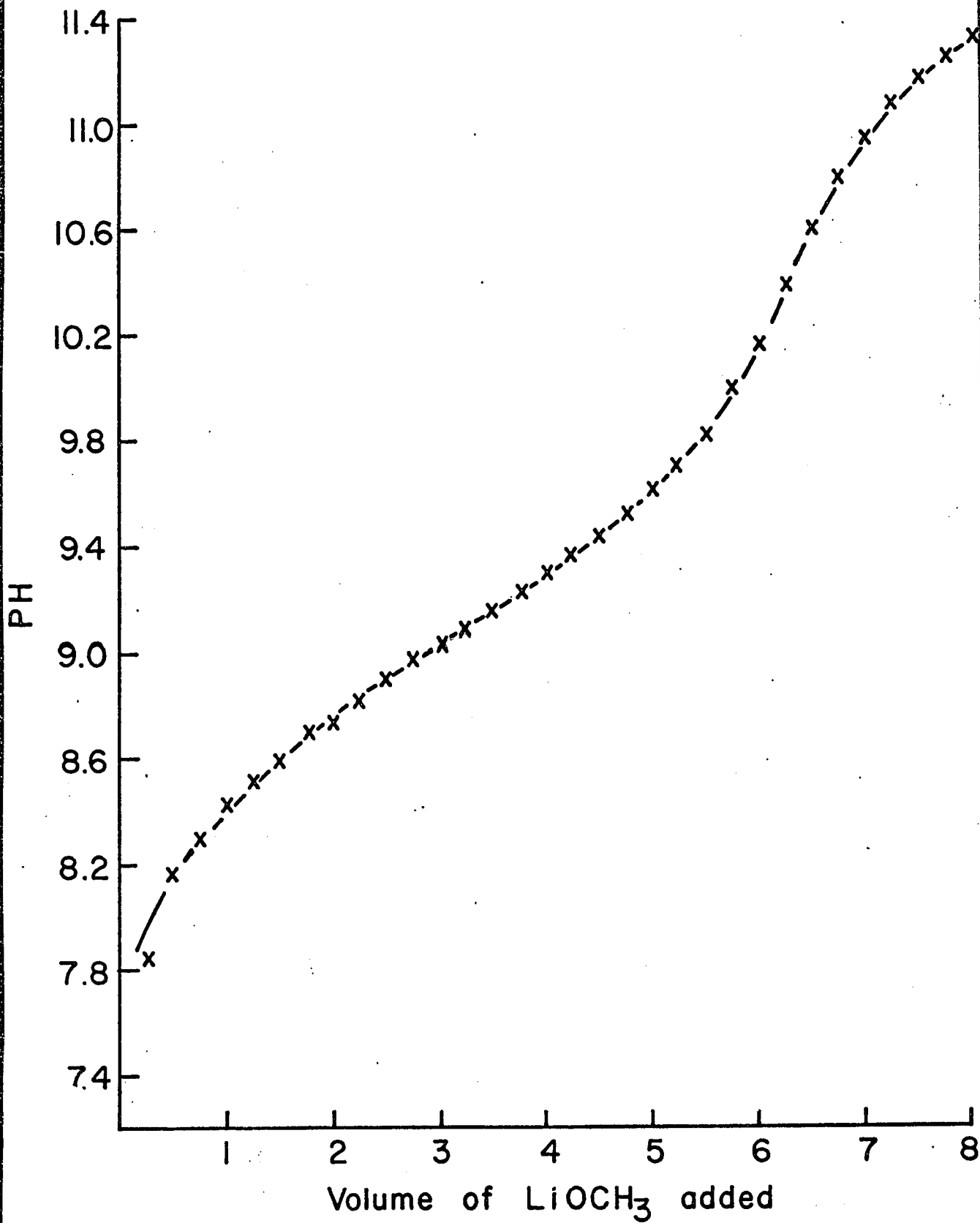


FIG. E-1.

water bath. The temperature of the water bath was controlled at $25^{\circ} \pm 0.05^{\circ}\text{C}$. The two solutions were mixed and the reaction began. The initial concentration for methoxide and the substrate were both 0.0271 M. Aliquots (5 ml) were withdrawn at recorded times and quenched in an Erlenmyer flask containing 20 ml of 0.1 M nitric acid and 30 ml of (chloride-free) ethyl ether. The aqueous layer was separated immediately by a separatory funnel, and the ethereal layer was washed with 3 ml of distilled water. The washing was then combined with the aqueous layer. The chloride content of the aqueous layer was determined by potentiometric titration with 0.06 N silver nitrate solution. The titrations were performed by Accumet pH meter (Fisher) with a silver-silver chloride electrode as the indicating electrode and a calomel saturated mercuric sulfate (K 601, radiometer) as the reference electrode. A one-milliliter microsyringe was used for titration and the volume was calibrated using pure water.

(3) In lithium thiophenoxide and substituted thiophenoxide runs:

The amount of thiol was weighed in a 25 ml volumetric flask; 10 ml of 0.1355N solution of lithium methoxide was added to the flask containing a weighed amount of thiol. The volume was made up to 25 ml with methanol. The solution was transferred to a 250 ml long-necked flask and 50 ml of methanol was added. (In the case of p-nitrothiophenol, the solution has to be warmed slowly in order to dissolve the thiol in methanol). A weighed amount of substrate was dissolved in a 25 ml volumetric flask and put in the water bath for 3 min. to reach thermal equilibrium. The initial concentration of the nucleophile and the substrate were 0.0135 N. Aliquots (5 ml) were withdrawn at recorded times and

quenched in a flask containing 20 ml of nitric acid (0.1 N) and 30 ml of ethyl ether. The aqueous layer was separated and combined with the washing from the ethereal layer. Four drops of 30% hydrogen peroxide were added to the aqueous solution to decompose the unreacted thiol. The chloride content of the aqueous layers was determined by potentiometric titration.

(4) Fast reactions in the solvent of dimethyl sulphoxide-methanol:

Five ml of nucleophile was mixed with 5 ml of substrate after thermal equilibrium. After certain intervals, the mixture was poured into a chilled flask containing 20 ml of 0.1 N of HNO_3 and 30 ml of ether and the aqueous layer was immediately separated.

(5) Solvolysis of substituted benzyl chlorides: A weighed amount of substrate was dissolved in methanol and placed in a temperature-controlled water bath. At recorded times, aliquots were withdrawn for analysis of the chloride content. (The procedure was the same as that for the reactions described under methoxide runs, except that no nucleophile was placed in it).

VII. SOLVENT EFFECT ON THE CHEMICAL SHIFTS OF SUBSTITUTED BENZYL CHLORIDES

Nmr data were obtained with a Varian model V-4302 spectrometer at 60 Mc/sec. The concentration for each measurement was 0.0542M, which was twice that of the initial concentration for the kinetic measurement. Purities of the compounds studied were checked

by gas-chromatographic analysis. Freshly prepared solutions were used. The mixed solvents were prepared by volume % and converted into mole fractions by the equation:

$$n_1 = (v_1 d_1 / M_1) / [(v_1 d_1 / M_1) + (1 - v_1) d_2 / M_2]$$

where n is the mole fraction of the solvent composition; d_1 and d_2 are the densities of the solvents; v is the volume % of a solvent composition, and M_1 and M_2 are the molecular weights of the solvents respectively.

VIII. MASS SPECTRA OF SUBSTITUTED DIPHENYL DISULFIDES

Mass spectra were taken on an RMU-6D mass spectrometer (Tokyo, Japan). Samples were introduced through a heated inlet system in a range from 100-200°C. The electron energy was 50 ev.

IX. TREATMENT OF THE DATA

(1) The reactions of lithium methoxide and thiophenoxides with benzyl chlorides are second-order and the values of $[(RCl)_0 - (Cl)]^{-1}$ were plotted against t , where $(RCl)_0$ is the initial concentration of reagent and (Cl) is the concentration of the chloride produced at the time t . The slope of this plot is equal to the observed second-order rate constant k_{app} of the reaction. A typical plot for these reactions is

shown in Fig. E-II. For the solvolysis in methanol, the first-order rate constants (k_1) were calculated from the slopes of the plots of $\log [(RCl)-(Cl^{-1})]$ vs. time, as shown in Fig. E-III. The observed rate constants k_{app} for the S_N2 reaction are not true values for the displacement reactions, as they contain some contribution from the solvolysis reaction. Correction is made by the following method⁹⁰:

$$dx/dt = k_1(a-x) + k_2(a-x)^2$$

$$dx/(a-x)^2 = [(k_1/a-x) + k_2]dt$$

As

$$x \rightarrow 0$$

$$dx/(a-x)^2 = \left(\frac{k_1}{a} + k_2\right)dt$$

$$k_{app} = \frac{k_1}{a} + k_2$$

It follows that k_{app} (the slope of the plot of $1/(a-x)$ vs. t) is, when the reaction has not progressed very far, approximately equal to k_2 (the true bimolecular rate coefficient) plus k_1/a ; k_1 is the solvolysis rate coefficient. The k_2 values reported are k_{app} less k_1/a . Since k_{app} was based on 40-60% of the reaction, the corrections are somewhat approximate. On the other hand, the corrections were highest at about 7% of k_{app} . Thus, the uncertainty due to the approximation is, in the most unfavorable case, only slightly greater than experimental error.

In the case of fast reactions such as those when thiophenoxides were used as the nucleophiles or when the reactions were carried out in high content of aprotic solvent, such corrections for the solvolysis would have been well within the experimental error, and were therefore neglected.

FIGURE E-II

Plot of the reciprocal concentration of the reagent against time for the reaction of m-NO₂-benzyl chloride with m-CH₃-thiophenoxide in CH₃OH at 25°

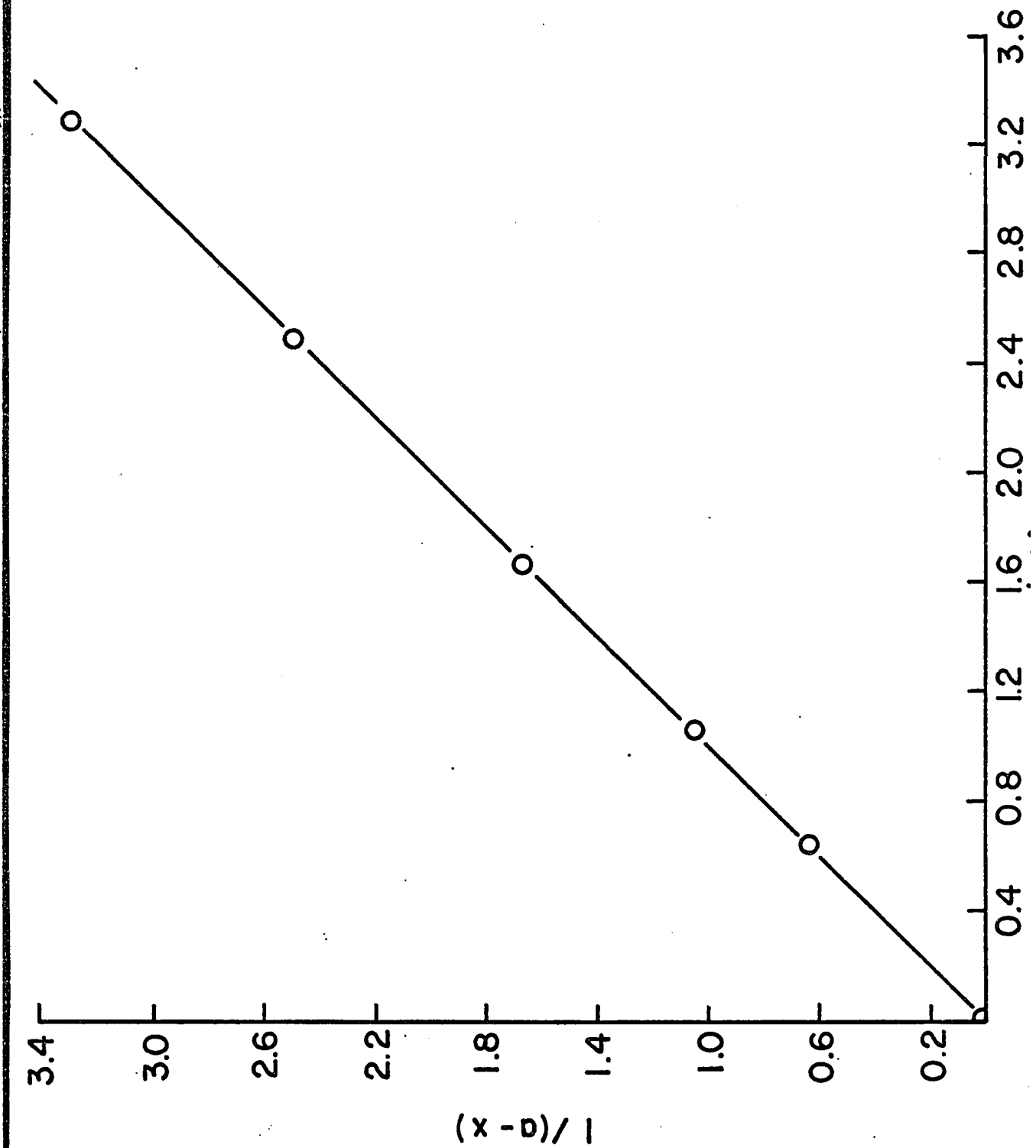
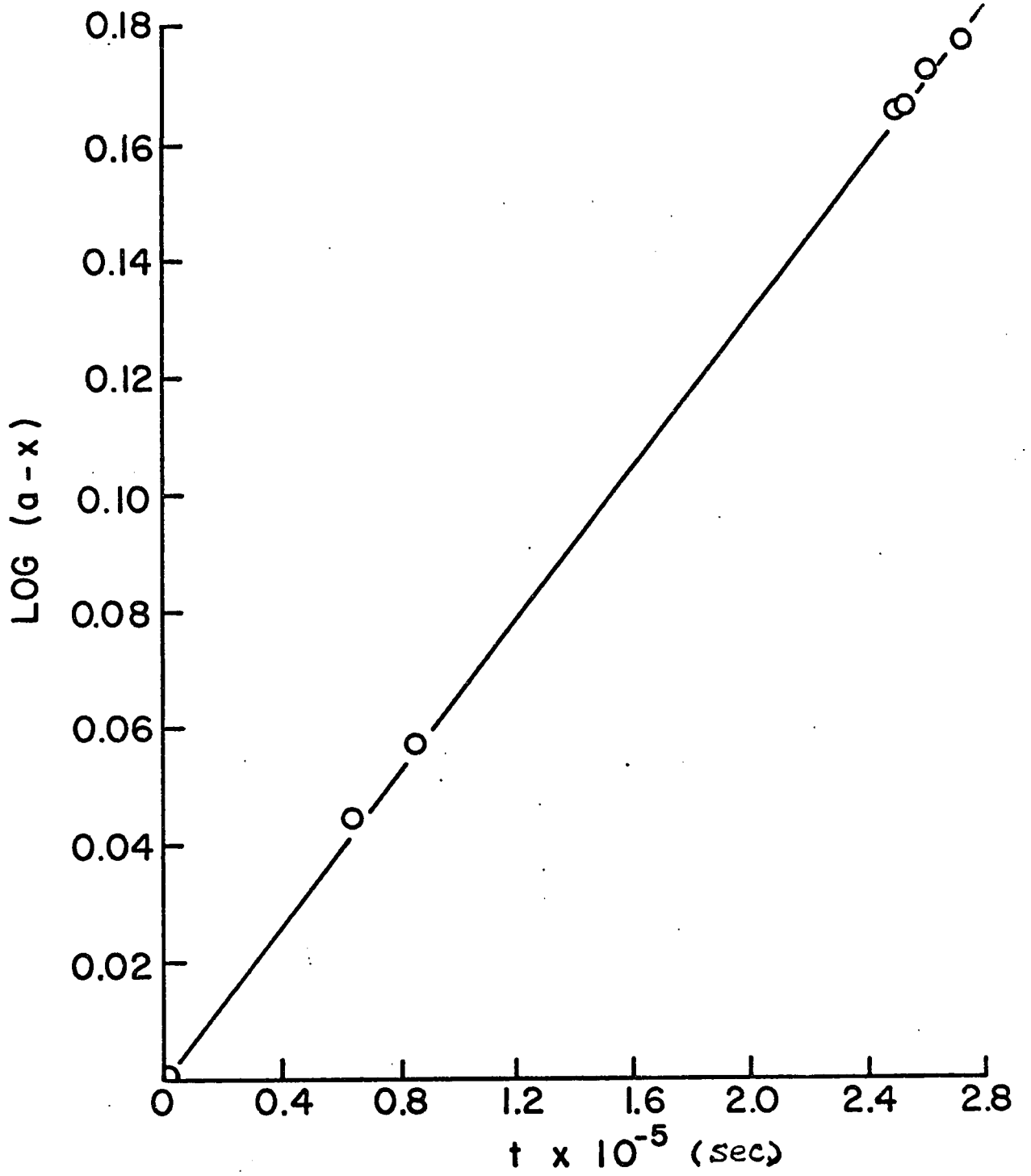


FIGURE E-III

Logarithms of (a-x) plotted against t for the
solvolysis of 2,6-dimethylbenzyl chloride in
CH₃OH at 25°



(2) Least square fitting: The reaction constants (f_N) were obtained from the slopes of the regression lines

$$\log k = m \log k' + b$$

where k is the rate constant for the bimolecular reaction of substituted benzyl chloride with substituted thiophenoxides, k' is the corresponding value for benzyl chloride as the substrate, and m is the relative reaction constant for the two reactions. The least-square fitting was performed by the computer.

In order to calculate the correlation constant r ¹²⁶, the dependent variable and independent variable are reversed, i. e.

$$\log k' = m' \log k + b'$$

The correlation coefficient was calculated by the equation¹²⁶

$$r = (mm')^{1/2}$$

(3) Thermodynamic calculations: The activation energy was obtained from the plot of $\log k$ vs. $1/T$

$$\log k = -E_a / 2.303 RT + C$$

$$E_a = -\text{slope} \cdot 2.303 R$$

where E_a is the activation energy. The enthalpy of activation (ΔH^\ddagger) is almost equivalent to the experimental energy of activation in the Arrhenius equation. In a liquid system the $P\Delta V$ term is negligible at ordinary pressure:

$$E_a = \Delta H^\ddagger + RT$$

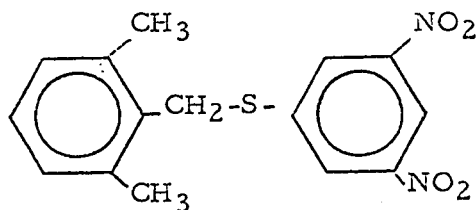
The entropy of activation can therefore be readily calculated from the activation enthalpy and the rate constant

$$k = \frac{kT}{h} e^{\Delta S^\ddagger/R} e^{-\Delta H^\ddagger/RT}$$

where k is Boltzmann's constant and h is Planck's constant.

X. ISOLATION OF THE PRODUCTS

The possibility of α -elimination for the reaction of *o*-substituted benzyl chlorides with methoxide has been shown by Bunnett et al⁹⁰ to be insignificant. Reiheimer et al isolated the products for the reactions of methoxide and thiophenoxide with benzyl chlorides to show that they are nucleophilic displacement reactions without the complication of other side reactions. The rate for the reaction of 2,6-dimethylbenzyl chloride with 3,5-dinitrothiophenoxide is abnormally fast. It was thought that the reaction mechanism might be different from the S_N2 reaction. Therefore, the product of this kinetic reaction was isolated; it is a bright yellow crystalline solid. The melting point is 151°C. The identity was characterized by nmr, as shown in the structure:



The chemical shifts of this compound were compared with the chemical shifts of 2,6-dimethylbenzyl chloride and that of the 3,5-dinitrothiophenoxide as shown in the following table:

Chemical Shifts of Various Substituents in ppm

| Compound | δ_{CH_3} | δ_{CH_2} | $\delta_{\text{H}(\text{Ar}_1)}$ | $\delta_{\text{H}(\text{Ar}_2)}$ |
|-----------------------------|------------------------|------------------------|----------------------------------|----------------------------------|
| 2,6-dimethylbenzyl chloride | 2.4 | 4.55 | 7.00 | |
| 3,5-dinitrothiophenol | | | | 8.5 (doublet) 8.8 (triplet) |
| product | 2.45 | 4.4 | 7.18, 7.35 | 8.5 (doublet) 8.9 (triplet) |

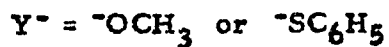
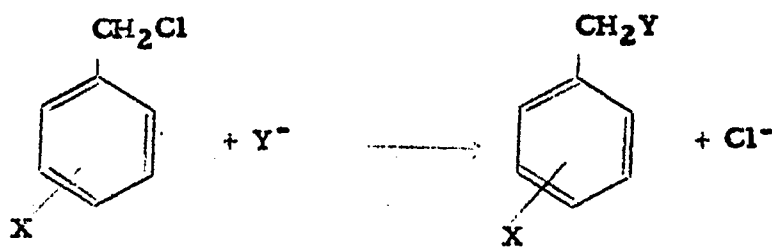
RESULTS AND DISCUSSION

I. SOLVENT EFFECTS

(1) Solvent Effect on Reaction Rates

There are four kinds of strong solvent-solute interactions⁶: ion dipole, dipole-dipole, π -complex-forming, and hydrogen bonding. In protic solvents, anions are solvated by ion-dipole interaction, on which is superimposed a strong hydrogen bonding which is greatest for small anions. In dipolar aprotic solvents, anions are solvated by ion-dipole interactions, on which is superimposed an interaction due to the mutual polarizability of the anion and the solvent molecule, which is greatest for the large anions.

In order to study the influence of solvent changes on Bunnett's rate ratios, the solvent mixtures of methanol and dimethyl sulphoxide (DMSO) in various proportions were chosen. The solvent pair MeOH-DMSO seems to be particularly attractive, because the dielectric constant of DMSO (ca. 46) is somewhat larger than that of methanol (ca. 34); [the former is the typical aprotic solvent while the latter is the protic solvent]. The rate constants for the reactions of o-methylbenzyl chloride and benzyl chloride with lithium methoxide or lithium thiophenoxide in various solvents at 25° are shown in Tables 1-2.



Addition of DMSO to methanol causes only a slight increase in the dielectric constant of the medium, but the rates increase greatly. According to Ingold², the direction of the change in rate in different solvents may be predicted by considering the extent of solvation of the initial and transition state.

TABLE I

Reactions of Substituted Benzyl Chloride with Lithium Methoxide in Various Solvents at 25°C

| ε of solvent | Solvent | Subst.- Benzyl Cl. | k _{app.} l mole ⁻¹ sec ⁻¹ | k _{solv.} sec. ⁻¹ | k ₂ l mole ⁻¹ sec. ⁻¹ (corrected) |
|--------------------|---------------------------------|-------------------------------------|--|---------------------------------------|--|
| 32.70 | CH ₃ OH | H | 2.52 × 10 ⁻⁵ | 0.62 × 10 ⁻⁷ | 2.41 × 10 ⁻⁵ |
| 43.82 ^a | 50% MeOH + 50% DMSO | H | 4.38 × 10 ⁻⁴ | 1.44 × 10 ⁻⁷ | 4.37 × 10 ⁻⁴ |
| 46.80 ^a | 25% MeCH + 75% DMSO | H | 4.11 × 10 ⁻³ | b | 4.11 × 10 ⁻³ |
| 45.0 | EtOH ^c | H | 3.73 × 10 ⁻⁵ | 0.16 × 10 ⁻⁷ | 3.67 × 10 ⁻⁵ |
| 45.02 | 90% DMF + 10% MeOH | H | 5.09 × 10 ⁻³ | b | 5.09 × 10 ⁻³ |
| | 25% H ₂ O + 75% MeOH | H | 1.36 × 10 ⁻⁴ | | |
| 32.7 | CH ₃ OH | o-CH ₃ | 7.40 × 10 ⁻⁵ | 2.85 × 10 ⁻⁷ | 6.87 × 10 ⁻⁵ |
| 43.82 | 50% MeOH + 50% DMSO | o-CH ₃ | 1.09 × 10 ⁻³ | b | 1.09 × 10 ⁻³ |
| 46.80 | 25% MeOH + 75% DMSO | o-CH ₃ | 1.21 × 10 ⁻² | b | 1.21 × 10 ⁻² |
| 45.0 | EtOH ^c | o-CH ₃ | 8.33 × 10 ⁻⁵ | 0.64 × 10 ⁻⁷ | 8.10 × 10 ⁻⁵ |
| 45.02 | 25% H ₂ O + 75% MeOH | o-CH ₃ | 4.14 × 10 ⁻⁴ | | |
| 42.70 | CH ₃ OH | 2,6-(CH ₃) ₂ | 2.61 × 10 ⁻⁴ | 1.50 × 10 ⁻⁶ | 2.06 × 10 ⁻⁴ |
| 43.82 | 50% MeOH + 50% DMSO | 2,6-(CH ₃) ₂ | 3.88 × 10 ⁻³ | b | 3.88 × 10 ⁻³ |
| | CH ₃ OH | p-CH ₃ | 5.52 × 10 ⁻⁵ | 3.33 × 10 ⁻⁷ | 4.92 × 10 ⁻⁵ |
| | 90% DMF + 10% MeOH | o-CH ₃ | 1.27 × 10 ⁻² | b | 1.27 × 10 ⁻² |

[For notes to Table I, please see p. 87]

NOTES TO TABLE I

k_{app} is the slope of a plot of $1/(a-x)$ vs. t .

k_{solv} is the first order rate constant for the solvolysis.

k_2 is the corrected second-order rate coefficient.

(a) = private communication from Tommila.

(b) = solvation is negligible in this case.

(c) = Lithium ethoxide was used as the nucleophile instead of methoxide.

TABLE 2

**Reactions of o-substituted Benzyl Chlorides with Lithium Thiophenoxide in Various Solvents
at 25°C**

| Solvents | ϵ | Substituent in ortho position | k (l mole ⁻¹ sec. ⁻¹) |
|---------------------|------------|-------------------------------------|--|
| CH ₃ OH | 32.70 | H | 2.46×10^{-2} |
| 50% MeOH + 50% DMSO | 43.82 | H | 1.99×10^{-1} |
| 25% MeOH + 75% DMSO | 46.80 | H | 9.70×10^{-1} |
| EtOH | 45.0 | H | 4.85×10^{-2} |
| CH ₃ OH | 32.70 | CH ₃ | 1.21×10^{-1} |
| 50% MeOH + 50% DMSO | 43.82 | CH ₃ | 8.82×10^{-1} |
| 25% MeOH + 75% DMSO | 46.80 | CH ₃ | 4.67×10^0 |
| EtOH | 45.0 | CH ₃ | 1.92×10^{-1} |
| CH ₃ OH | 32.70 | 2,6-(CH ₃) ₂ | 7.42×10^{-1} |

Since the reaction involves a transition state with dispersed charge, the rate should decrease as the dielectric constant of the solvent increases. This is in agreement with the theory of Hughes and Ingold², i. e. the plot of the logarithm of the rate constant against the reciprocal dielectric constant of the solvent should be linear with a positive slope³. In fact, this plot does not give the straight lines as shown in Fig. 1-2, and the rates go in opposite directions to those predicted by this theory.

Treatments based on electrostatic considerations only, which regard the solvent as a continuum having a bulk dielectric constant⁷, sometimes fail completely to predict solvent effects^{5,6}. Most anions in dipolar aprotic solvents are much less solvated than in protic solvents⁸, but polarizable charged transition states in dipolar aprotic solvents are more solvated than in protic solvents.

It has been observed that the rates of bimolecular reactions of anions passing through a large polarizable transition state are much faster in dipolar aprotic solvents^{9,10}. The rate enhancement of these reactions at high DMSO concentration (mole fraction of DMSO > 0.5%) was attributed by Tommila et al⁴⁹ to an increase in anion reactivity caused by reduced solvation of the anion in the aprotic solvent (whereas at low concentrations of DMSO, it was found that DMSO has the catalytic activity⁴⁹).

FIGURE 1.

Logarithms of k for the reactions of *o*-
substituted benzyl chloride with methoxide
plotted against reciprocal of the dielectrical
constants of the solvents

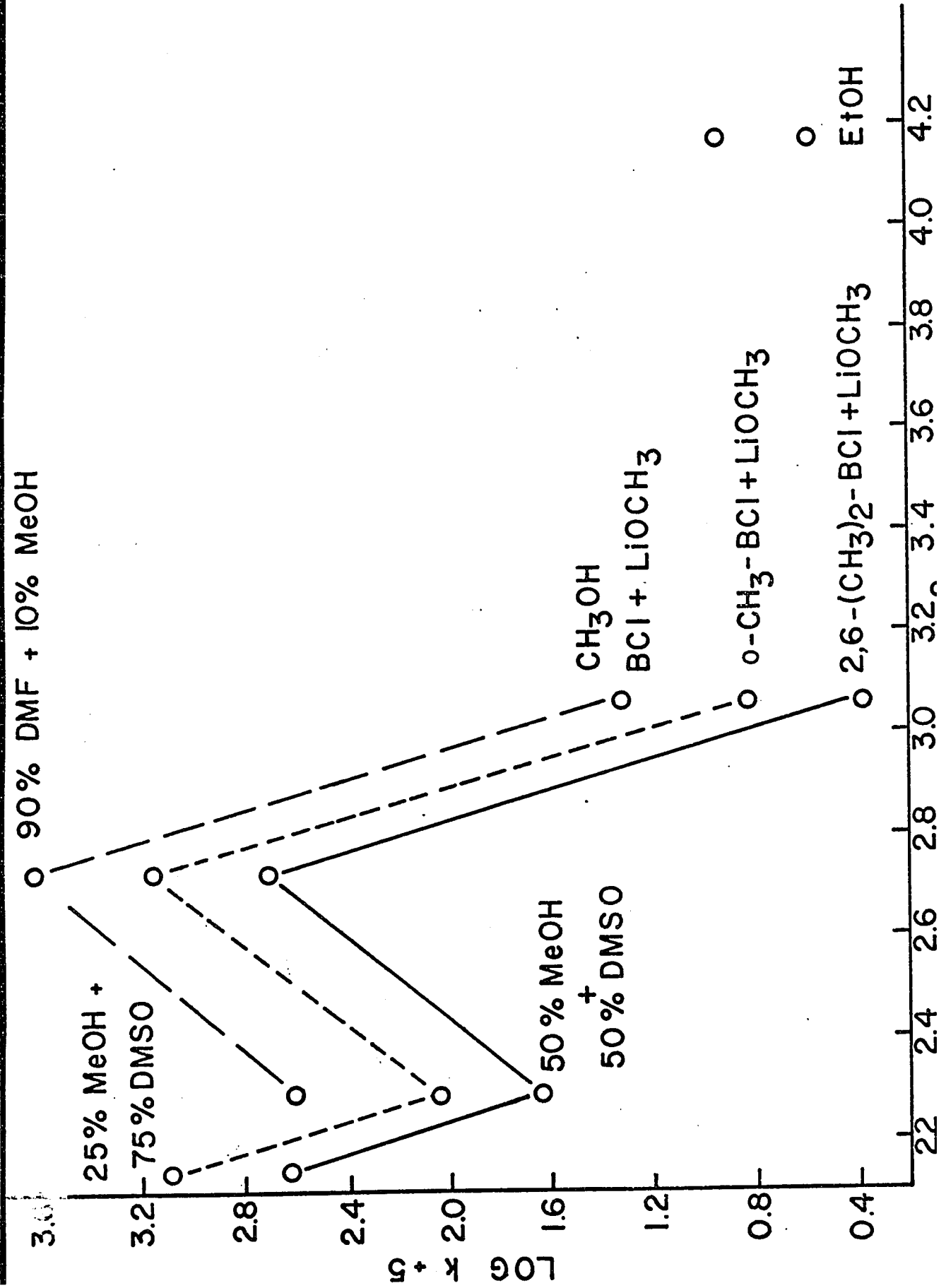


FIGURE 2.

Logarithms of k for the reactions of *o*-substituted benzyl chloride with thiophenoxide plotted against reciprocal of the dielectrical constants of the solvents.

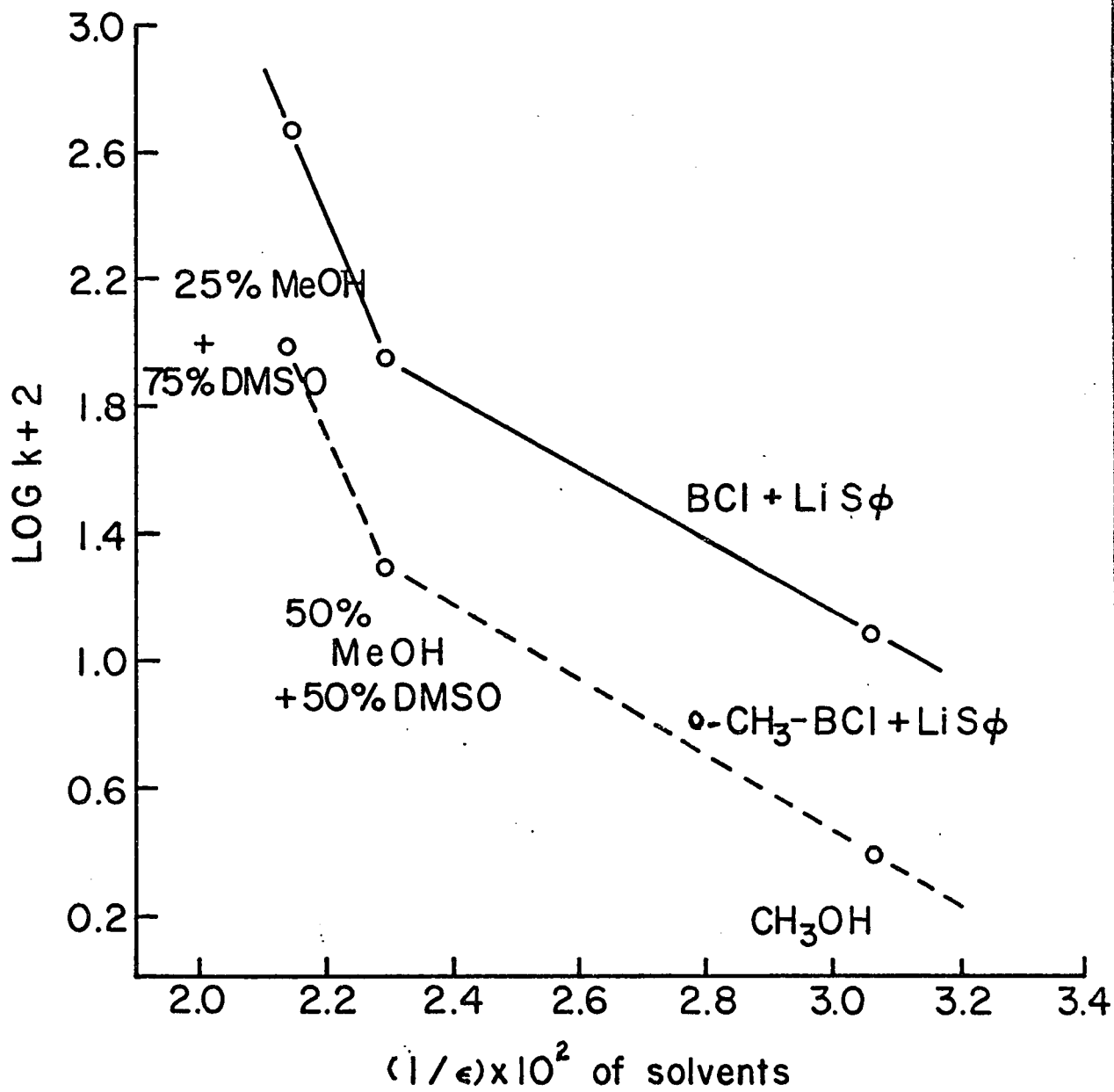


FIG. 2

It is also possible that ion-pair dissociation of the nucleophile in DMSO, which has a higher dielectric constant than methanol, may contribute to the rate increase in high DMSO concentration of the solvent. Ion pairs are generally considered to have less or no reactivity relative to their free anions^{29,23,24,28}. This possibility is ruled out by the fact that the rate constant for the reaction of benzyl chloride with methoxide in 90% DMF-MeOH is 211 times faster than the corresponding reaction in methanol. Both solvents possess similar dielectric constants.

In solvent of DMSO composition higher than 75% DMSO-MeOH, the rate of the reaction of *o*-methyl benzyl chloride with thiophenoxide is too fast to be measured by the method we used.

Support for the favourable solvent effect on the S_N2 reaction in aprotic solvent⁸ can also be seen from the relatively small change for the rate of solvolysis in various solvents as compared to the corresponding nucleophilic displacement reaction, as shown in Table 1.

(2) Solvent effect on the adjusted rate ratios

In spite of the fact that the change of reaction rates in these solvent mixtures is at least an order of magnitude larger than in other solvents, the Bunnett adjusted rate ratios remain constant, as shown in Table 3. The adjusted ratio contains four rate constants which serve as a parameter for the energy of the interaction between the ortho substituent and the incoming nucleophile in the transition state.⁹⁰

$$(k_Y/k_{MeO^-})_{o-R} / (k_Y/k_{MeO^-})_H$$

The solvent effects do not appear to change the Bunnett ratios. These ratios may be solvent independent only if $\Delta\Delta\Delta F^{solv} = 0$;

$$\Delta\Delta\Delta F^{solv} = (\Delta F_{t-o}^{solv} - \Delta F_{g-o}^{solv}) - (\Delta F_{t-H}^{solv} - \Delta F_{g-H}^{solv})$$

where ΔF_{t-o}^{solv} is the solvation energy of the transition state for the ortho substituted substrate, and ΔF_{g-o}^{solv} is the solvation energy of the ground state of the ortho compound.

Similarly, ΔF_{t-H}^{solv} and ΔF_{g-H}^{solv} are the solvation energies of the transition state and the ground state for benzyl chloride respectively. Thus, $\Delta\Delta\Delta F^{solv}$ is the gross difference of solvation energy between the reactions of benzyl chloride and the ortho substituted compound with the same nucleophile. It will be zero if:

(a) $\Delta F_{t-o}^{solv} = \Delta F_{g-o}^{solv}$, $\Delta F_{t-H}^{solv} = \Delta F_{g-H}^{solv}$: or

(b) if the first term is equal to the second term,

$$(\Delta F_{t-o}^{solv} - \Delta F_{g-o}^{solv}) - (\Delta F_{t-H}^{solv} - \Delta F_{g-H}^{solv}) : \text{ or}$$

(c) if $\Delta F_{t-o}^{solv} = \Delta F_{t-H}^{solv}$, $\Delta F_{g-o}^{solv} = \Delta F_{g-H}^{solv}$.

Among these possibilities, (a) is not reasonable.

TABLE 3

ADJUSTED RATE RATIO IN VARIOUS SOLVENTS

| Solvent | $k_Y - / k_{RO-}$ | | $\frac{(k_Y - / k_{RO-})_R}{(k_Y - / k_{RO-})_H}$ | |
|---------------------|-------------------|-------------------|---|-------------------|
| | H | o-CH ₃ | H | o-CH ₃ |
| CH ₃ OH | 1019 | 1755 | 1.00 | 1.72 |
| 50% MeOH + 50% DMSO | 455 | 809.7 | 1.00 | 1.78 |
| 25% MeOH + 75% DMSO | 236 | 387.0 | 1.00 | 1.64 |
| EtOH ^a | 1357 | 275.2 | 1.00 | 1.75 |

(a) - ethoxide was used as nucleophile instead of methoxide

Since the distribution of the charge in the reagent and the transition state is different, the degree of solvation in the ground state and the transition state is not likely to be equal. If (c) is true, (b) will be true automatically. Therefore, the relative solvation for o-substituted and unsubstituted benzyl chloride at the transition state was examined. The ground-state solvation of the neutral molecules is considered to be small compared to that of charged species.

- (3) Comparisons of the transition state solvation for reactions of o-CH₃; 2,6-(CH₃)₂, and benzyl chloride with methoxide

For the bimolecular reaction:



the equilibrium constant between activated complex and the reagents may be expressed as

$$K^* = a_{X^*} / a_A \cdot a_B \quad (\text{R-1})$$

where a is the activity, and K^* is the equilibrium constant of the activated state. The rate of the reaction is proportional to the concentration (X^*), not activity a_{X^*} , i.e.

$$v \propto (X^*) \quad (\text{R-2})$$

Substitution of equation (R-1) to equation (R-2)

leads to:

$$v \propto K^* [A][B] \gamma_A \cdot \gamma_B / \gamma_{X^*}$$

The rate constant is given by the equation

$$k \propto K^* \cdot \gamma_A \cdot \gamma_B / \gamma_{X^*}$$

Since the activity coefficient for an ideal gaseous system is unity¹, the rate constants in solution can be related to those in the gas phase by the equation:

$$k = k_g \cdot \gamma_A \cdot \gamma_B / \gamma_{X^*}$$

Using a similar principle, Parker²⁰ estimated the relative transition state activity coefficient by measuring the rate constants in methanol and dimethyl formamide (DMF) respectively (see Introduction). Methanol and DMF are solvents with similar dielectric constants. The former is a protic solvent with $\epsilon = 32.7$, the latter an aprotic solvent with $\epsilon = 37.6$. The effect of solvation by methanol relative to DMF may be conveniently described in terms of the hydrogen-bonding activity coefficient⁴¹. An assumption that other effects for solvent-solute interactions are similar in both solvents leads to:

$$k^m = k^d \cdot \gamma_Y^H / \gamma_{(YRX)}^H$$

where k^m is the rate constant in methanol, and k^d is the rate constant in DMF. The activity coefficient γ^H is a function of the charge in free energy of the solute due to hydrogen-bond by methanol.

A comparison between rate constants (k_H) for the reactions of benzyl chloride with Y^- and the rate constants (k_{o-CH_3}) for the reaction of o-methylbenzyl chloride with Y^- in MeOH and DMF gives the hydrogen-bonding activity coefficient of the transition state $[Y\cdots CH_2(C_6H_5)\cdots Cl]^-$ relative to $[Y\cdots CH_2(C_6H_4)(CH_3)\cdots Cl]^-$, if the reaction for benzyl chloride is used as standard:

$$\gamma^H(YC_6H_5CH_2Cl)^- = 1.$$

$$\begin{aligned} k_H^m/k_H^d \cdot k_{o-CH_3}^d/k_{o-CH_3}^m &= \gamma^H(YC_6H_4(CH_3)CH_2Cl)^- / \gamma^H(YC_6H_5CH_2Cl)^- \\ &= \gamma^H(YC_6H_4(CH_3)CH_2Cl)^- \end{aligned}$$

where k_H^m and k_H^d are the rate constants for benzyl chloride in methanol and DMF respectively, and $k_{o-CH_3}^m$ and $k_{o-CH_3}^d$ are the corresponding constants for the ortho compound.

An equation equivalent to the above equation can also be derived from the reactions of 2,6-dimethylbenzyl chloride relative to reactions of benzyl chloride, with Y^- .

Values of the transition-state activity coefficients are given in Table 4. These ratios must be mostly due to the transition-state solvation for these three substrates, since the ground state solvation of the neutral molecule is small. In Table 4, the differences in activity coefficients of the transition state for the three reactions are shown to be only about 10%. These small differences may arise from the approximation in assumption or the experimental error. It seems that the degree of solvation of transition states for o-methyl, 2,6-dimethyl and benzyl chloride with methoxide are very similar.

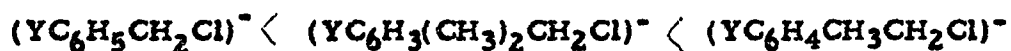
TABLE 4

Reactions of o-substituted Benzyl Chlorides with Lithium Methoxide in CH₃OH and 90% DMF-MeOH at 25°

$$\frac{k_H^m}{k_H^d} \cdot \frac{k^d(\text{CH}_3)_n}{k^m(\text{CH}_3)_n} = \gamma^H (\text{CH}_3\text{O} \text{---} \text{CH}_2 \text{---} \text{C}_6\text{H}_4 \text{---} \text{R} \text{---} \text{Cl})^-$$

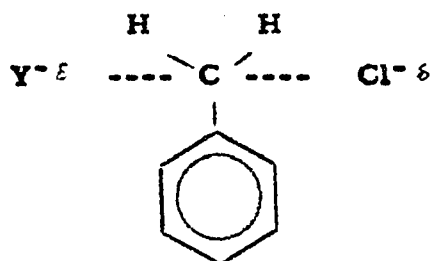
| o-Substrate | k_m | k_d | γ^H |
|-------------------------------------|-----------------------|------------------------|------------|
| H | 2.41×10^{-5} | 5.086×10^{-3} | 1.00 |
| o-CH ₃ | 6.87×10^{-5} | 1.27×10^{-2} | 0.87 |
| 2,6-(CH ₃) ₂ | 2.06×10^{-4} | 4.06×10^{-2} | 0.93 |

From Table 4 the order for the transition-state solvation of the three compounds is:



in methanol relative to DMF. These differences can be explained as follows.

It is known that a substituent in the benzyl compound can alter the degree of resemblance of the actual mechanism to the $\text{S}_{\text{N}}1$ and $\text{S}_{\text{N}}2$ models¹²⁷. An electron-donating substituent interacts strongly with positive charges of the reaction center and shifts the mechanism towards the formalistic $\text{S}_{\text{N}}1$ extreme. The two charged ends of the transition state are methoxide and chloride as shown in Structure I:



Structure I

If one examines the solvation of the chloride "end" first, hydrogen bonding solvation by methanol relative to DMF should be in the order :



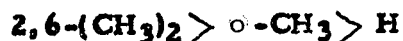
because the degree of bond breaking increases in this series. If the solvation of the methoxide "end" is considered, the order in the series should be the same as that of the chloride "end", since the degree of bond forming increases as the sigma value of the substituents increase⁹⁸. This is reflected in the change of the reaction constants with the change of the substituents of benzyl chlorides, as shown in Table 16 (details will be given later):

$f_N = 1$ for benzyl chloride which is used as a standard;

$f_N = 0.91$ for o-methylbenzyl chloride;

$f_N = 0.77$ for 2,6-dimethyl benzyl chloride.

The less the degree of bond formation in the transition state, the more the charge remains on the nucleophile Y⁻. Thus, if the steric and other specific effects are ignored, the order for the overall transition-state solvation should be:



when the solvation of the two charged ends are considered alone.

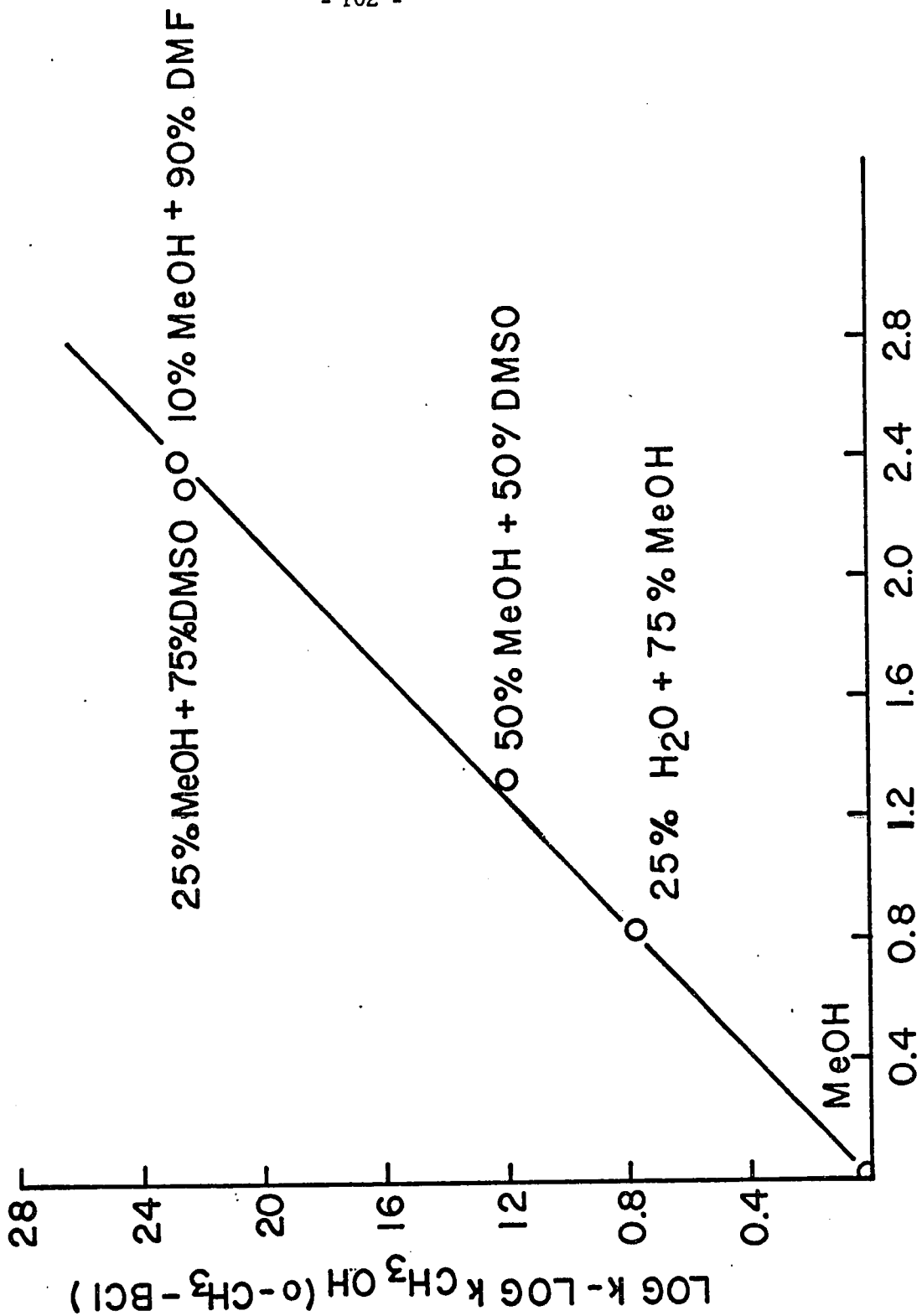
However, the observed transition state solvation of 2,6-dimethylbenzyl chloride is almost the same as that of o-methylbenzyl chloride. This is less than would be expected from its transition state structure, as explained above. The reason for this may be that the steric hindrance for solvation of the transition state is more pronounced when the second methyl group is introduced into the ortho position.

(4) Relative Sensitivity to Solvent Changes for the Reactions of Substituted Benzyl Chlorides

Another approach to the overall solvation energy of a reaction relative to the other reaction of similar reaction mechanisms is to obtain the relative sensitivity of these reactions to the solvent changes. The plots of $\log k/k_0$ for the reaction of substituted benzyl chloride with methoxide in various solvents vs. the corresponding reactions of benzyl chloride are shown in Fig. 3. The rate data for Fig. 4 - 6 were collected from Tommila's work⁴⁹. Good straight lines were obtained except for the reactions of p-NO₂-benzyl chloride relative to benzyl chloride. The curve obtained in Fig. 6 (p-NO₂ vs. H) implies that the mechanisms for the two reactions are different. Tommila proposed that the p-NO₂ compound involved a reversible carbanion intermediate. The product of trans-4,4'-dinitrostilbene was obtained instead of the ether from the displacement reaction.

FIGURE 3.

Relative sensitivity to the solvent changes for the reactions of o -CH₃-benzyl chloride with methoxide and the corresponding reactions of benzyl chloride at 25°



LOG k-LOG kCH₃OH(BCI)

FIG. 3

FIGURE 4.

Relative sensitivity to the solvent changes for the reactions of p-CH₃-benzyl chloride with methoxide in the mixed solvent of MeOH-DMSO and the corresponding reactions of benzyl chloride at 25° (rate data from Ref. 49)

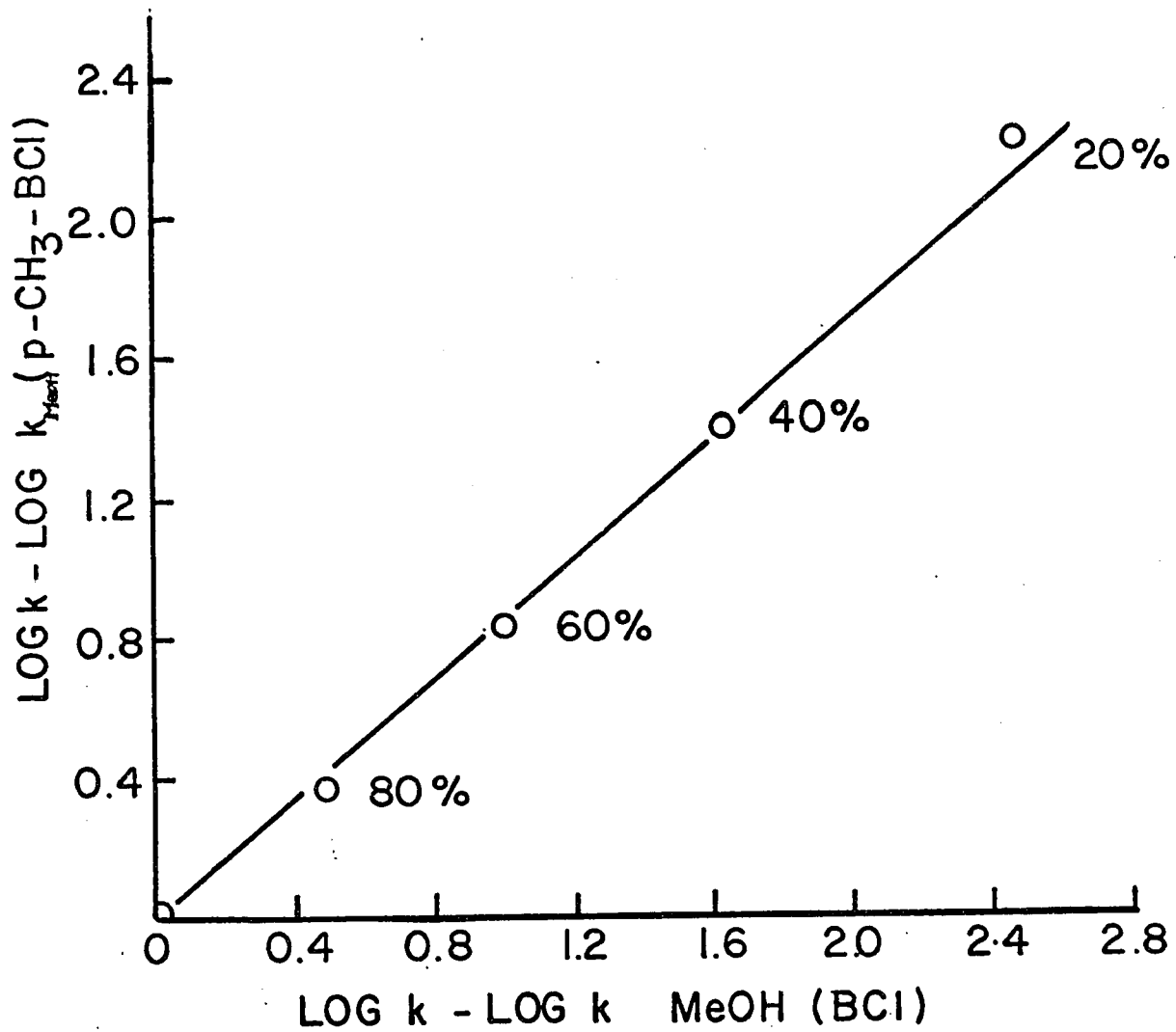


FIG. 4

FIGURE 5.

Relative sensitivity to solvent changes for
the reactions of p-Cl-benzyl chloride with
methoxide in the mixed solvent of MeOH-DMSO
and the corresponding reactions of benzyl
chloride at 25° (rate data from Ref. 49)

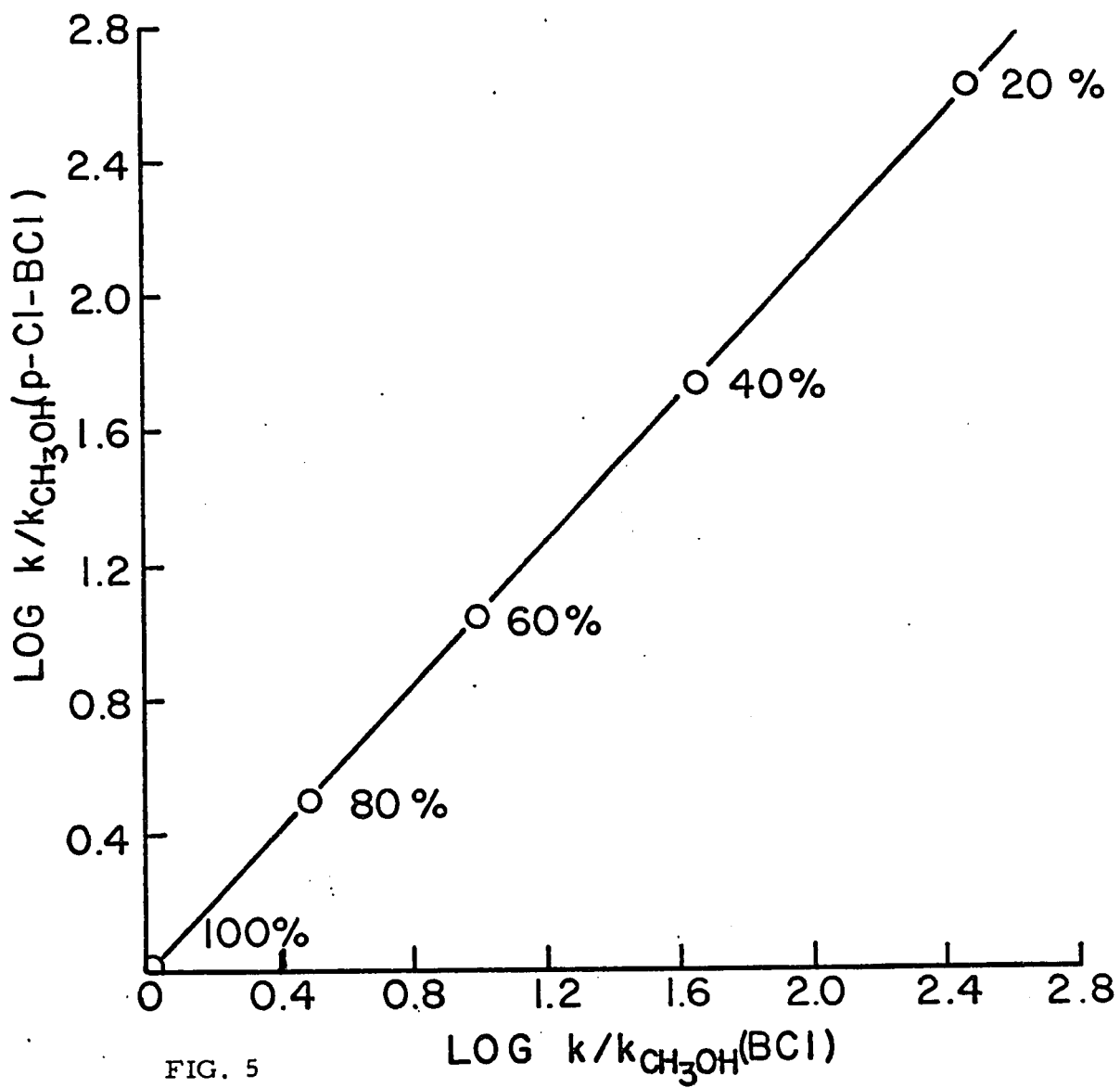
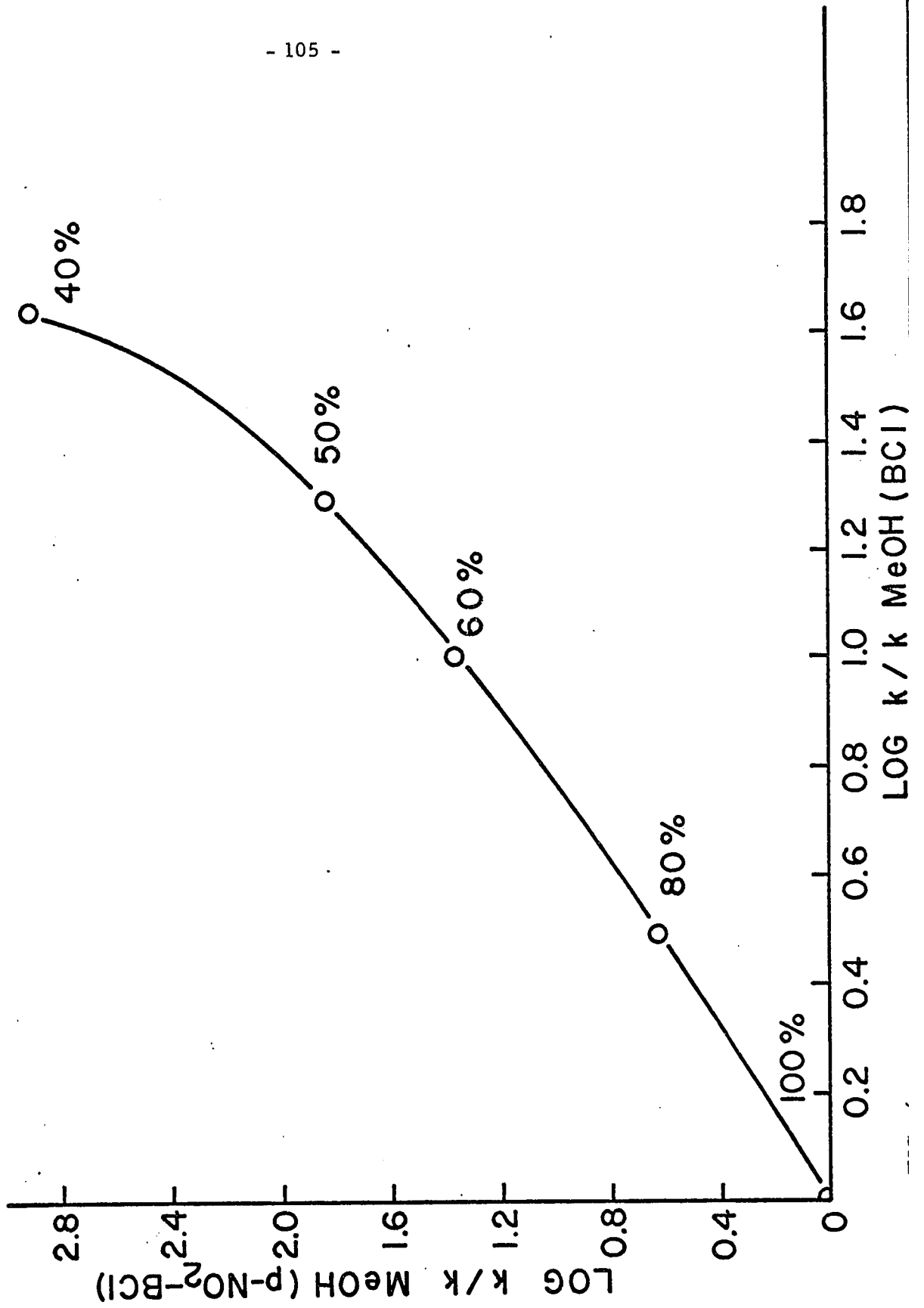
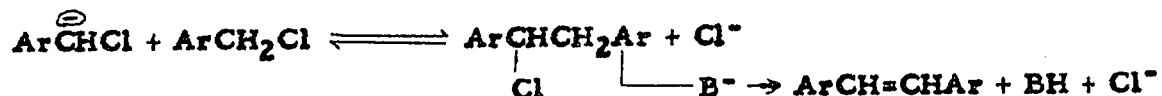
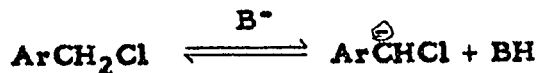


FIG. 5

FIGURE 6.

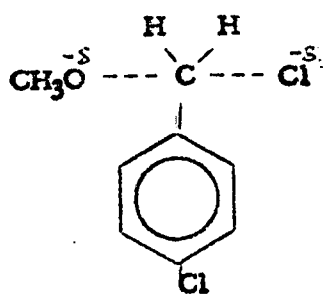
Logarithms of k/k_{MeOH} for the reactions of p-NO₂-benzyl chloride in the mixed solvent of MeOH-DMSO plotted against logarithms of k/k_{MeOH} for the corresponding reactions of benzyl chloride at 25° (data from Ref. 49).



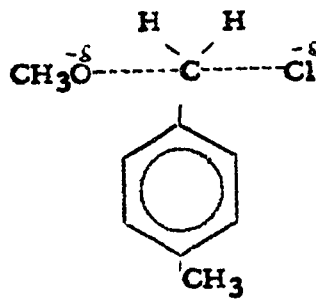


The free-energy changes for the rest of the reactions of substituted benzyl chlorides in various solvents are linearly related to one another (Fig. 3-5). The slopes of these plots also change regularly as shown in Table 5. The sensitivities of the reactions to the solvent changes increase as the electron-withdrawing power of the substituent of benzyl chloride increases. These sensitivities can be discussed in terms of the relative solvation energies of the initial and the transition state.

The transition state for p-chlorobenzyl chloride is relatively tighter than that of the methyl compound with less bond breaking of the C-Cl bond and more bond formation of the O-C bond as shown in Structures II and III. The result is that Structure III is more solvated in the transition state than Structure II, as explained above.

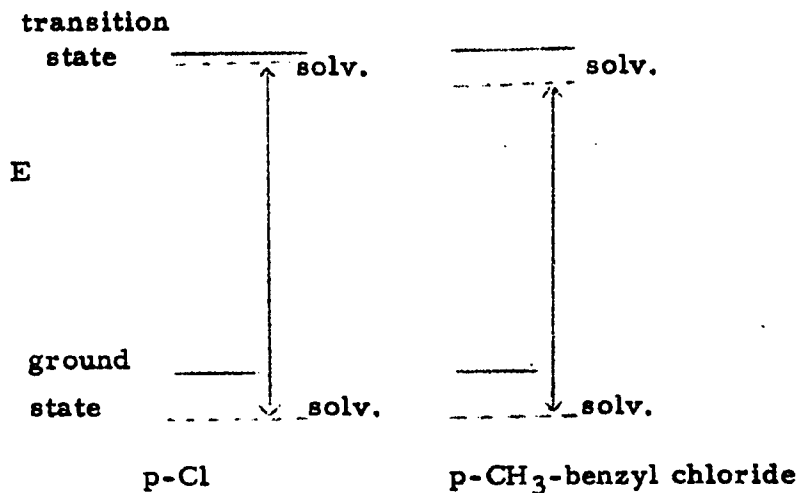


II



III

Therefore, there is relatively little loss of solvation energy for Structure III accompanying the formation of the transition state from the ionic reactant, as shown in the following schematic diagram:



Consequently, the former is more sensitive to the solvent changes than the latter, owing to its large gross loss of solvation energy from the initial to the transition state. Fuchs⁴⁷ made a similar observation but with a different approach. The rate ratios in two different solvents vary from benzyl chloride to substituted benzyl chlorides, and appear to be a linear function of the substituent constants.

TABLE 5

Relative Sensitivities of Substituted Benzyl Chlorides with Nucleophile to the Solvent Changes

| Substituents | Nucleophile | Sensitivities |
|-------------------|------------------|---------------|
| H | OCH ₃ | 1 |
| o-CH ₃ | " | 0.95 |
| p-CH ₃ | " | 0.84 |
| p-Cl | " | 1.06 |
| H | OH | 1 |
| p-CH ₃ | " | 0.98 |
| m-Cl | " | 1.11 |
| p-CH ₃ | " | 1.13 |

Similar plots of $\log k$ for the reactions of substituted benzyl chlorides with hydroxide in various compositions of mixed solvents of DMSO- H_2O vs. $\log k$ for the corresponding reactions of benzyl chloride with hydroxide are shown in Figs. 7-9 (rate data from Reference 33). The slopes show that the sensitivity increases as the electron-withdrawing power of the substituent increases. This solvent effect also serves as an indication for the variation of the transition-state structure.

The linear free-energy relationship between *o*-methyl benzyl chloride and benzyl chloride in a wide variety of solvents from methanol to 90% DMF implies that there is no specific interaction between the *ortho* methyl group and the solvent molecules, or that the presence of the *ortho* methyl group does not have the specific effect of changing the solvation shell of the reaction centre ($-CH_2-Cl$). If there was any specific solvent effect due to the presence of the *ortho* methyl substituent relative to the unsubstituted compound, the free-energy relationship would not be expected to remain linear when large changes in solvent composition are made.

The reason that Bunnett adjusted rate ratios remain constant can be easily demonstrated from Fig. 3. The closeness of the slope to unity (0.954) indicates that the relative solvent effect for the reaction of *o*-methyl and unsubstituted benzyl chloride are very similar. This is also in agreement with the previous results that the difference for the transition state solvation of benzyl chloride and *o*-methyl benzyl chloride with methoxide is small.

FIGURE 7.

Relative sensitivity to the solvent changes for
reactions of p-CH₃-benzyl chloride with hydroxide
and the corresponding reactions of benzyl chloride
at 50° (data from Ref. 33)

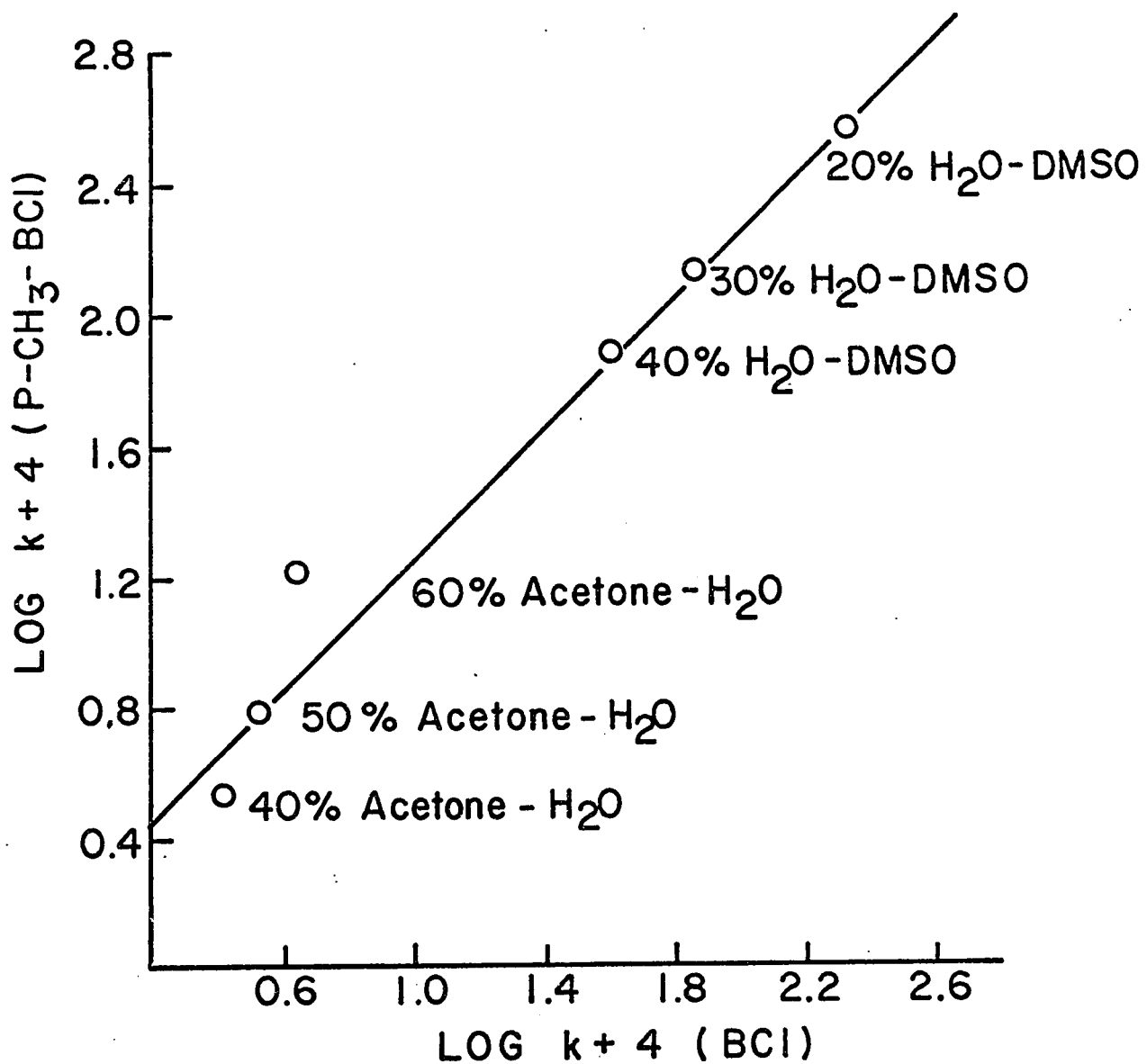


FIG. 7

FIGURE 8.

Relative sensitivity to the solvent changes for
reactions of m-Cl-benzyl chloride with hydroxide
and the corresponding reactions of benzyl chloride
at 50° (data from Ref. 33)

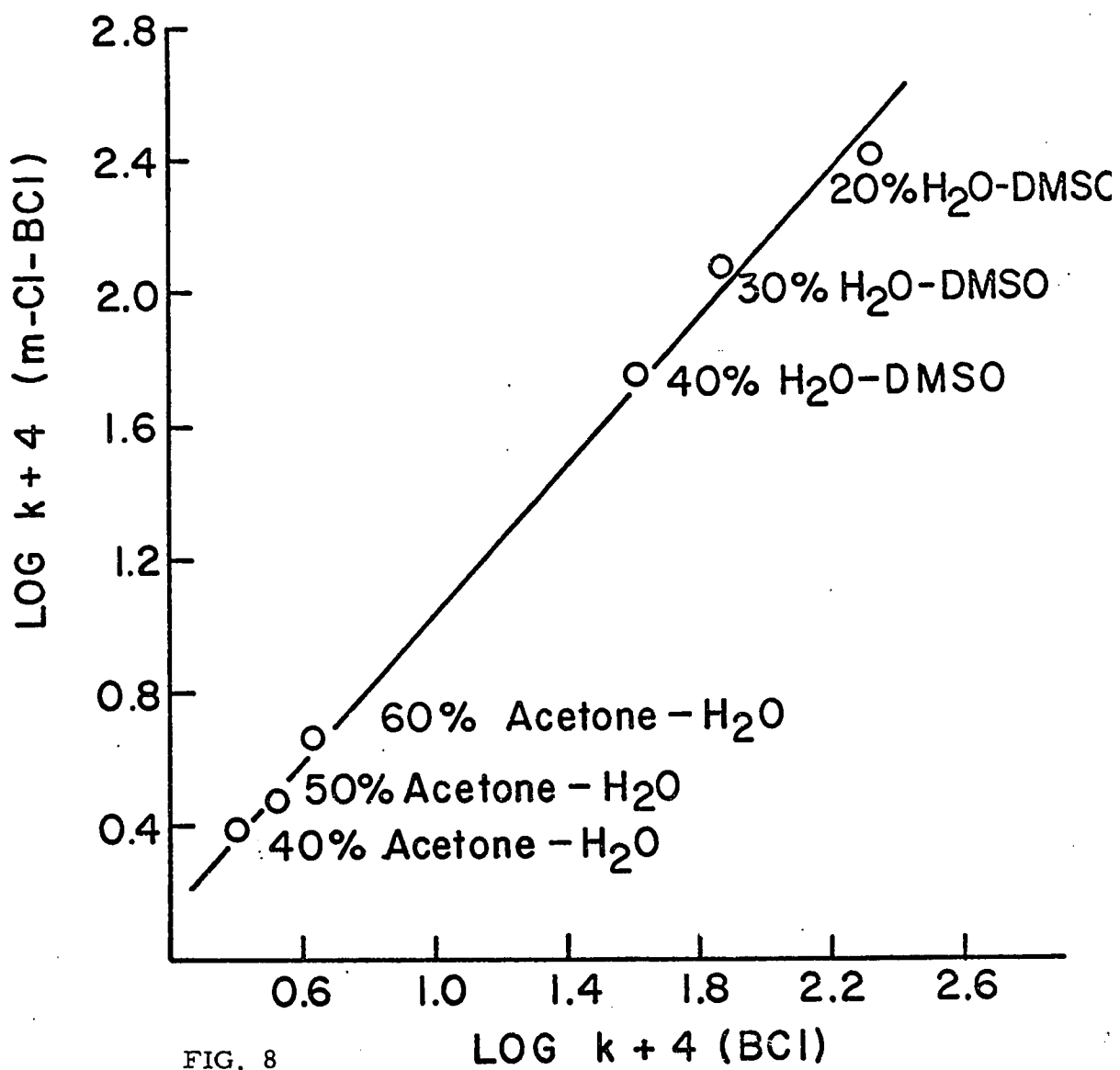


FIG. 8

FIGURE 9.

Relative sensitivity to the solvent changes for
reactions of p-Cl-benzyl chloride (data from
Ref. 33)

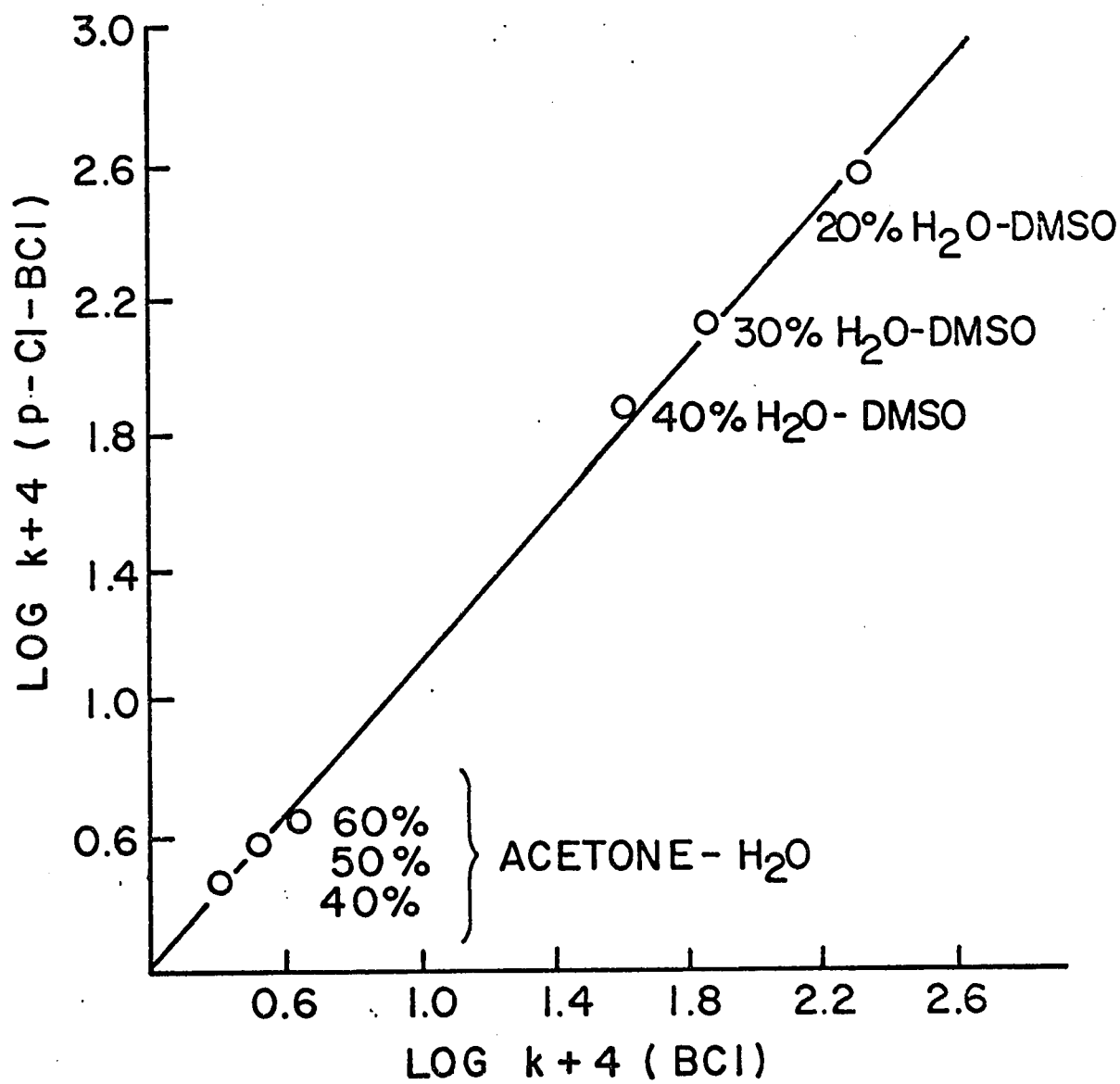


FIG. 9

II. GROUND STATE STRUCTURE CORRELATION OF SUBSTRATES AND NUCLEOPHILES

(1) Examination of the steric effect in ortho-substituted benzyl chloride by n.m.r. spectroscopy

The n.m.r. spectra of benzyl chloride, o-methyl and 2,6-dimethylbenzyl chloride were taken in various solvent mixtures (DMSO-MeOH, dioxane-MeOH, monoglyme-MeOH) at 0.054 M using tetramethylsilane as the internal reference. The chemical shifts of the CH₂ groups of o-methyl, 2,6-dimethyl and unsubstituted benzyl chloride are shown in Tables 6-8. The spectra were measured at room temperature, and the reproducibility is ± 0.5 c.p.s. It is interesting to note that the order of the τ values of the methylene groups for the three benzyl chlorides studied are $H > o\text{-methyl} > 2,6\text{-dimethyl}$. The substituent effect, in principle, will affect the nuclear screening directly by changes in the local electron density distribution¹²⁸.

It was suggested that the shielding must be interpreted in terms of both inductive and resonance effects of the substituents¹²⁹. However, Spiesscke and Schneider¹²⁸ observed that the large low field shifts of the ortho proton resonance in bromo and iodobenzene cannot be accounted for either on the basis of electron inductive or resonance effects only. This low field shift due to the presence of the ortho substituent was ascribed to magnetic anisotropy of the ortho substituent. If the chemical shifts of the methylene groups in these three benzyl chlorides are predicted by the electronic effect of the substituent alone, the order for τ values should be the

TABLE 6

Chemical Shifts of CH₂-Groups of Benzyl Chlorides in Mixed Solvents Methanol - DMSO

| Compounds | Solvents | | δ CH ₂ c.p.s. from TMS |
|--|------------------|----------------------|--|
| | Volume % MeOH | Molar fract. MeOH | |
| Benzyl chloride | 100 | 100 | 275.5 |
| " | 87.5 | 92.47 | 277.7 |
| " | 75 | 84.05 | 278.5 |
| " | 50 | 63.66 | 280.5 |
| " | 25 | 36.89 | 282.4 |
| " | 12.5 | 20.02 | 283.1 |
| " | 0 | 0 | 283.6 |
| <hr/> | | | |
| o-CH ₃ -benzyl chloride | 100 | 100 | 278.0 |
| " | 75 | 84.05 | 281.2 |
| " | 50 | 63.66 | 282.7 |
| " | 25 | 36.89 | 284.4 |
| " | 0 | 0 | 284.8 |
| <hr/> | | | |
| 2,6-(CH ₃) ₂ -benzyl chl. | 100 | 100 | 282.0 |
| " | 75 | 84.05 | 284.5 |
| " | 50 | 63.66 | 285.0 |
| " | 25 | 36.89 | 285.5 |
| " | 12.5 | 20.02 | 286.0 |
| " | 0 | 0 | 286.3 |

TABLE 7

Chemical Shifts of CH₂ Groups of Benzyl Chlorides in Mixed Solvent Methanol-Dioxane

| Compounds | Solvents | | δ CH ₂ c.p.s. from TMS |
|------------------------------------|------------------|--------------|--|
| | Volume % MeOH | Molar fract. | |
| Benzyl chloride | 100 | 100 | 275.7 |
| " | 87.5 | 93.63 | 276.2 |
| " | 50 | 67.75 | 277.0 |
| " | 25 | 41.18 | 276.8 |
| " | 12.5 | 23.09 | 276.2 |
| " | 0 | 0 | 275.5 |
| o-CH ₃ -benzyl chloride | 100 | 100 | 277.9 |
| " | 87.5 | 93.63 | 278.2 |
| " | 75.0 | 86.31 | 278.8 |
| " | 50 | 67.75 | 279.0 |
| " | 25 | 41.18 | 278.6 |
| " | 12.5 | 23.09 | 278.0 |
| " | 0 | 0 | 277.1 |
| 2,6-di-Me-BCl | 100 | 100 | 282.0 |
| " | 75 | 86.31 | 282.8 |
| " | 50 | 67.75 | 282.5 |
| " | 25 | 41.18 | 282.1 |
| " | 12.5 | 23.09 | 282.0 |
| " | 0 | 0 | 281.3 |

TABLE 8

Chemical Shifts of CH₂-Groups of Benzyl Chlorides in Mixed Solvent Mono-Ethyl Ether of Ethylene Glycol-DMSO

| Compounds | Solvents | | δ CH ₂ c.p.s. from TMS |
|--|-------------|-----------------|--|
| | Volume % EG | Molar fract. EG | |
| Benzyl Chloride | 100 | 100 | 276.6 |
| " | 87.5 | 83.70 | 278.0 |
| " | 75 | 68.76 | 279.0 |
| " | 50 | 42.28 | 280.6 |
| " | 25 | 19.64 | 282.4 |
| " | 12.5 | 9.49 | 283.2 |
| " | 0 | 0 | 283.6 |
| <i>o</i> -CH ₃ -benzyl chloride | 100 | 100 | 278.0 |
| " | 87.5 | 83.70 | 279.3 |
| " | 75 | 68.76 | 280.0 |
| " | 50 | 42.28 | 281.7 |
| " | 25 | 19.64 | 283.8 |
| " | 12.5 | 9.49 | 284.4 |
| " | 0 | 0 | 284.8 |
| 2,6-di-(CH ₃) ₂ benzyl chl. | 100 | 100 | 281.0 |
| " | 87.5 | 83.70 | 281.9 |
| " | 75 | 68.76 | 282.5 |
| " | 50 | 42.28 | 283.9 |
| " | 0 | 0 | 286.3 |

reverse of that of the observed order. This may be due to the magnetic anisotropy overshadowing the electronic effects.

Stegling¹³⁰ also observed that the chemical shift of the methylene hydrogen in Ar-CH₂X is independent of the identity of X and that ortho substituents of -CH₂-X-halogen cause the methylene absorption to shift downfield relative to the unsubstituted compound.

The changes in chemical shifts in various compositions of solvents are quite regular. Figs. 10-12 show the plots of chemical shifts of methylene hydrogen vs. mole fraction of the solvent composition. N.m.r. chemical shifts are known to be solvent dependent¹³¹. The variations in chemical shift show that the electronic distribution of the methylene is perturbed by changing solvent composition.

There are four effects from the contribution of molecular interactions of solvent to measured proton chemical shifts¹³²: (a) hydrogen bonding; (b) Van der Waals interaction; (c) diamagnetic anisotropy of the solvent molecule (such as the ring current effect of aromatic solvents); (d) polar effect [an electron field E acting along the axis of an X-H bond tends to draw electrons away from the proton. When a polar molecule is dissolved, it polarizes its surrounding and this polarization leads to an electronic field at the solute¹³³].

The following equation was derived to correlate dielectric constants of the solvents and the chemical shifts¹³² :

FIGURE 10.

Plot of chemical shift (δ_{CH_2}) of o-substituted
benzyl chloride against the mole fraction of the
mixed solvent MeOH-DMSO

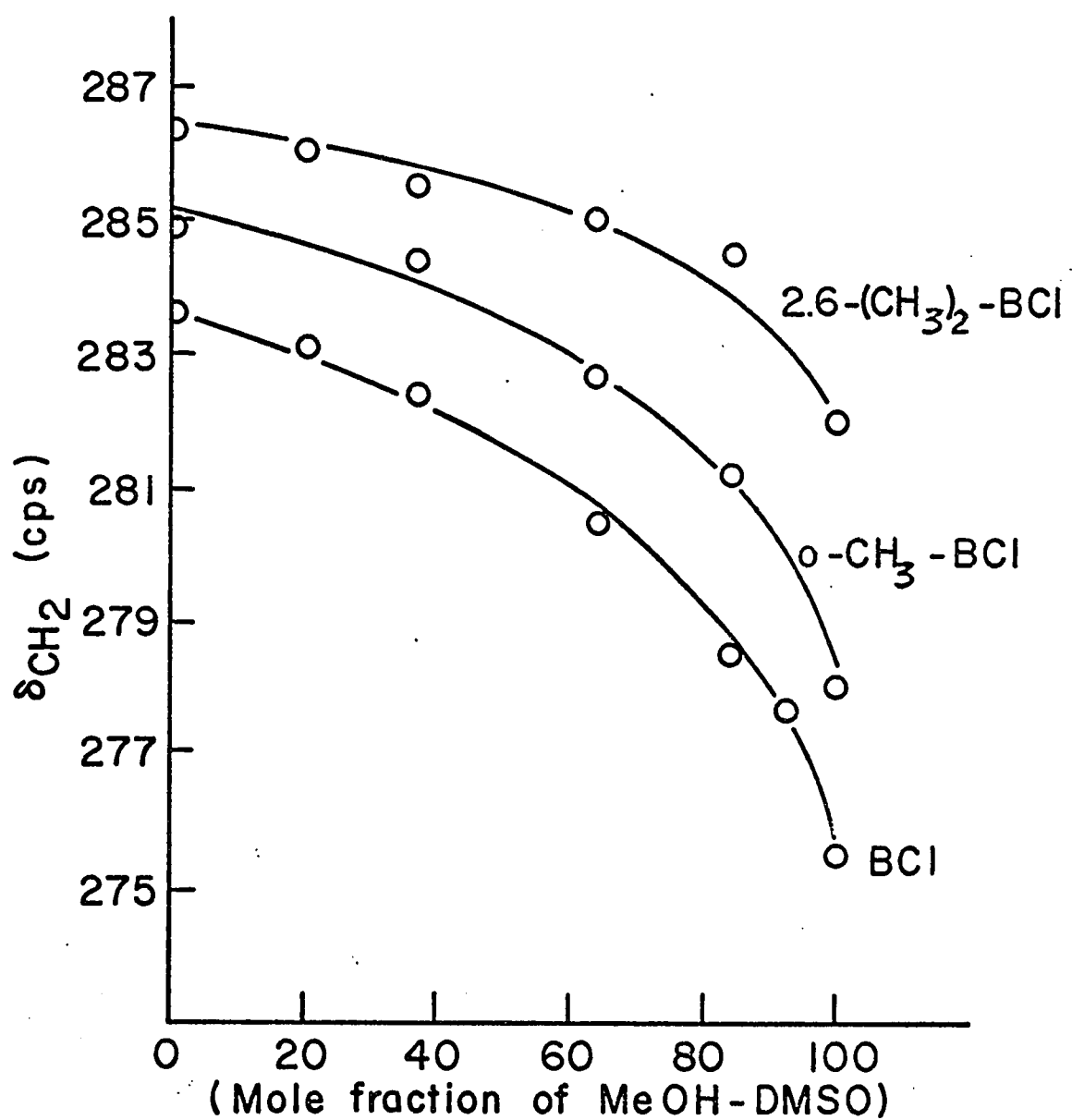


FIG. 10

FIGURE 11.

Plot of chemical shift (δ_{CH_2}) of o-substituted
benzyl chloride against the mole fraction of the
mixed solvent HO-CH₂CH₂OEt-DMSO

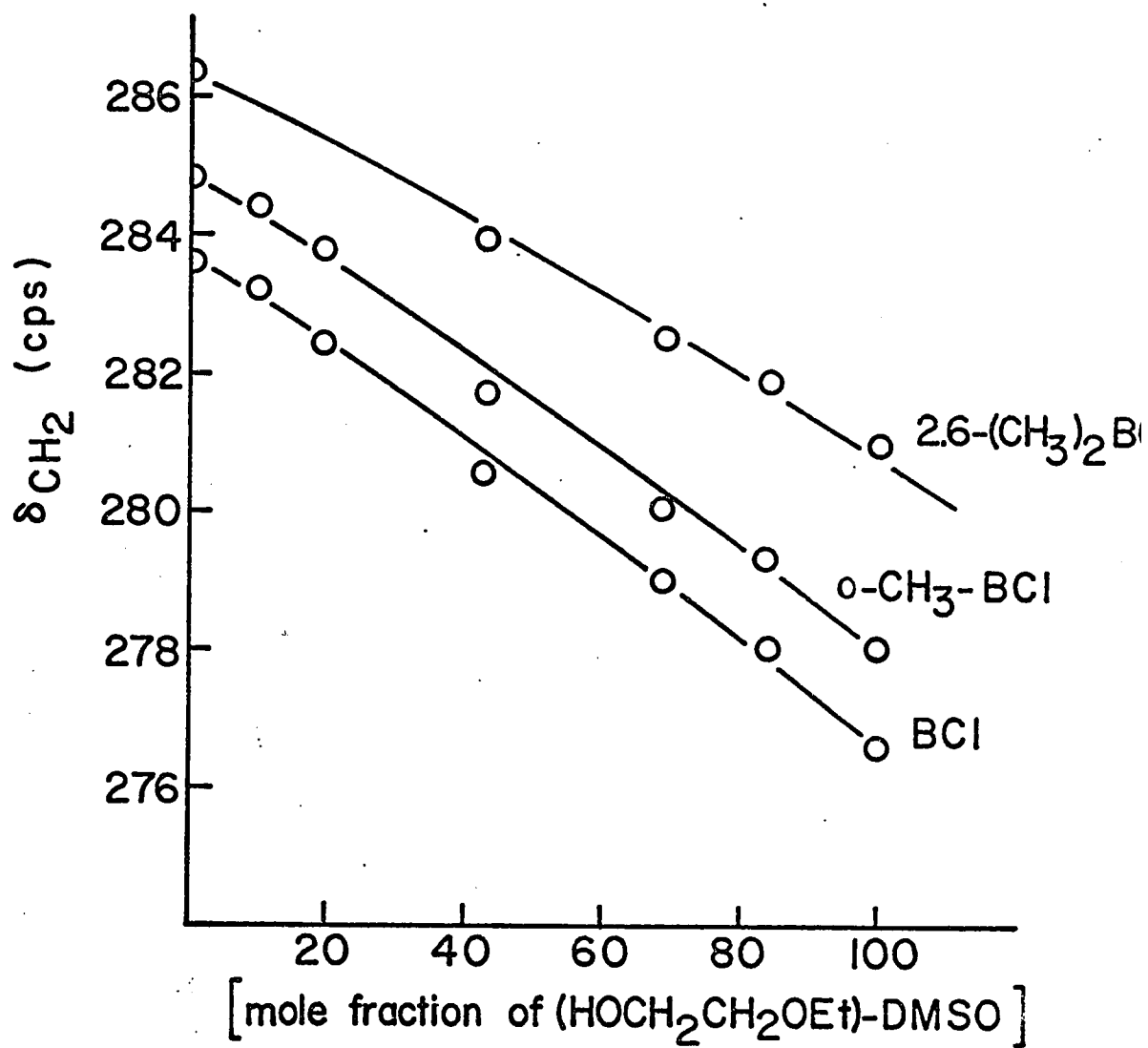


FIG. 11

FIGURE 12.

Plot of chemical shift (δ_{CH_2}) of o-substituted
benzyl chloride against the mole fraction of the
mixed solvent MeOH-dioxane

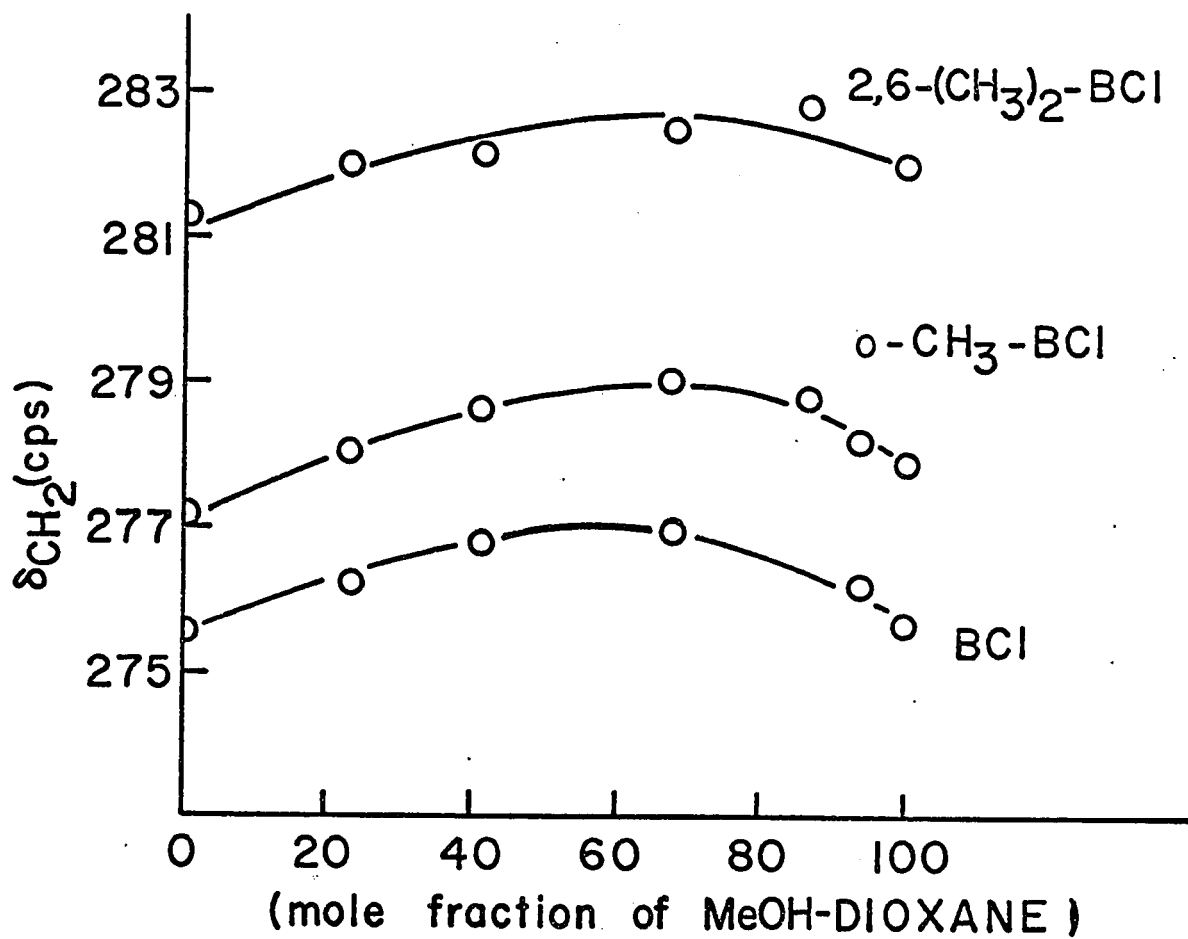


FIG. 12

$$\sigma_E = -2 \times 10^{-12} [(\epsilon - 1)/(2\epsilon + 2.5)] (\mu \cos \phi / a) - 10^{-18} [(\epsilon - 1)/(2\epsilon + 2.5)]^2 (\mu^2 / a^2)$$

where μ is the permanent dipole moment of the solute; a is its polarizability and ϕ is the angle between μ and the X-H bond.

Abraham¹³⁴ examined the solvent effect by directly comparing the chemical shifts of the polar and non-polar solute in the same solvent. The difference in chemical shift is due to the difference in chemical nature of the solute proton only. The obvious explanation for the low field shift of the solute in solution relative to gas was ascribed to the reaction field of the solvent when the polar compound was used as the solute.

Buckingham et al¹³⁵ confirmed this by the use of a non-polar solute as an internal reference in the same solvent. The non-polar solute serves to isolate the "reaction field" in a straightforward manner. It is believed that solvent shifts of the reaction field are roughly in proportion to a function of the dielectric constant of the solvent $[(\epsilon - 1)/(\epsilon + 1)]$ or $[(\epsilon - 1)/(2\epsilon + 2.5)]$ ¹³¹⁻¹³⁶.

The solvent chosen in the present studies is not a disk or rod-like molecule; hence the effect of the diamagnetic anisotropy of the solvent should not be involved. The chemical shifts were measured in dilute solution (0.05± M) to avoid the Van der Waals interaction between the solute and solute molecules. It is felt that solvent shift is caused by the reaction field effect which depends on the chemical nature of the solute proton and the polarity of the solvent.

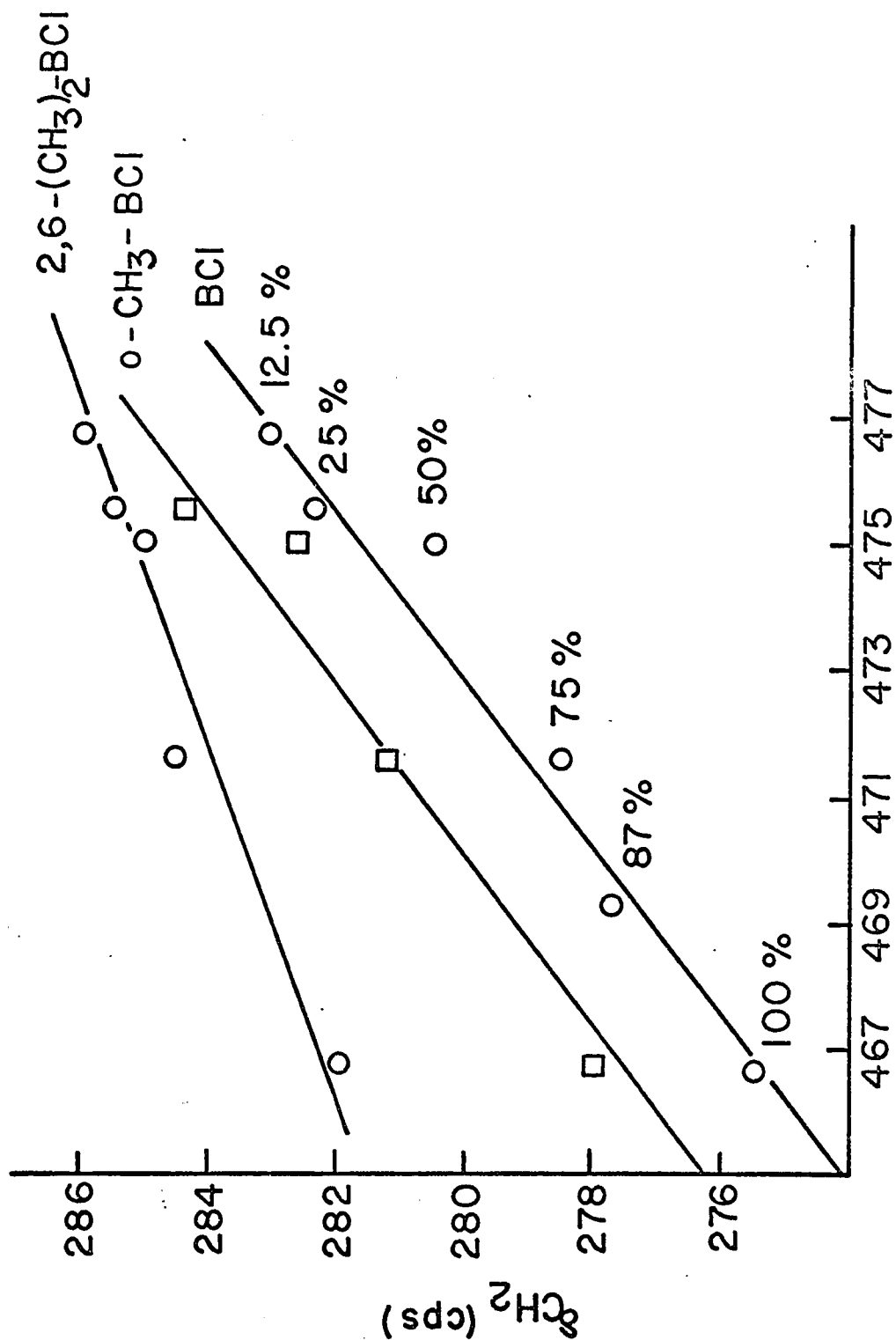
The chemical shifts of methylene hydrogen of H, *o*-CH₃, and 2,6-dimethylbenzyl chloride were plotted against the $(\epsilon - 1)/(\epsilon + 2.5)$ function of the mixed solvents, as shown in Fig. 13.

The dielectric constants of the mixed solvent DMSO-MeOH at 25° were given by Tommila¹³⁷. There is a roughly linear correlation between the solvent shifts and the dielectric constant of the solvents. The two lines for benzyl chloride and *o*-methylbenzyl chloride appear to be parallel. It is suggested that the ground state of methylene groups of *o*-methyl and unsubstituted benzyl chloride have a similar chemical environment for their interaction with the medium. However, the slope for 2,6-dimethylbenzyl chloride drops significantly. It seems that when the second methyl group is introduced into the other ortho position, there is appreciable steric hindrance for the interaction of the methylene in 2,6-dimethyl compound with the solvent molecules.

Since we do not have the data for dielectric constants of the mixed solvents monoglyme-DMSO, the correlation between chemical shifts and the dielectric constant of the solvent cannot be obtained. Instead, the chemical shifts (δ CH₂) of ortho substituted benzyl chloride in various compositions of the mixed solvent monoglyme-DMSO were plotted against the corresponding chemical δ CH₂ of benzyl chloride, as shown in Figs. 14-15. Again, the solvent effect on the chemical shifts of methylene hydrogen of H, and *o*-CH₃-benzyl chloride are similar. The slope for the plot of *o*-CH₃ vs. H (Fig. 14) is 0.98, which is very close to unity, but the plot for 2,6-(CH₃)₂ suddenly decreases to 0.78 (Fig. 15). This may be due to the fact that the two ortho methyl substituents interfere in the interaction of the methylene group with the medium in the ground state.

FIGURE 13.

Plot of chemical shift (δ_{CH_2}) of o-substituted benzyl chloride against the function of dielectric constants ($\epsilon - 1/2\epsilon + 2.5$) of the solvent)



$\epsilon - 1 / (2\epsilon + 2.5)$ (MeOH - DMSO)

FIG. 13

FIGURE 14

Plot of chemical shift (δ_{CH_2}) of o-CH₃-benzyl chloride against chemical shift (δ_{CH_2}) of benzyl chloride in the mixed solvent of monoglyme-DMSO

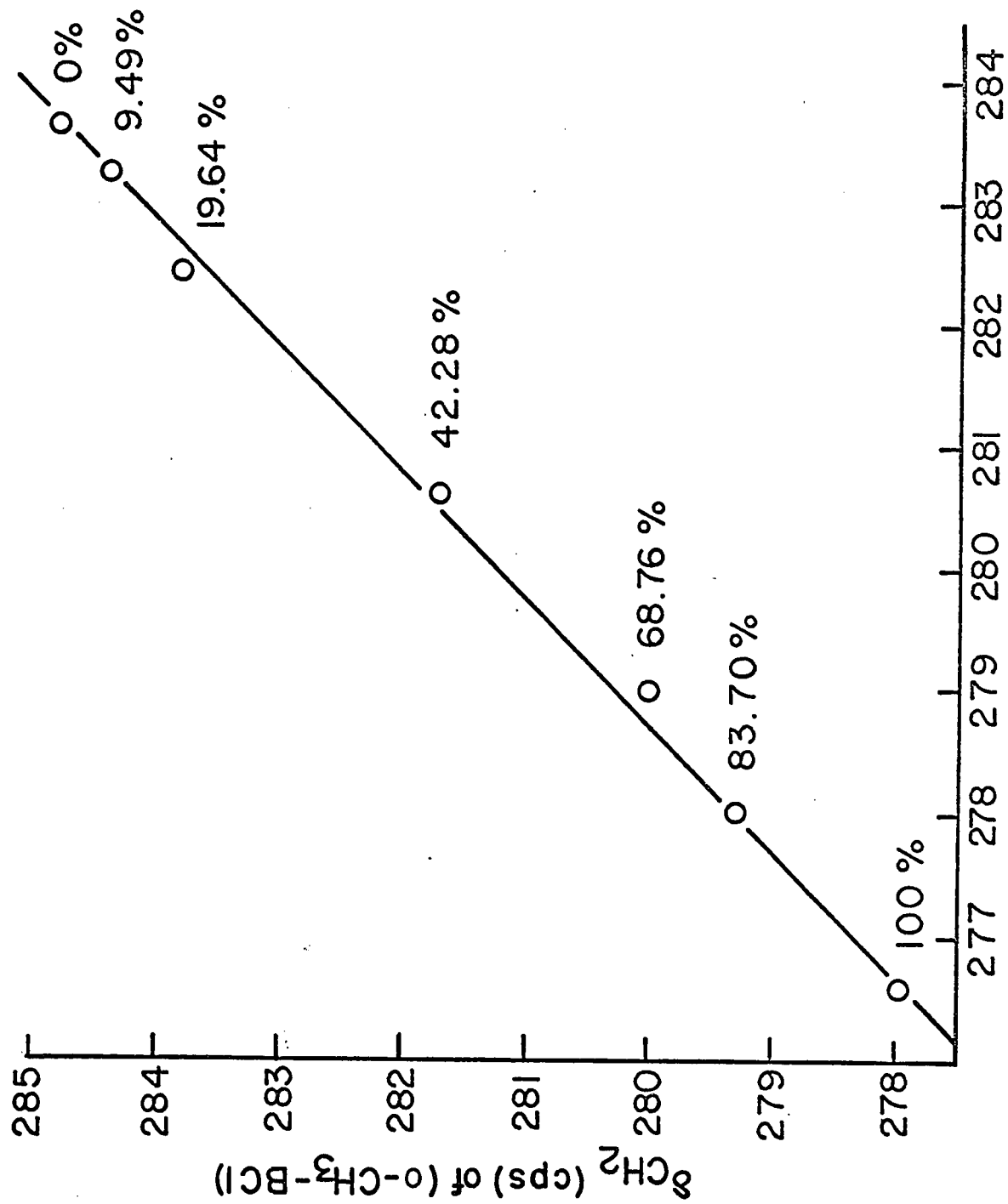


FIG. 14 δ_{CH_2} (cps) of BCI in monoglyme-DMSO

FIGURE 15

Plot of chemical shift (δ_{CH_2}) of 2,6-(CH₃)₂-benzyl chloride against chemical shift (δ_{CH_2}) of benzyl chloride in the mixed solvent of monoglyme-DMSO

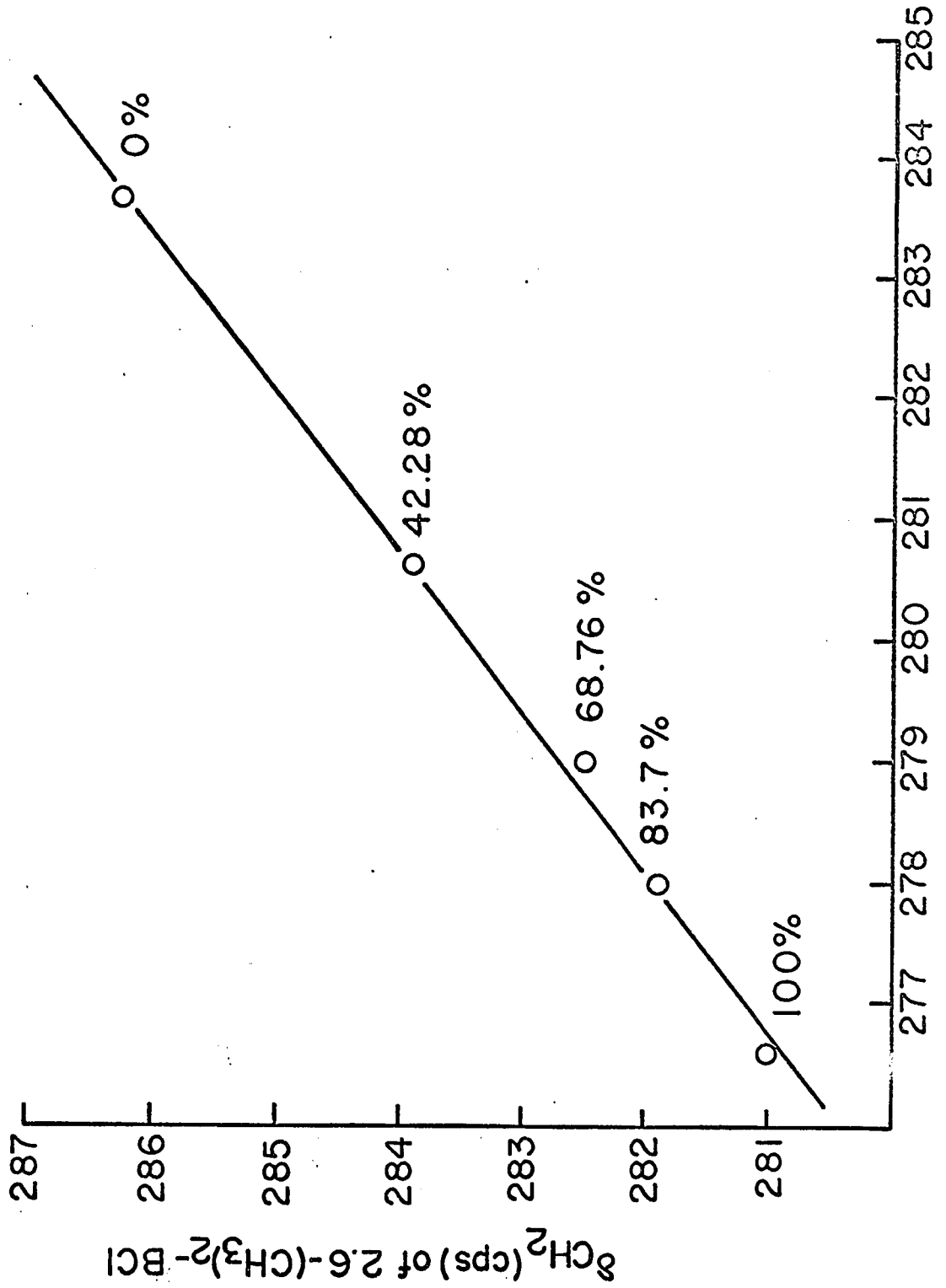


FIG. 15 δ_{CH_2} (cps) of BCl in monoglyme - DMSO

(2) Acidities of the nucleophiles

Generally, the nucleophilic reactivity and the basicity of a nucleophile towards a proton are related. A series of m- and p-substituted thiophenols were synthesized. Eight of the nine thiols studied are known, with the exception of 3,5-dinitrothiophenol. m-Nitrothiophenol was reported by Leuckart and Holtzapfel¹¹⁴ as a dark red oil by xanthate ester hydrolysis. Bordwell and Andersen, following the same route, obtained a straw-coloured oil¹¹⁵. They made two attempts to analyse this compound, and a value about 1% low in carbon was obtained.

We followed the same method several times and a golden brown oil was obtained. It showed a definite S-H stretching absorption in infrared (2250 cm^{-1}) but there was an extra absorption band at the 3400 cm^{-1} region in I.R., even after distilling twice. Reduction of bis(m-nitrophenyl)-disulfide was then tried, and a clear yellow oil of m-nitrothiophenol was obtained after column chromatography. Its identity was checked by I.R., n.m.r. and mass spectra. It also gave good element analysis (see Experimental section).

The acidity constants of substituted thiophenols were measured according to Hudson⁹⁸. The results of duplicate runs are given in Table 9, and indicate that the reproducibility is about ± 0.02 pH (maximum error). Comparison of the results with the literature shows good agreement. Our pK_a values are equal to 9.055 ± 0.015 for p- CH_3 -thiophenol and 7.93 ± 0.02 for p-bromothiophenol. Hudson's values are 8.96 ± 0.1 and 7.82 ± 0.16 respectively. All the acidity constants were measured in absolute methanol which was the same medium as that used for the kinetic measurements. Since aqueous buffer solutions were used for standardization, the acidity constants measured are not the absolute values.

TABLE 9

pKa Values for Substituted Thiophenols in MeOH at 25°C

| Subst. | Initial conc. | | pKa ₁ | pKa ₂ | pKa aver. |
|----------------------|-----------------|-----------------|------------------|------------------|---------------|
| | $\times 10^3$ M | $\times 10^3$ M | | | |
| p-CH ₃ | 3 | 2.5 | 9.07 | 9.04 | 9.055 ± 0.015 |
| m-CH ₃ | 3 | 2.5 | 8.91 | 8.91 | 8.91 ± 0 |
| H * | | | | | 8.65 |
| p-Br | 3 | 2.5 | 7.95 | 7.91 | 7.93 ± 0.02 |
| m-NO ₂ | 3 | 2.5 | 6.70 | 6.71 | 6.705 ± 0.005 |
| p-NO ₂ | 3 | 2.5 | 6.13 | 6.09 | 6.11 ± 0.02 |
| m-di-NO ₂ | 3 | 2.5 | 4.75 | 4.74 | 4.745 ± 0.005 |
| p-OCH ₃ * | | | | | 8.95 |
| m-OCH ₃ * | | | | | 8.3 |

* Value taken from R. T. Hudson and G. Klopman, J. C.S., 1062 (1962).

The acidity constants of substituted thiophenols were plotted against their substituent constants σ , as shown in Fig. 16. Sigma values were taken from the ionization of the phenol series¹³⁸ except for p-NO₂. Excellent correlation was obtained. The acidities of these thiophenols behave normally, as one would expect from their substituent effects. The slope of the regression line determined by the method of least squares is -2.606 and the intercept is equal to 8.618. The Hammett correlation for the acidities of thiophenols in methanol at 25° can be described by the following equation (with the correlation constant = 0.995):

$$\text{pK}_a = -2.66 \sigma + 8.618 \quad (\text{R-3})$$

The negative slope means that an increase of the electron-withdrawing power of the substituent will increase the acidity of the compound. The σ -values for the strongly resonance interacting para nitro substituent vary depending on the substrate (in contrast to those of the meta-nitro group). The value becomes increasingly great when determined for benzoic acid [$\sigma_{\text{p-NO}_2} = 0.778$ ¹³⁹], for thiophenol [$\sigma_{\text{p-NO}_2} = 1.00$ ¹¹⁵], for phenol [$\sigma_{\text{p-NO}_2} = 1.22$ ¹³⁸], and for anilinium ions [$\sigma_{\text{p-NO}_2} = 1.27$ ¹¹⁵]. The $\sigma_{\text{p-NO}_2} = 1$ observed from Fig. 16 is the same as value determined by Bordwell and Andersen¹⁰⁹ for the dissociation of the thiophenols in 48% ethanol-water. The increase of $\sigma_{\text{p-NO}_2}$ values as the electron affinity of the functional groups increase is usually interpreted as a varying degree of resonance interaction, as shown in Structure IV.

FIGURE 16

Plot of pK_a of substituted thiophenols
against substituent constant σ

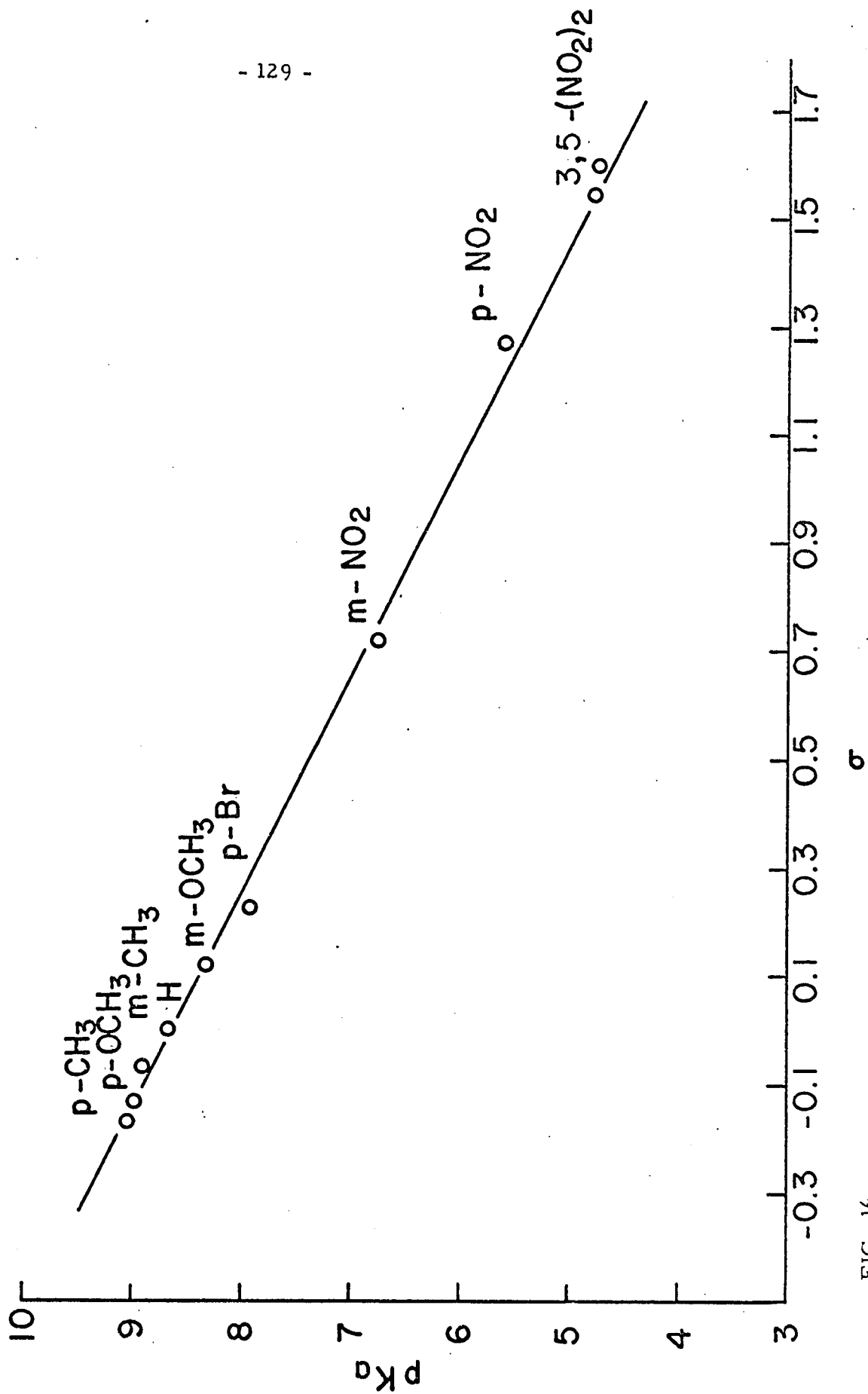
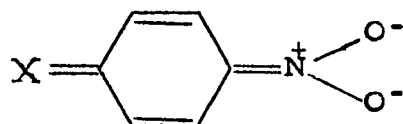


FIG. 16



Structure IV

The effect of multiple substitution has been well established¹⁴⁰ as the sum of the individual effects of the substituents in the corresponding monosubstituted compounds:

$$\sigma_{\text{total}} = \sum \sigma \quad (\text{R-4})$$

The additive relationship should be expected to hold for 3,5-dinitrothiophenol, since the two nitro substituents are not adjacent to each other, nor to the functional group (SH). The prediction for the substituent constant of 3,5-dinitro substituent from equation (R-4) will be:

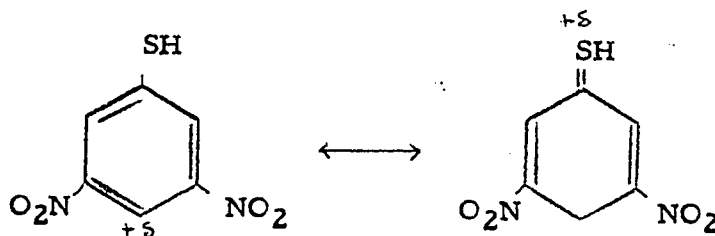
$$\sigma_{3,5(\text{NO}_2)_2} = 2 \sigma_{\text{m}} = 2 \times 0.71 = 1.42$$

The observed values from the regression line (equation R-3) is 1.5, which deviates from its additive relationship by 0.08 unit.

The $\sigma_{3,5-(\text{NO}_2)_2}$ value for the dissociation of the benzoic acid series was found to be 1.395^{140,141}. The greater effectiveness of 3,5-dinitro substituent in thiophenol

[$\sigma_{3,5-(\text{NO}_2)_2} = 1.5$] as compared to the same substituent in benzoic acid [$\sigma_{3,5-(\text{NO}_2)_2} = 1.395$] in the transmission of the

electronic effect to the reacting center may be ascribed to the difference in the nature of the center atom sulfur (SH) and the carbon (COOH) respectively. Although the resonance effect acts more strongly from the para position than from the meta or ortho positions, resonance does have some importance for meta substituents¹⁴². The para carbon adjacent to the two strongly electron-withdrawing meta nitro groups is made positive by inductive contribution of the two neighbouring groups. This positive charge may have direct interaction with the reacting sulfur atom as follows:



The difference in the substituent constant of 3, 5-dinitro substituent of thiophenol and of benzoic acid may be due to the difference in the ability of the reacting center to conjugate with the aromatic ring.

(3) Ground State Structure Correlation of Nucleophiles by n.m.r.

The chemical reactivity at the m- and p-positions in various substituted benzenes can be expressed in terms of Hammett substituent constants. If these constants are related in any way to the electron densities at the m- and p-atom, one might expect Hammett substituent constants to show a correlation with the chemical shift of the nuclei involved¹²⁹. Taft¹⁴³ correlated the chemical shift successfully with inductive and resonance parameters.

The chemical shifts of nine substituted thiophenols were measured in CDCl_3 solution (approximately 5-20%). Tetramethylsilane was used as the internal reference and the chemical shifts of S-H groups are given in Table 10. Solutions of p-Br-thiophenol and p-methylthiophenol were examined over a range of concentrations in order to demonstrate that the chemical shifts of S-H groups are concentration independent, unlike those of acidic hydrogen which are easily hydrogen bonded and show marked shifting of resonance with change of either the type or the concentration of solvent¹⁴⁴. The present results indicate that the mercapto groups of the thiophenols are not hydrogen bonded under this condition.

Since the pK_a value is the measure of the acidity of the hydrogen, it should be strongly related to its electron density. The assumption that chemical shifts of SH groups of substituted thiophenols are linearly related to their acidity constants is reasonable. The $\tau_{\text{S-H}}$ values vary from 6.67 for p- OCH_3 -thiophenol to 5.93 for 3,5-dinitrothiophenol.

TABLE 10

Chemical Shifts (δ_{S-H}) of Substituted Thiophenols

| Thiophenols | pK_a | δ_{S-H} c.p.s. from TMS |
|---------------------------------------|--------|--------------------------------|
| p-CH ₃ | 9.055 | 200 |
| m-CH ₃ | 8.91 | 201 |
| H | 8.65 | 202 |
| p-OCH ₃ | 8.95 | 200 |
| m-OCH ₃ | 8.30 | 207 |
| p-Br | 7.93 | 206 |
| m-NO ₂ | 6.705 | 222 |
| p-NO ₂ | 6.11 | 226 |
| 3, 5 -(NO ₂) ₂ | 4.745 | 244 |

Fig. 17 shows the plot of δ_{S-H} against their pK_a values. All the points fall very close to the line. The slope is equal to -10.034 and the intercept is 289.38 c. p. s. away from TMS. The slope and the intercept were obtained from least-square fitting by computer, and the equation for the normal regression is

$$\delta_{S-H} = -10.034 pK_a + 289.38$$

An important implication of this is that under favourable circumstances (for example, in the absence of neighbouring magnetic anisotropy or other interfering effects), proton resonance shifts can be employed to obtain information about the electron densities in the functional group studied.

FIGURE 17

Plot of chemical shift (δ_{CH_2}) of substituted
thiophenols against pKa

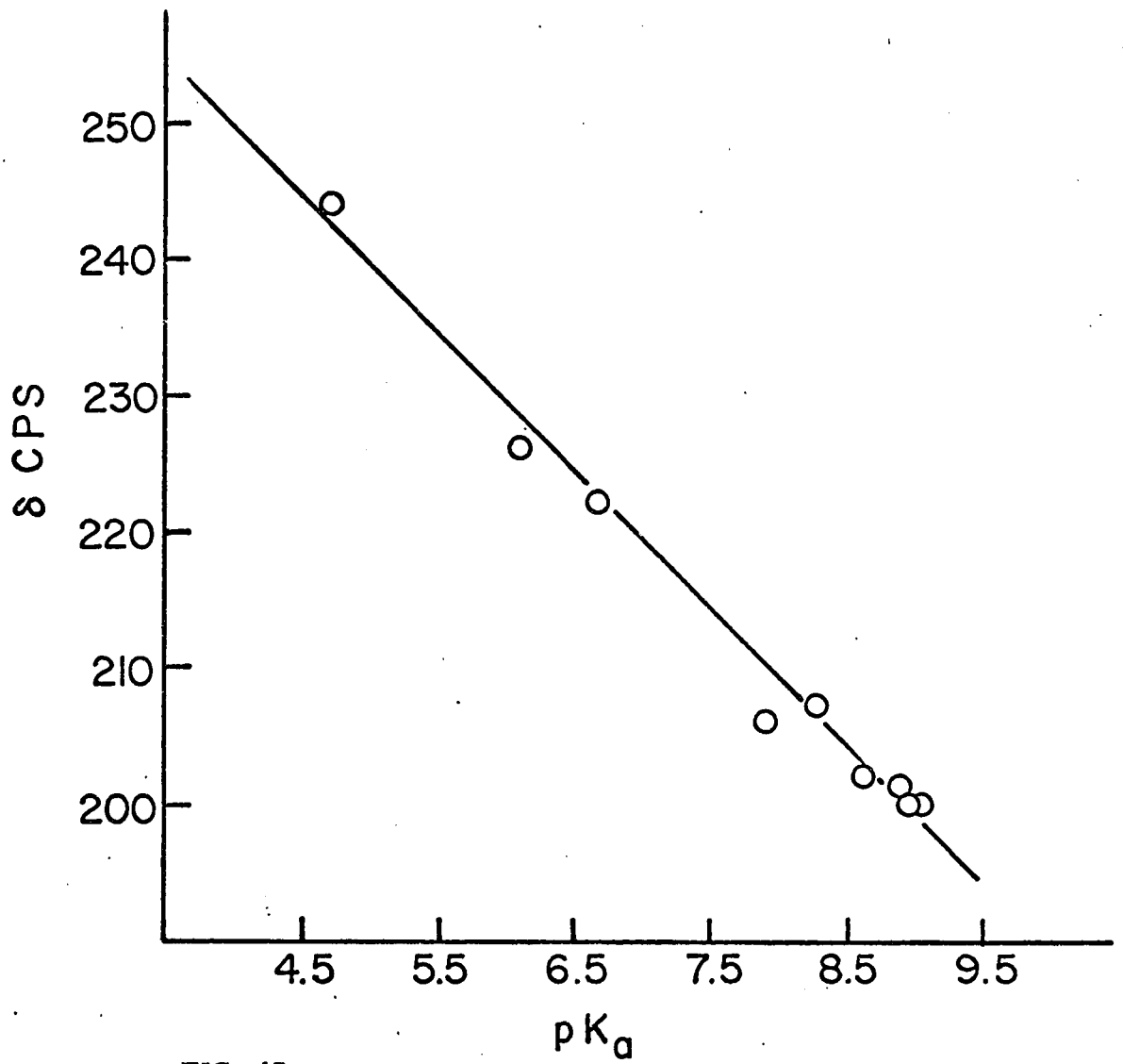


FIG. 17

III. ADDITIVE LONDON INTERACTION ENERGIES IN NUCLEOPHILIC DISPLACEMENT REACTIONS

(1) Nucleophilic reactivities of substituted thiophenols

Bunnett⁹⁰, Reinheimer⁹² and Sisti⁹¹ estimated the London interaction energies between the ortho substituent and the nucleophile at the transition state by adjusted rate ratios, as discussed in the "Introduction". They all assumed that differences in inherent nucleophilic reactivity can be cancelled out if the reaction constant ρ for the reaction of o-substituted benzyl chloride and the corresponding reaction of the reference compound (benzyl chloride or p-substituted benzyl chloride) are the same.

It is known that the reaction mechanism changes continuously for each substituted benzyl halide⁹⁶. This assumption may lead to appreciable error in the calculation of the London energy if the change of the reaction constant in the ortho and reference compounds is large.

Our approach here, in order to investigate the effect of London energies in the displacement reaction of o-CH₃ and 2,6-(CH₃)₂-benzyl chloride, is to measure the ρ values of the reactions first.

The general Hammett ρ - σ relation is usually used for nucleophilic displacement reactions¹⁴⁵. The value of the reaction constant ρ is considered as a criterion of the transition state structure relative to the ground state. The Hammett plot cannot be used for the estimation of the rho values of the benzyl chloride system⁹⁶, since the plot is known to be a curve, as previously discussed.

The Brønsted catalysis law, which was originally taken as a measure of the degree of proton transfer to the base in a rate determining step, has been applied to nucleophilic reactions such as alkylation⁵⁵, acylation^{55,56}, or aromatic substitution^{57,58,59}.

For reactions involving a series of nucleophiles of constant functional type with a common substrate, the value β (the slope of the plot of $\log k$ vs. pK_a of the nucleophiles) gives the degree of bond formation in the transition state⁵⁵.

A series of m- and p-substituted thiophenols were synthesized. The rates of reactions of nine substituted thiophenols were benzyl chloride, p-methylbenzyl chloride, o-methyl, 2,6-dimethyl and m-nitrobenzyl chloride were measured in methanol at 25°C, as shown in Tables 11-15. The error limits given are based on the values obtained from duplicate runs. The reproducibility is within 3%. Comparison of the data with known values in the literature shows acceptable agreement^{90,92}.

TABLE II

Reactions of Benzyl Chloride with Substituted Thiophenols in CH₃OH at 25°C.

| Nucleophile | $k_2 \times 10^{-2}$ l mole ⁻¹ sec ⁻¹ | $\bar{k}_2 \times 10^{-2}$ (l mole ⁻¹ sec ⁻¹) |
|-------------------------------------|---|--|
| p-CH ₃ | 3.08 3.01 | 3.04 ± 0.04 |
| m-CH ₃ | 2.98 2.98 | 2.98 |
| H | 2.43 2.48 | 2.46 ± 0.05 |
| p-OCH ₃ | 3.79 | 3.79 |
| m-OCH ₃ | 2.62 2.62 | 2.62 |
| p-Br | 1.96 1.99 | 1.97 ± 0.02 |
| m-NO ₂ | 1.58 1.55 | 1.57 ± 0.02 |
| p-NO ₂ | 0.71 0.69 | 0.70 ± 0.01 |
| 3,5-(NO ₂) ₂ | 1.17 1.17 | 1.17 ± 0.01 |

TABLE 12

Reactions of p-CH₃-Benzyl Chloride with Substituted Thiophenols in CH₃OH at 25°C

| Nucleophiles | k (l mole ⁻¹ sec ⁻¹) |
|-------------------------------------|---|
| p-CH ₃ | 4.57 x 10 ⁻² |
| m-CH ₃ | 4.96 x 10 ⁻² |
| H | 3.78 x 10 ⁻² |
| p-OCH ₃ | 5.96 x 10 ⁻² |
| m-OCH ₃ | 4.14 x 10 ⁻² |
| p-Br | 3.60 x 10 ⁻² |
| m-NO ₂ | 3.39 x 10 ⁻² |
| p-NO ₂ | 1.45 x 10 ⁻² |
| 3,5-(NO ₂) ₂ | 3.06 x 10 ⁻² |

TABLE 13

Reactions of o-CH₃-Benzyl Chloride with Substituted Thiophenols in CH₃OH at 25°C

| Nucleophile | $k_2 \times 10^{-2}$ l mole ⁻¹ sec ⁻¹ | $\bar{k}_2 \times 10^{-2}$ l mole ⁻¹ sec ⁻¹ |
|-------------------------------------|---|---|
| p-CH ₃ | 13.9 | 13.9 |
| | 13.9 | |
| m-CH ₃ | 14.3 | 14.6 ± 0.3 |
| | 14.8 | |
| H | 11.9 | 12.1 ± 0.2 |
| | 12.4 | |
| p-OCH ₃ | 18.6 | 18.6 |
| m-OCH ₃ | 12.2 | 12.0 ± 0.2 |
| | 11.9 | |
| p-Br | 10.0 | 10.0 ± 0.2 |
| | 10.0 | |
| m-NO ₂ | 9.14 | 8.94 ± 0.2 |
| | 8.73 | |
| p-NO ₂ | 3.90 | 3.8 ± 0.1 |
| | 3.72 | |
| 3,5-(NO ₂) ₂ | 7.96 | 7.9 ± 0.1 |
| | 7.91 | |

TABLE 14

Reactions of 2,6-Dimethylbenzyl Chloride with Substituted Thiophenols in CH₃OH
at 25°C

| Nucleophile | $k_2 \times 10^{-1} \text{ l mole}^{-1} \text{ sec}^{-1}$ | $k_2 \times 10^{-1} \text{ l mole}^{-1} \text{ sec}^{-1}$ |
|-------------------------------------|---|---|
| p-CH ₃ | 9.06 | 8.71 ± 0.35 |
| | 8.36 | |
| m-CH ₃ | 9.72 | 9.55 ± 0.16 |
| | 9.39 | |
| H | 7.42 | 7.42 |
| | 7.42 | |
| p-OCH ₃ | 10.62 | 10.62 |
| m-OCH ₃ | 7.74 | 7.78 ± 0.04 |
| | 7.82 | |
| p-Br | 6.31 | 6.65 ± 0.35 |
| | 6.70 | |
| m-NO ₂ | 7.17 | 7.04 ± 0.12 |
| | 6.92 | |
| p-NO ₂ | 2.92 | 2.90 ± 0.02 |
| | 2.88 | |
| 3,5-(NO ₂) ₂ | 7.48 | 7.48 |
| | 7.48 | |

TABLE 15

Reactions of m-NO₂-Benzyl Chloride with Substituted Thiophenols in MeOH
at 25°C

| Nucleophile | k ₂ (l mole ⁻¹ sec ⁻¹) |
|-------------------------------------|--|
| p-CH ₃ | 1.81 × 10 ⁻¹ |
| m-CH ₃ | 1.66 × 10 ⁻¹ |
| H | 1.03 × 10 ⁻¹ |
| p-OCH ₃ | 2.38 × 10 ⁻¹ |
| p-Br | 6.88 × 10 ⁻² |
| m-NO ₂ | 4.09 × 10 ⁻² |
| p-NO ₂ | 8.14 × 10 ⁻³ |
| 3,5-(NO ₂) ₂ | 1.52 × 10 ⁻² |

Rate constants experimentally observed for the reactions of benzyl chloride with methoxide and thiophenoxide at 25°C are 2.41×10^{-5} l mole⁻¹ sec⁻¹ and 2.46×10^{-2} l mole⁻¹ sec⁻¹ respectively. The values reported by Reinheimer et al⁹² are 2.44×10^{-5} l mole⁻¹ sec⁻¹ for the former and 2.28×10^{-2} l mole⁻¹ sec⁻¹ for the latter.

The rate constants for the reactions of o-methylbenzyl chloride with thiophenoxide and methoxide at 25°C are 1.21×10^{-1} l mole⁻¹sec⁻¹ and 6.87×10^{-5} , while the corresponding values reported by Bunnett et al⁹⁰ at 24.6°C are 1.15×10^{-1} l mole⁻¹sec⁻¹ and 6.62 respectively.

Our results for the reactions of p-methylbenzyl chloride, however, are not in acceptable agreement with the results of Reinheimer and co-workers⁹²; with methoxide they gave $k = 2.29 \times 10^{-5}$ l/mole sec., with thiophenoxide $k = 4.85 \times 10^{-2}$, for methanolysis $k = 1.3 \times 10^{-7}$. Our results are; $k = 4.29 \times 10^{-5}$ l/mole sec. for methoxide; $k = 3.78 \times 10^{-2}$ for thiophenoxide, and $k = 3.33 \times 10^{-7}$ sec⁻¹ for methanolysis. We believe we have the correct rate constants for the following reasons:

(a) Purity: The purity of p-methylbenzyl chloride was checked by v.p.c., indicating that there is only one compound in the spectrum, and the blank test was made to show that p-xylene (starting material in synthesis) did not come with the same peak as p-methylbenzyl chloride under the conditions used for analysis.

(b) Tommila⁴⁹ reported $k_{\text{obs}} = 4.78 \times 10^{-5}$ l/mole sec. for reaction of p-methylbenzyl chloride with methoxide in methanol at 25°C. This k_{obs} includes the rate of solvolysis. Correction was made by the equation

$$k_{\text{obs}} = k + k_{\text{solv.}}/a \quad (\text{see Experimental Section})$$

Using our results for the rate of solvolysis, the corrected rate constant is equal to 4.21×10^{-5} l/mole sec., which is only 1.8% different from our result.

(c) Charton and Hughes¹⁴⁶ gave 5.1×10^{-5} and 5.46×10^{-5} l/mole sec for the reaction of p-methylbenzyl chloride with KI at 0°. Extrapolation of Reinheimer's result for the reaction gave a value of $k = 3.3. \times 10^{-5}$.

(i) Correlation of Nucleophilicity and Basicity of the Nucleophiles:

The plots of $\log k$ against the pK_a values of substituted thiophenols for their reactions with various substituted benzyl chlorides are shown in Figs. 18 - 22. There are systematic deviations from this Brønsted relation. The rates for reactions of p-methoxy and p-bromothiophenol are systematically greater than would be expected from their basicities, and m-nitro, 3,5-dinitrothiophenol shows even larger deviations.

Hudson proposed that substitution of the nucleophile changes the electron affinity, the energy for the polarization and the bond formation energy of the nucleophile. According to Hudson's hypothetical equation⁹⁸ (see Introduction), if all these variables change regularly and are linearly related to the conjugation energy E_c , due to the introduction of the substituent, the activation energy

FIGURE 18

Logarithms of k for the reactions of benzyl chloride with substituted thiophenoxides plotted against pK_a of the thiols

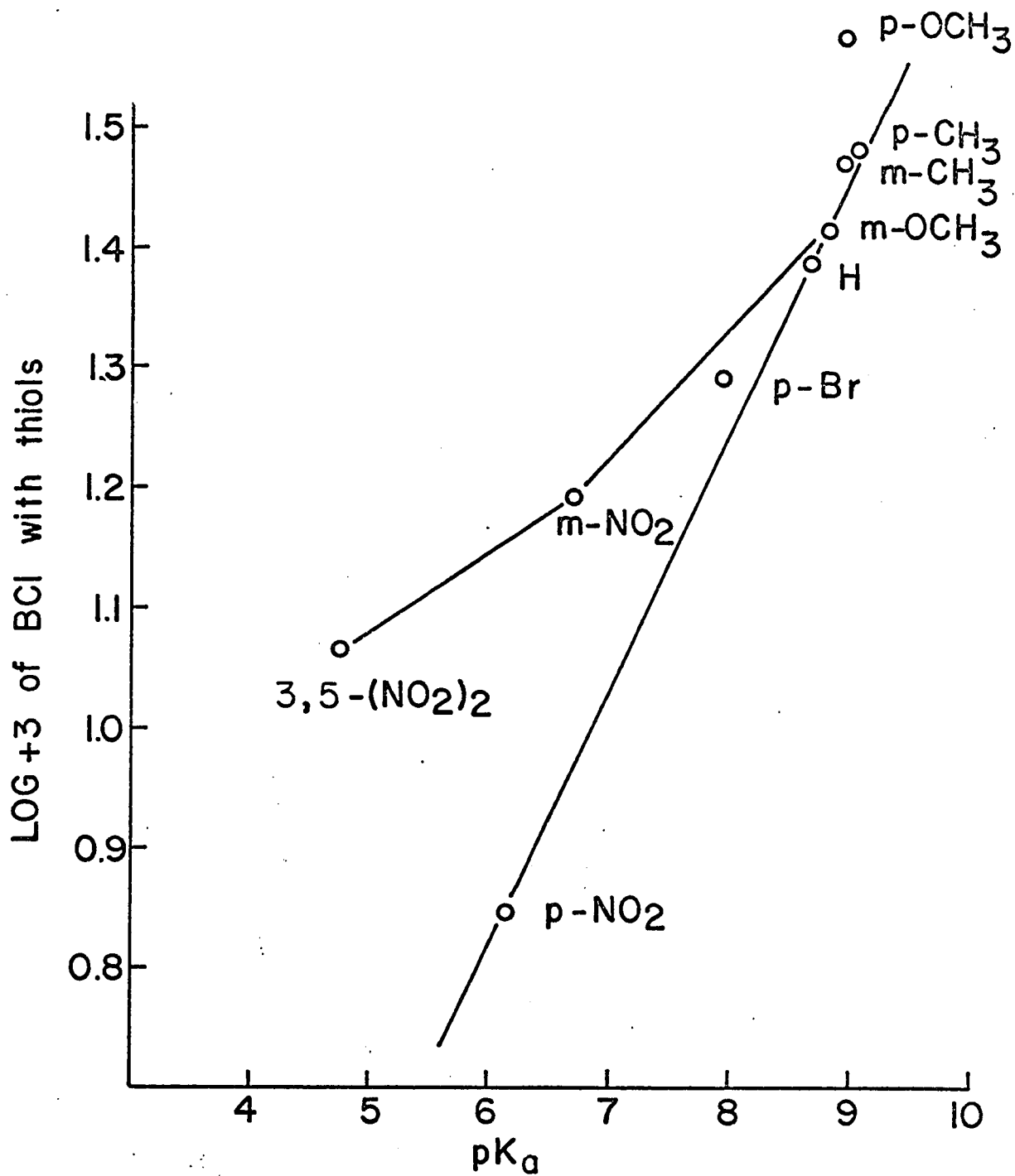


FIG. 18

FIGURE 19

Logarithms of k for the reactions of p -CH₃-benzyl chloride with substituted thiophenoxides plotted against pK_a of the thiols

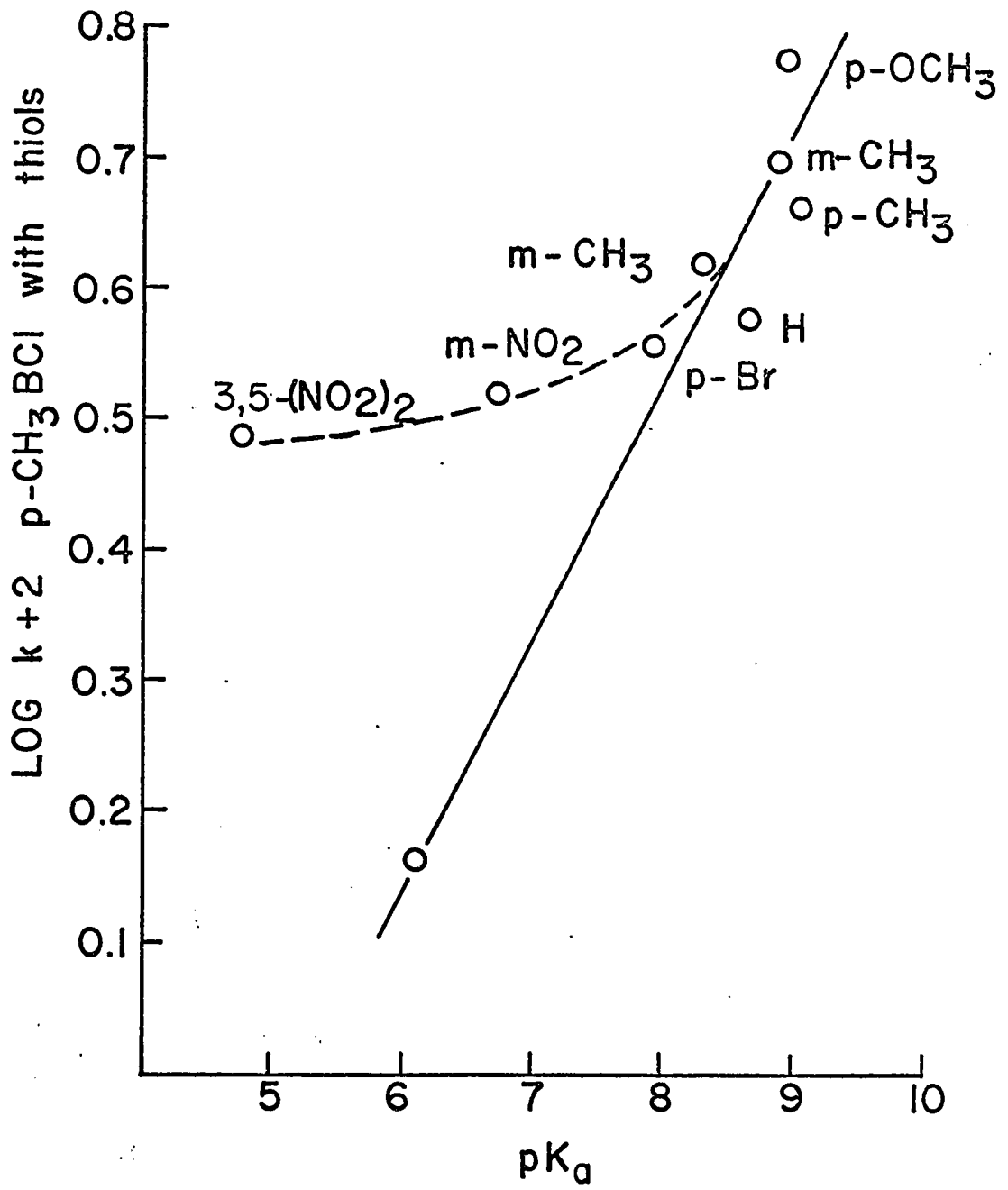


FIG. 19

FIGURE 20

Logarithms of k for the reactions of o -CH₃-benzyl chloride with substituted thiophenoxides plotted against pK_a of the thiols

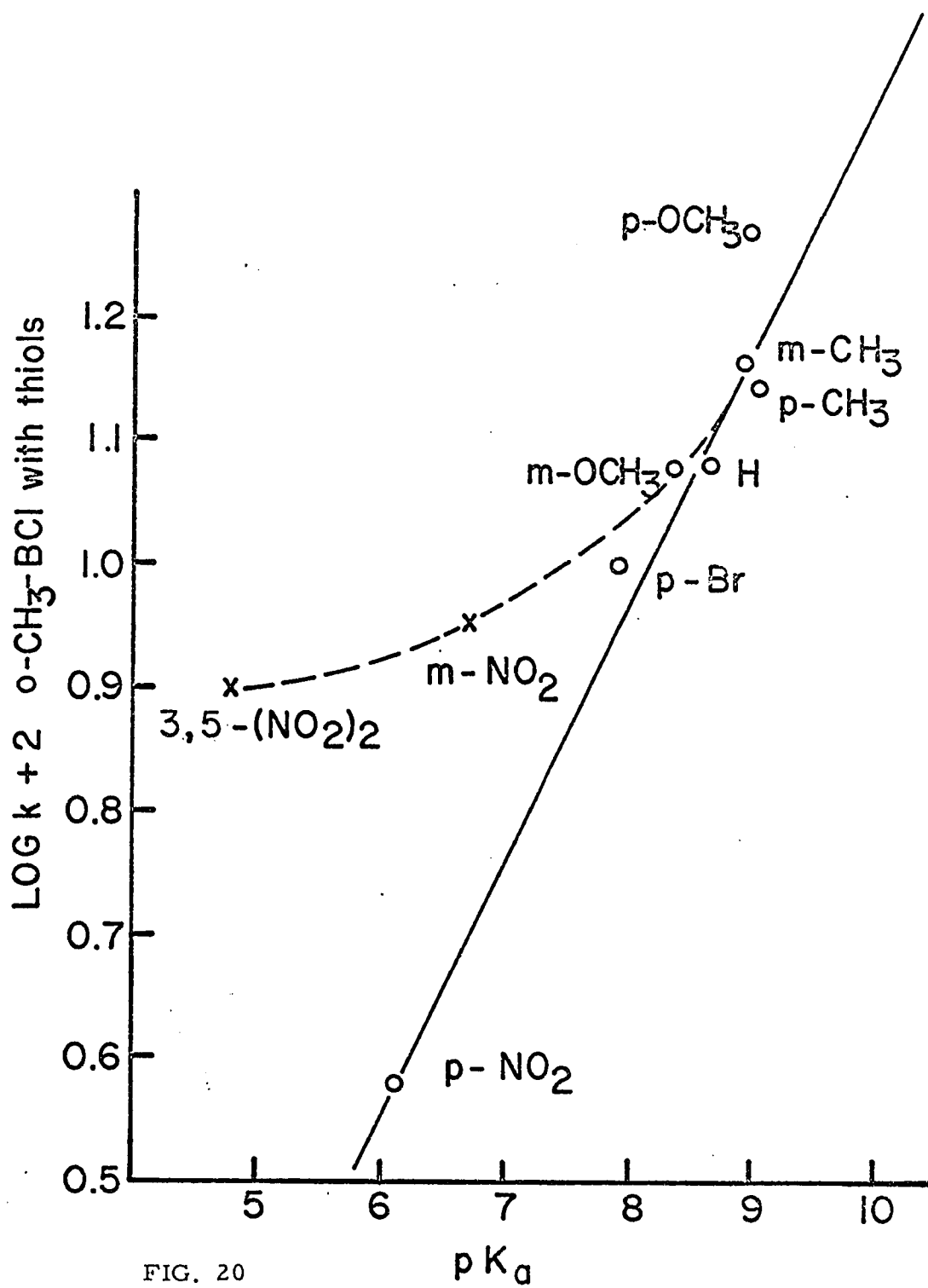


FIG. 20

FIGURE 21

Logarithms of k for the reactions of 2,6-(CH₃)₂-benzyl chloride with substituted thiophenoxides plotted against pK_a of the thiols

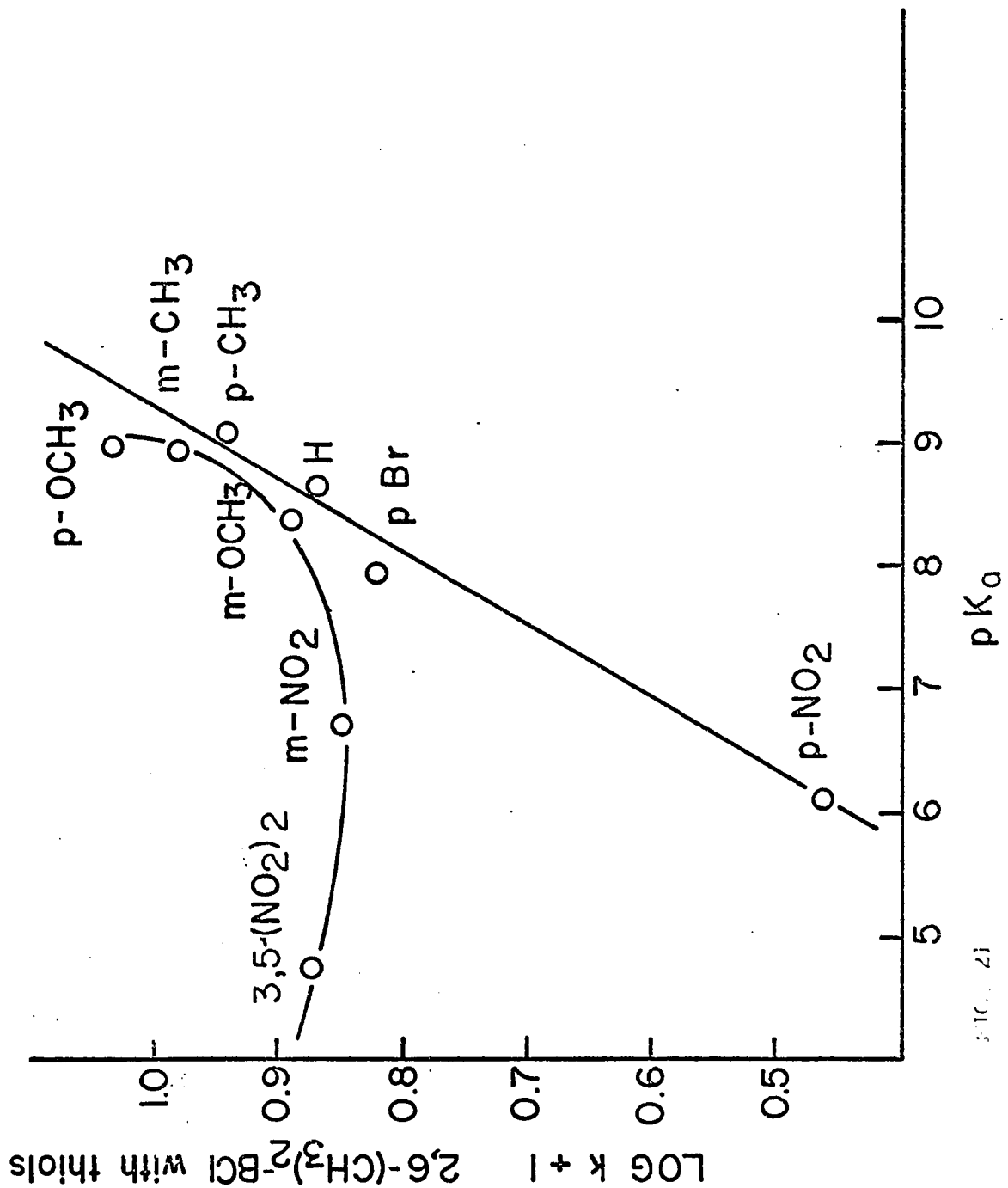


FIG. 21

FIGURE 22

Logarithms of k for the reactions of m -NO₂-
benzyl chloride with substituted thiophenoxides
plotted against pK_a of the thiols

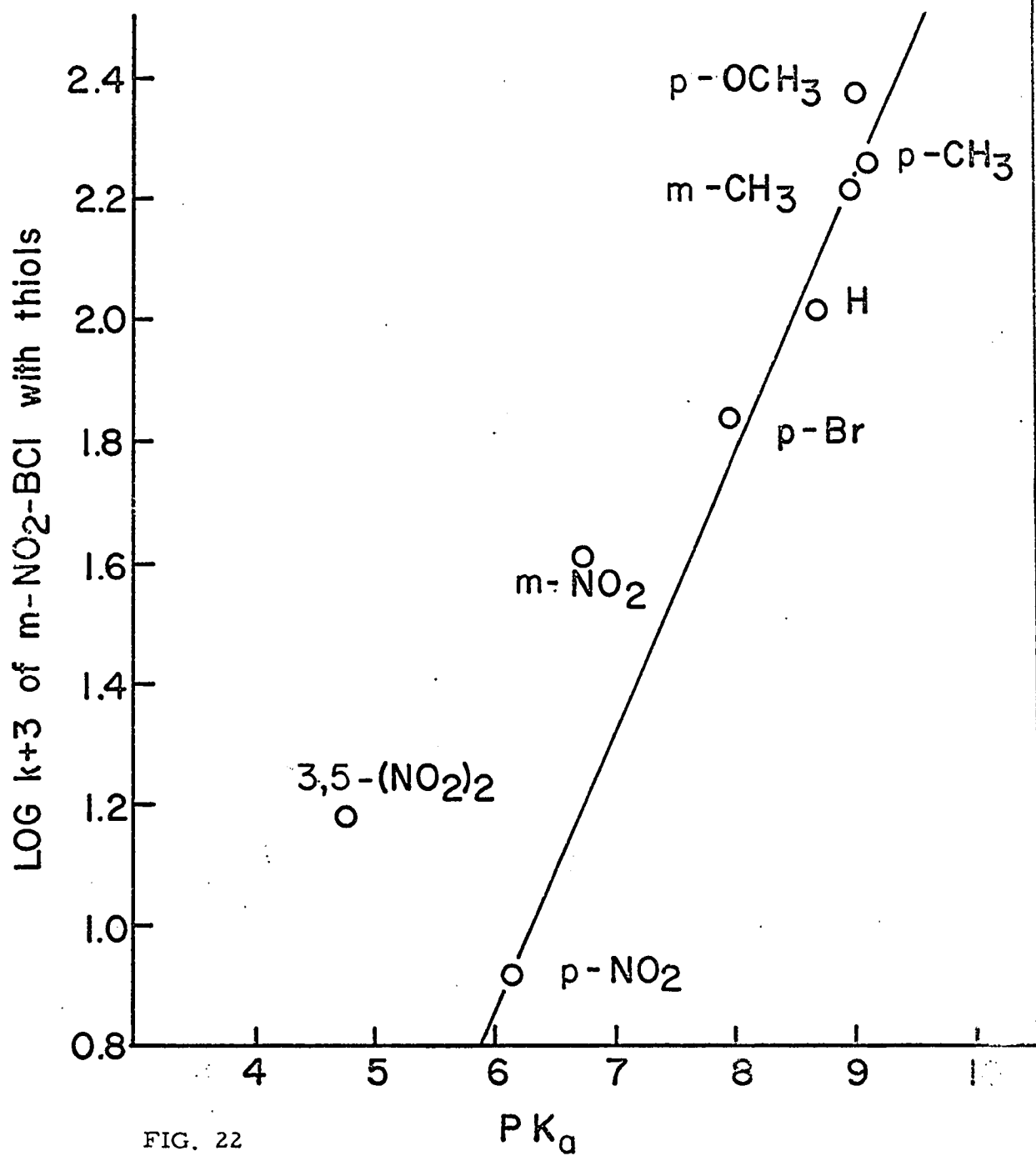


FIG. 22

will then be proportional to the dissociation energy of the nucleophile. Any deviation from these proportional changes will produce the deviations in the Brønsted relation⁹⁸.

(ii) Attempts to Correlate the Nucleophilicity with Edwards' Equation:

In the nucleophilic displacement reactions of a saturated carbon center, Swain and Scott⁶¹ have used an empirical equation to define the nucleophilicity n by the reaction of the nucleophile with methyl bromide in water at 25°C. In view of the limited validity of this parameter, Edwards⁵² devised a two-parameter equation:

$$\log k/k_0 = \alpha E_n + \beta H$$

where E_n is the oxidation potential for the oxidative dimerization of the donor relative to water, H is the acidity constant of the nucleophile relative to water, and α and β are the susceptibility of the reaction. Edwards' equation has been considered to give a better fit and wider application than that of Swain and Scott.

Freedman and Corwin¹⁴⁷ confirmed that the oxidation-reduction potential of the thiourea-formamidine disulfide system estimated by Preisler¹⁴⁸ is reversible;



$$E = E_0 + RT/2F \cdot \ln(\text{RSSR})/(\text{RSH})^2$$

where E is the potential of the system and E_0 is the constant characteristic of the specific system.

An attempt was made to correlate the nucleophilicity of substituted thiophenoxides with Edwards' equation. The disulfides were synthesized from the corresponding nine thiophenols by the oxidation of thiols with H_2O_2 . The oxidation potentials were measured according to Freedman and Corwin's procedure¹⁴⁷ by mixing different proportions of thiol and disulfide of known concentration at a constant pH. The potentials were measured at 25°C under a nitrogen atmosphere to prevent the oxidation of the thiol by air. A calomel electrode was used as the reference electrode and platinum wire as the indicating electrode.

However, we were unable to obtain reproducible results with this system. It appeared that the platinum electrode was poisoned by the reagents. Other inert metals were tried (such as iridium and rhodium) with similar results. Due to the insolubility of the materials, the system could not be measured in water, as Freedman and Corwin had done for the thiourea system. Various other solvent systems were tried (methanol-water, dioxane-water and acetone-water) but without success.

(iii) Determination of the reaction constants of substituted benzyl chlorides:

The Hammett plots for para and meta substituted benzyl chlorides are known to be curves⁹⁶. Similar plots for ortho substituted benzyl chlorides with methoxide and thiophenoxide are shown in Figs. 23-24. The σ_p -values were used for ortho substituents,

FIGURE 23

Logarithms of k for the reactions of *o*-substituted
benzyl chlorides with methoxide in MeOH at 25°
plotted against σ

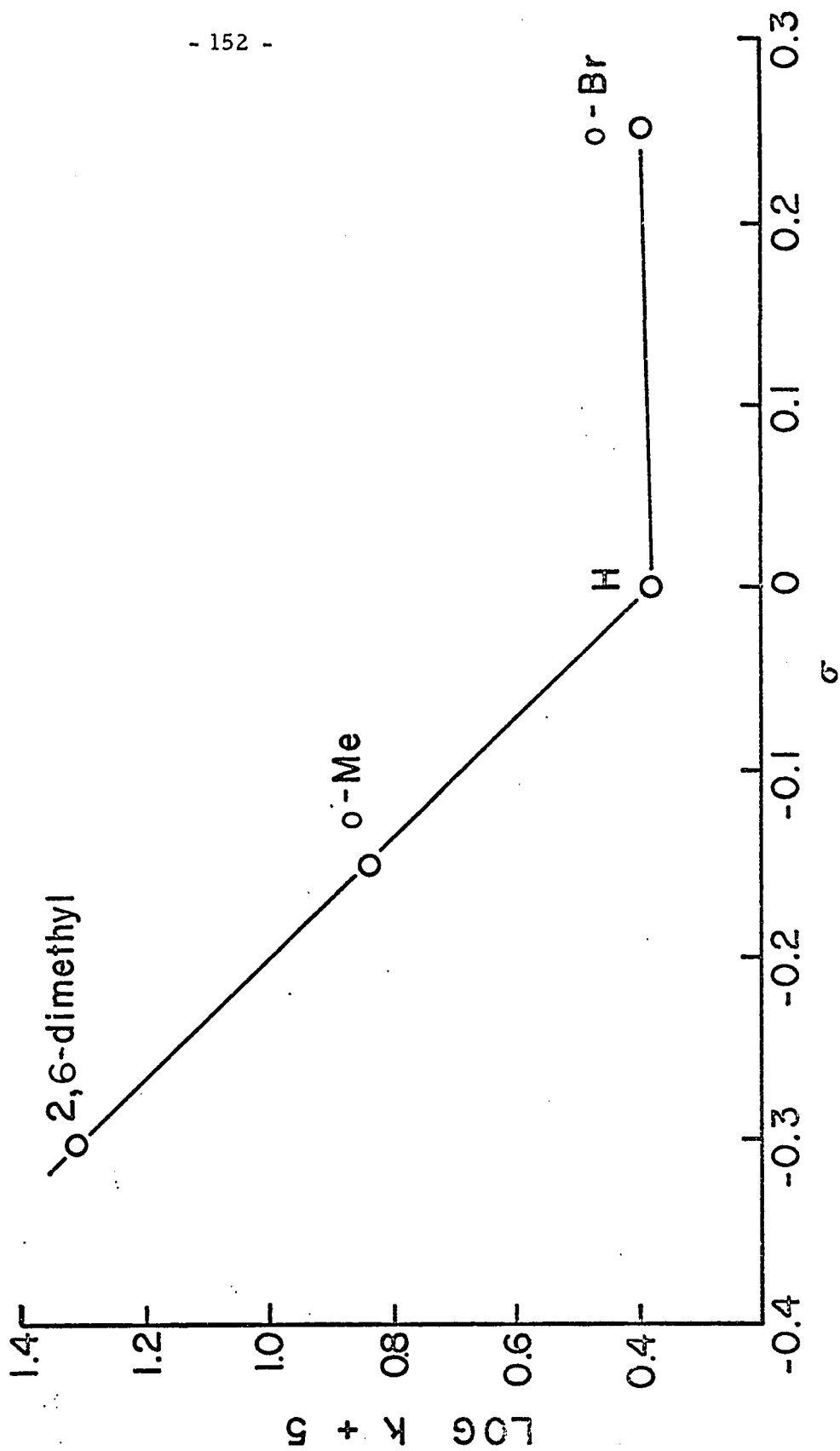
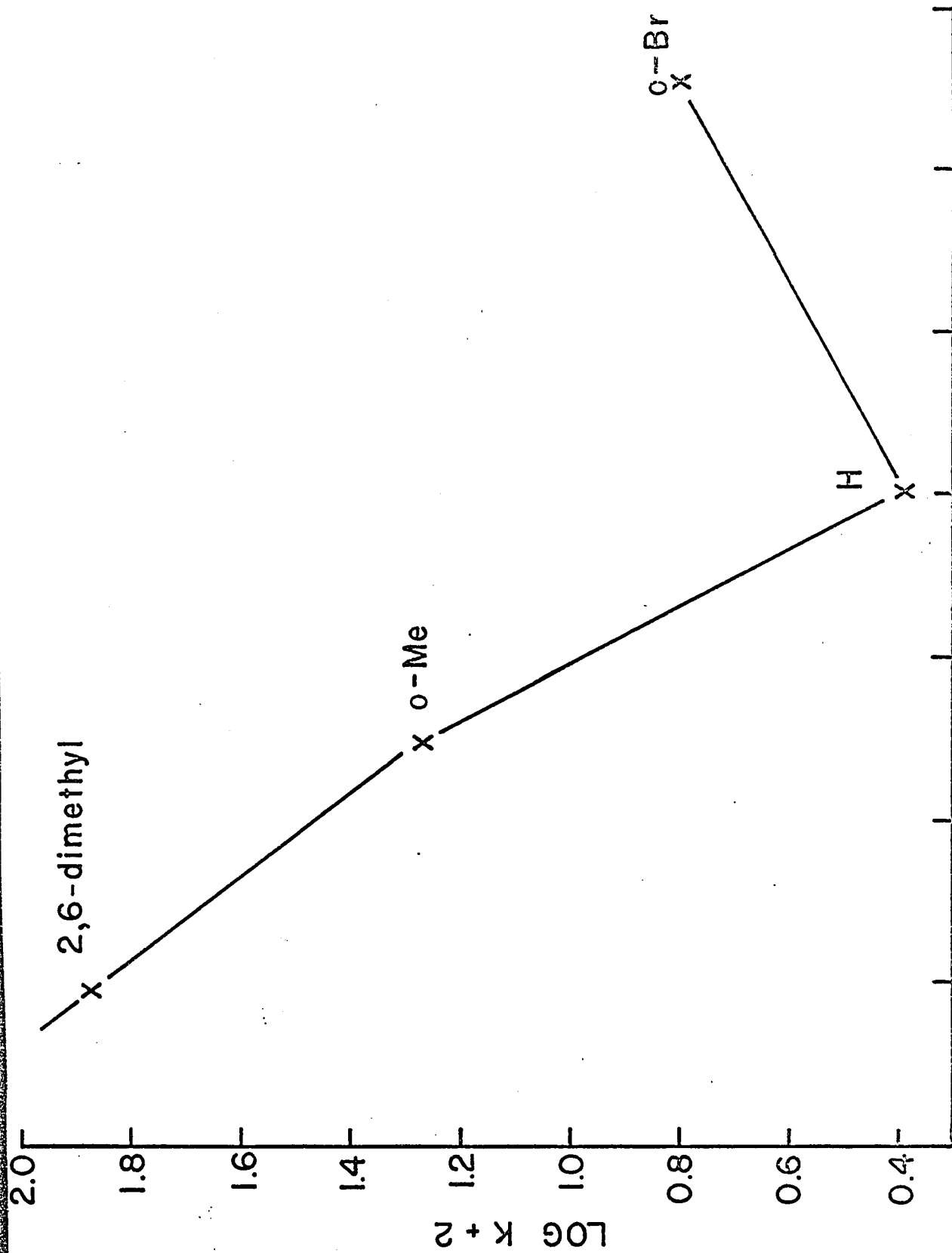


FIG. 23

FIGURE 24

Logarithms of k for the reactions of *o*-substituted
benzyl chlorides with thiophenoxide in CH_3OH at
 25° plotted against σ



and the value for the 2,6-dimethyl substituents was taken as twice that of the o-methyl group. These plots appear to be curves with positive curvatures like those for the reactions of m- and p-substituted benzyl chlorides. The transition states for the nucleophilic reactions of ortho compounds must also vary between the S_N1 and S_N2 extremes, i. e. electron-donating substituents will assist bond breaking while electron-withdrawing substituents favour more completion of bond making relative to bond breaking in the transition state. In addition to this polar factor, an ortho substituted benzyl chloride is subject to two other effects:

Steric effect due to the substituent located in proximity to the reaction center can be of importance. Ortho substituents having different sizes exert different steric effects on rates. Steric effects in such cases do not seem to be of primary importance since all the ortho substituents whether they are electron-donating or electron-withdrawing, enhance the rates. The rate increases further when both ortho positions are substituted by two methyl groups, as compared to the o-methylbenzyl chloride, even though the steric factor is relatively unfavourable for the former.

The rate ratios for reactions of o-methyl, p-methyl and 2,6-dimethylbenzyl chloride with thiophenoxide and the corresponding reaction of benzyl chloride are shown in the following table:

| Substrate | k (1 mole ⁻¹ sec ⁻¹) | k_x/k_H |
|-------------------------------------|---|-----------------|
| H | 2.45×10^{-2} | 1 |
| p-CH ₃ | 3.78×10^{-2} | 1.54 |
| o-CH ₃ | 1.21×10^{-1} | 4.9 |
| 2,6-(CH ₃) ₂ | 7.46×10^{-1} | 3.0×10 |

London interaction may be present. Polarizable ortho substituents increase the reactivity of nucleophilic displacement interaction between the ortho substituents and the polarizable nucleophile. From Figs. 23 and 24, it can be seen that the curve becomes steeper when the more polarizable thiophenoxide is used as a nucleophile instead of methoxide. This would appear to indicate that the London energy of interaction increases as the polarizability of the nucleophile increases.

In order to determine the modified reaction constants (ρ_N)⁹⁸, the log k_2 values for the reactions of each chloride with the substituted thiophenoxides were plotted against log k_2 values for the corresponding reactions of benzyl chloride. A series of lines with varying slopes is shown in Figs. 25-28. As pointed out previously, the slopes give the reaction parameter ρ_N , which is similar in significance to the Brønsted β value. It is a measure of the sensitivity of the rate of reaction to changes in the degree of the bond formation in the transition state⁹⁸.

FIGURE 25

Logarithms of k for the reactions of p -CH₃-benzyl chloride with substituted thiophenoxides plotted against logarithms of k for the corresponding reactions of benzyl chloride.

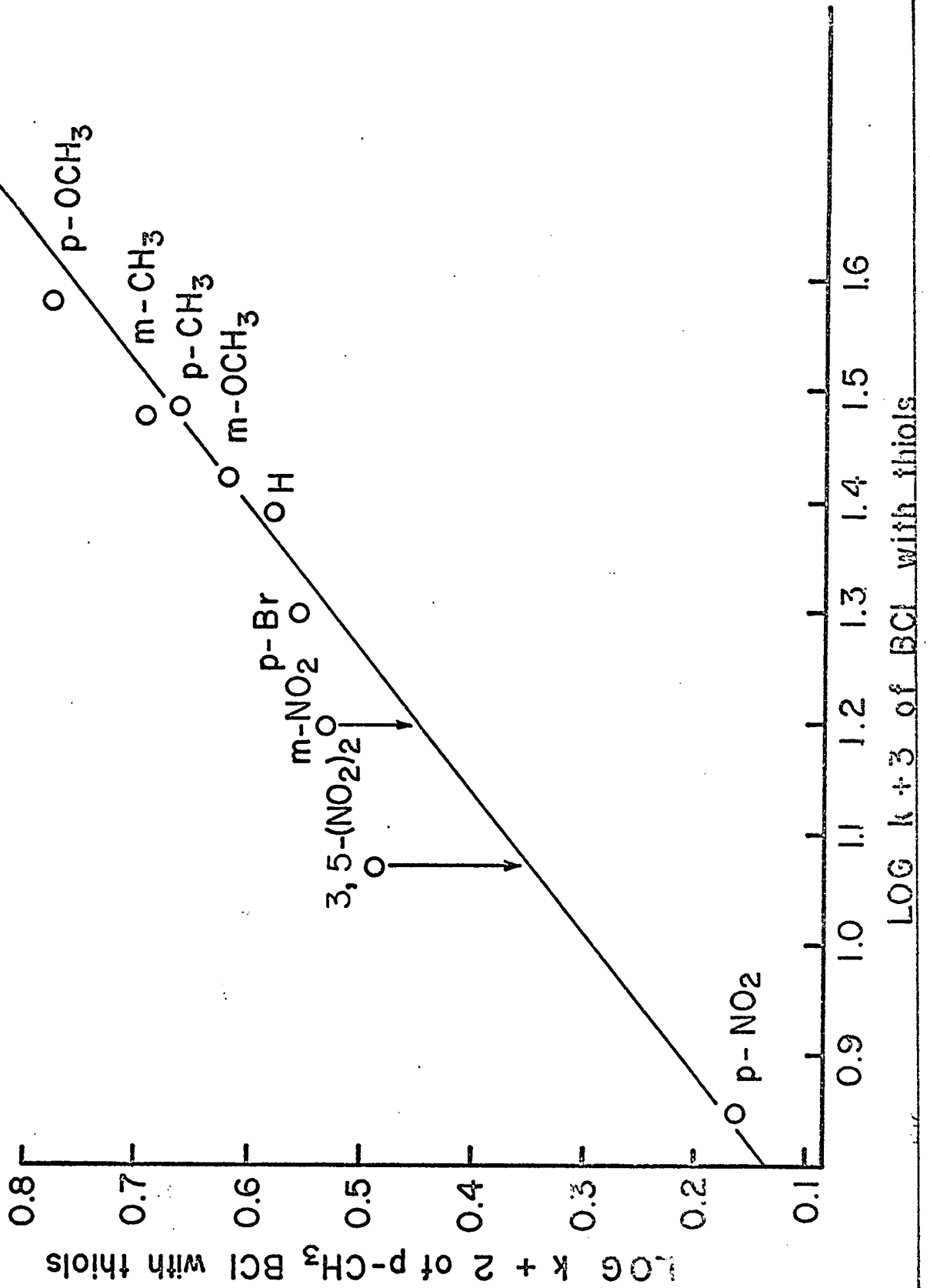


FIGURE 26

Logarithms of k for the reactions of o -CH₃-benzyl chloride with substituted thiophenoxides plotted against logarithms of k for the corresponding reactions of benzyl chloride.

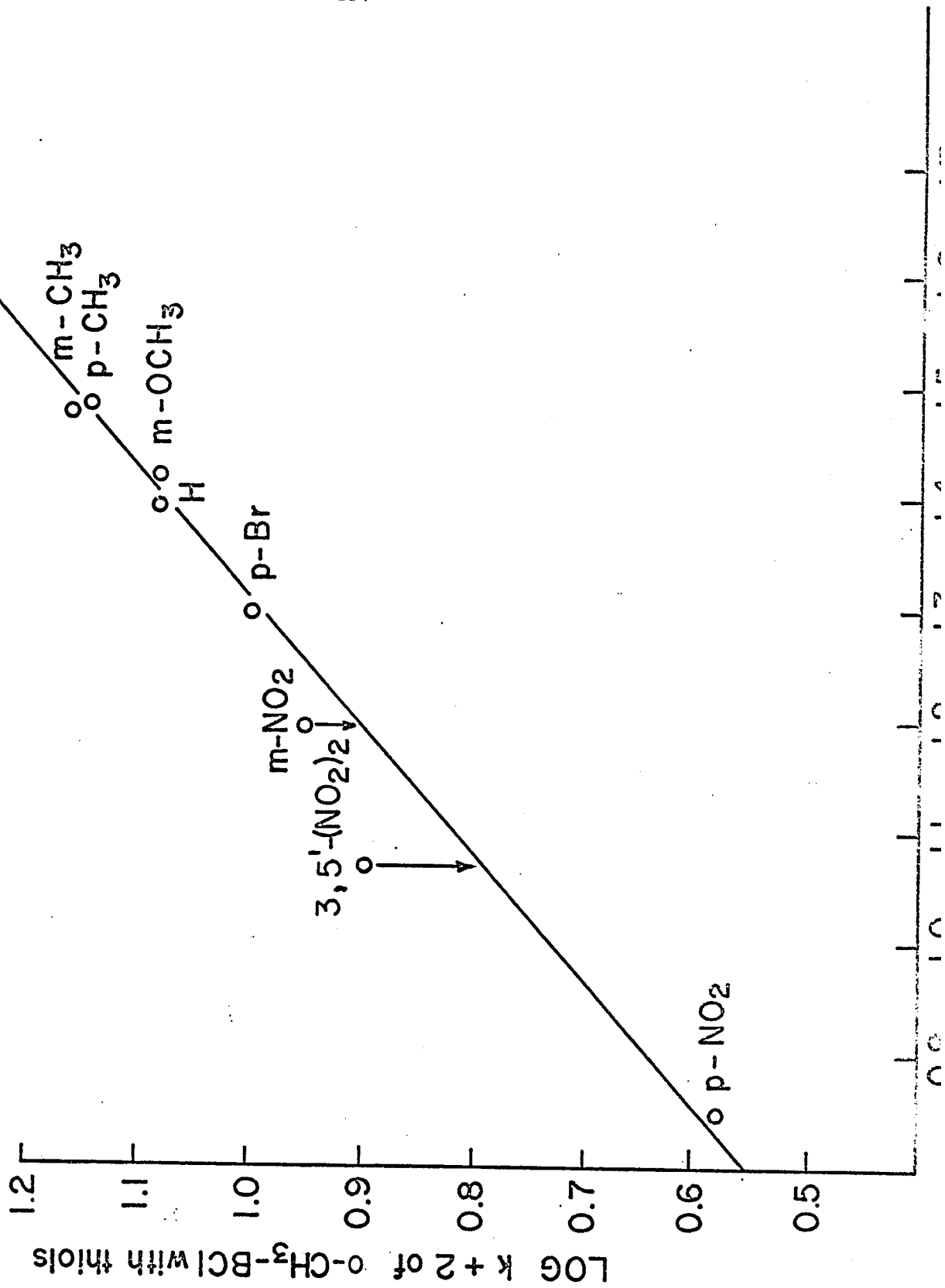


FIGURE 27

Logarithms of k for the reactions of 2,6-(CH₃)₂-benzyl chloride with substituted thiophenoxides plotted against logarithms of k for the corresponding reactions of benzyl chloride.

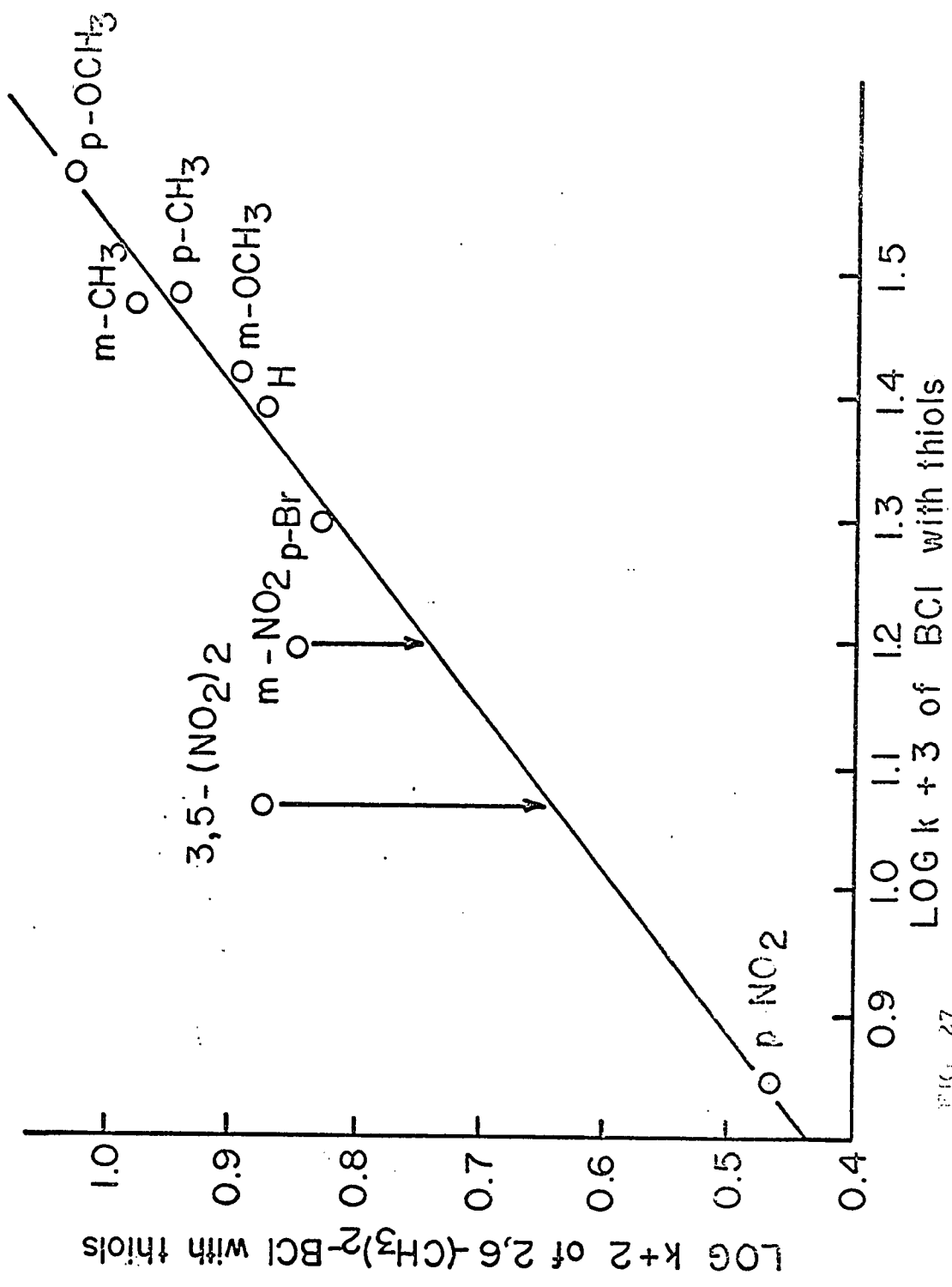


FIG. 27

FIGURE 28

Logarithms of k for the reactions of m -NO₂-benzyl chloride with substituted thiophenoxides plotted against logarithms of k for the corresponding reactions of benzyl chloride.

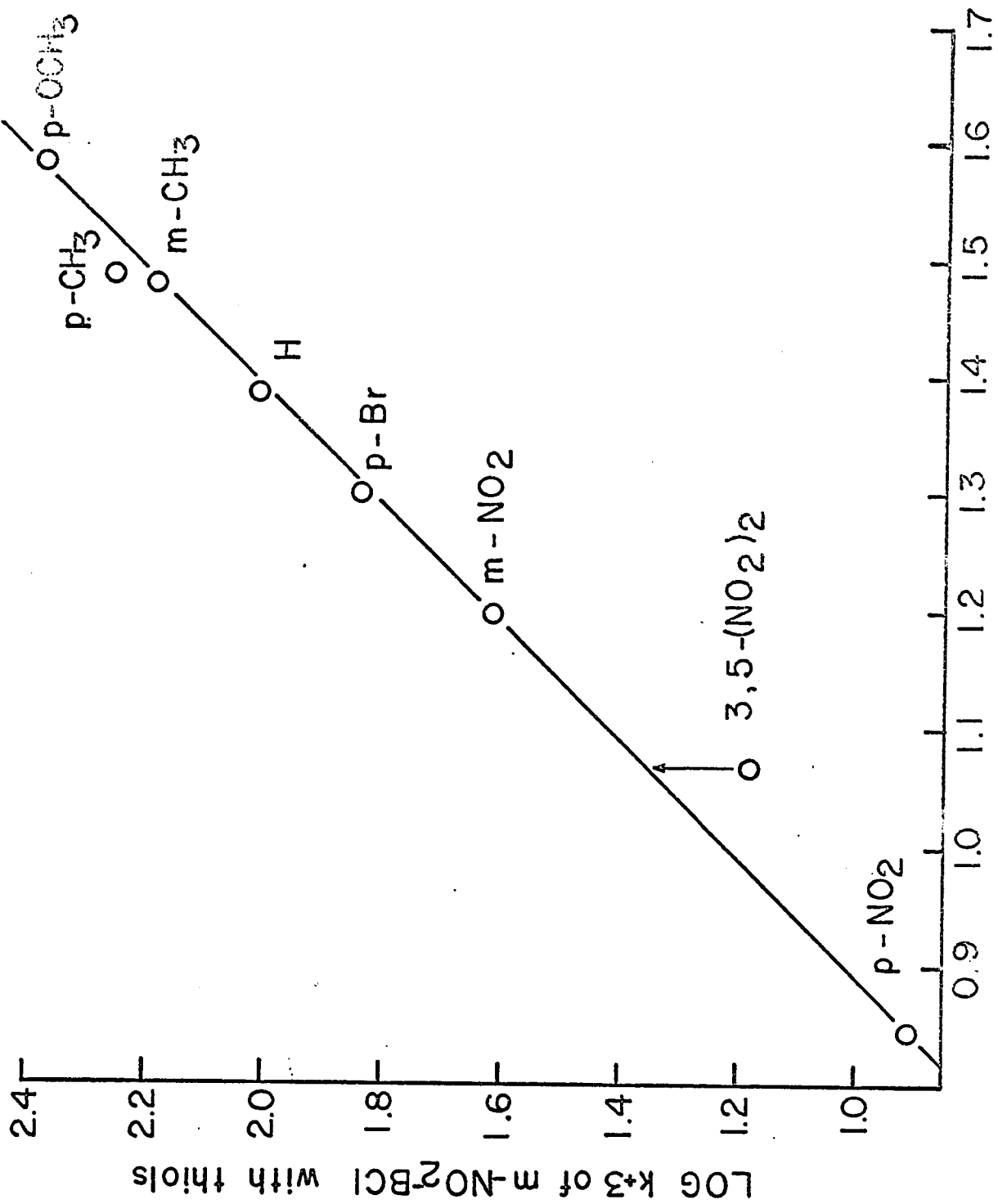


FIG. 28 LOG k+3 of BCl with thiols

The relative reaction constants for the substituted benzyl chlorides are given in Table 16. The reaction constants for meta or para substituted benzyl chlorides (in which steric and London interactions are assumed to be small) increase as the σ -values of the substituents increase. The linear relationship of ρ_N and σ for m- and p-substituted benzyl chlorides is shown in Fig. 29. This agrees with the proposal that the reaction parameter ρ_N should increase regularly with the decrease in electron density at the reaction center^{98,140}.

The inference is that the transition state of nucleophilic displacement has the greatest degree of C-S bond formation for p-nitro and the least with p-methyl benzyl chloride as substrates. Thus, electron-donating substituents conjugate with the reaction center which, for a nucleophilic displacement, behaves to some extent like an incipient carbonium ion; the interaction of the nucleophile and the leaving group with the reaction center is thereby reduced. The electron-withdrawing substituents promote conjugation between the π -orbitals of the benzene ring and the reaction center and thereby increase the interaction of the nucleophile with that center^{97,98}.

FIGURE 29

Plot of the reaction constants (ρ_N) of substituted
benzyl chloride against substituent constants.

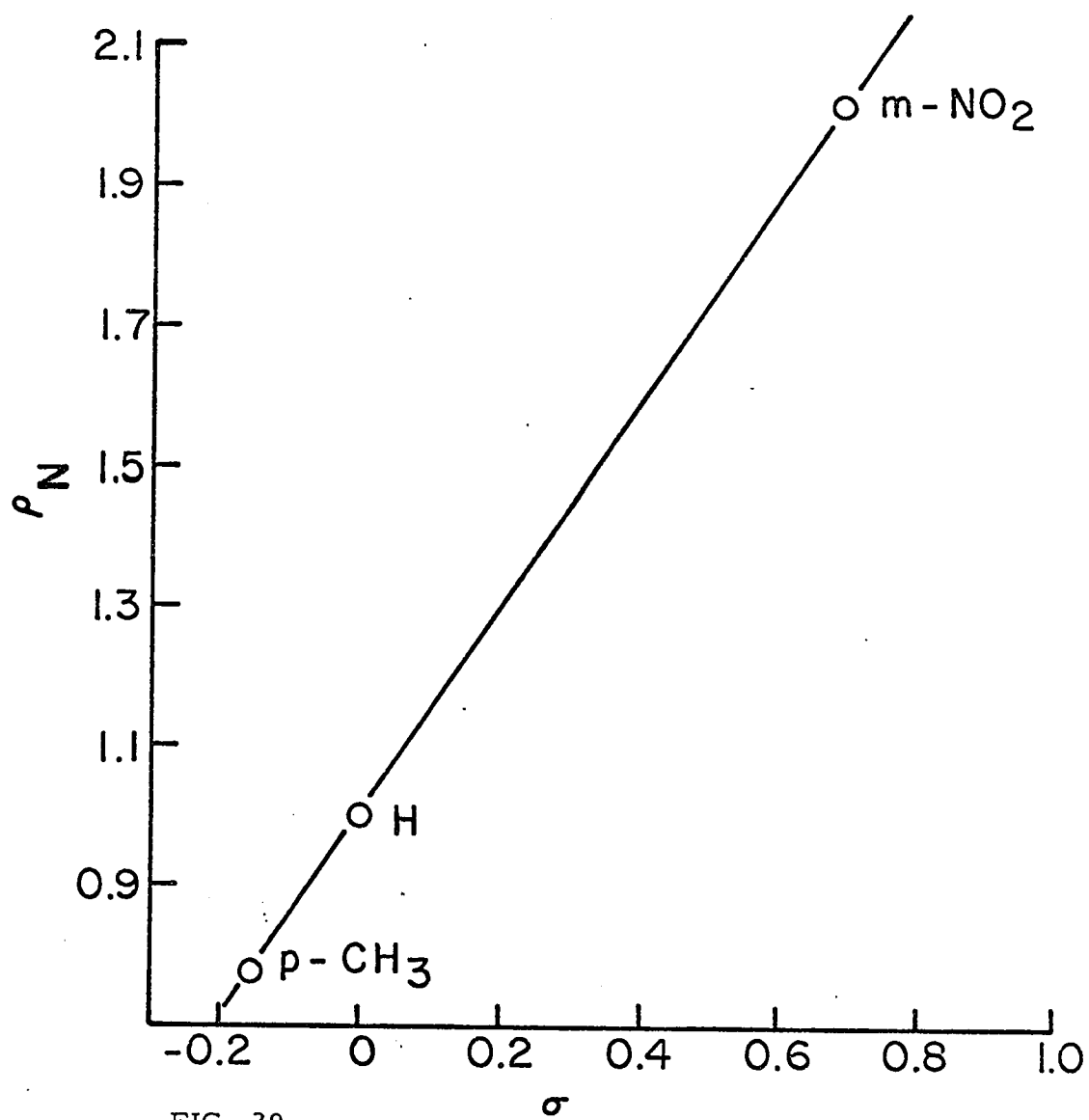


FIG. 29

TABLE 16
Reaction Constants for Substituted Benzyl Chlorides in CH₃OH at 25°C

| Substituted B: Cl. | ρ_N | γ (correlation coefficient) |
|-------------------------------------|----------|---------------------------------------|
| H | 1 | |
| p-CH ₃ | 0.81 | 1.000 |
| o-CH ₃ | 0.91 | 0.995 |
| 2,6-(CH ₃) ₂ | 0.77 | 0.992 |
| m-NO ₂ | 2.06 | 0.998 |

The reaction constant for o-methylbenzyl chloride ($\rho_N = 0.87$) is only slightly larger than that for the p-methyl isomer ($\rho_N = 0.78$), indicating that steric effect contributions to the reaction of the ortho methyl compound are not very large. The reaction constant ρ_N of 2,6-dimethyl benzyl chloride is further reduced to 0.77, as one would expect on the basis of electronic effects, but this value is too large if a comparison is made with the reaction constant of p-methylbenzyl chloride (see Fig. 29). These results are consistent with the explanation that the electronic effect of the methyl substituents lowers the reaction constant, while the steric effect raises it owing to the decrease in the transmission of electronic effect of the methyl substituents to the reaction center. It may be concluded that ortho substituents reduce the delocalization of π -electrons more than do the corresponding para substituents. This may be attributed to the interference of the ortho substituent with the coplanarity of the ring and CH_2 group in the transition state.

(iv) Re-estimation of the London energy

Bunnett⁹⁰ estimated the beneficial London energy by the adjusted rate ratios

$$(k_Y/k_{\text{CH}_3\text{O}^-})_{\text{o-R}} / (k_Y/k_{\text{CH}_3\text{O}^-})_{\text{H}}$$

using benzyl chloride as the reference for comparison. The reaction constants for the ortho substituted compounds and benzyl chloride were assumed to be similar in order to cancel the inherent difference

in nucleophilicity. Table 16 shows that benzyl chloride is not a good reference because the reaction constant of benzyl chloride is not equal to that of the ortho compounds.

Reinheimer⁹² and Sisti⁹¹ used the corresponding para substituted benzyl chloride as the standard and assumed that the polar effect for the ortho and para isomers are nearly identical.

In order to study the London effect of o-methyl and 2,6-dimethyl substituents, p-methylbenzyl chloride was chosen as a reference substrate. This compound has a closer reaction constant to o-methyl and 2,6-dimethylbenzyl chloride than has benzyl chloride, as shown in Table 16. This likeness can also be seen from the plots of $\log k$ for the reactions of ortho substituted benzyl chlorides with substituted thiophenoxides vs. $\log k$ for the corresponding reactions of p-methyl benzyl chloride, as shown in Figs. 30-31. The slope of these plots is the measure of the relative reaction constant between the two compounds. The ratios ρ'_N/ρ_N are close to unity for the o-methyl and 2,6-dimethyl benzyl chlorides relative to p-methylbenzyl chloride than if one used benzyl chloride as a reference substrate.

The energy differences between reactions of methoxide and thiophenoxide with the same substrate may be expressed as the differences in its nucleophilicity plus an additional term for the differences in London energy.

FIGURE 30

Logarithms of k for the reactions of p - CH_3 -benzyl chloride with substituted thiophenoxides plotted against logarithms of k for the corresponding reactions of o - CH_3 -benzyl chloride.

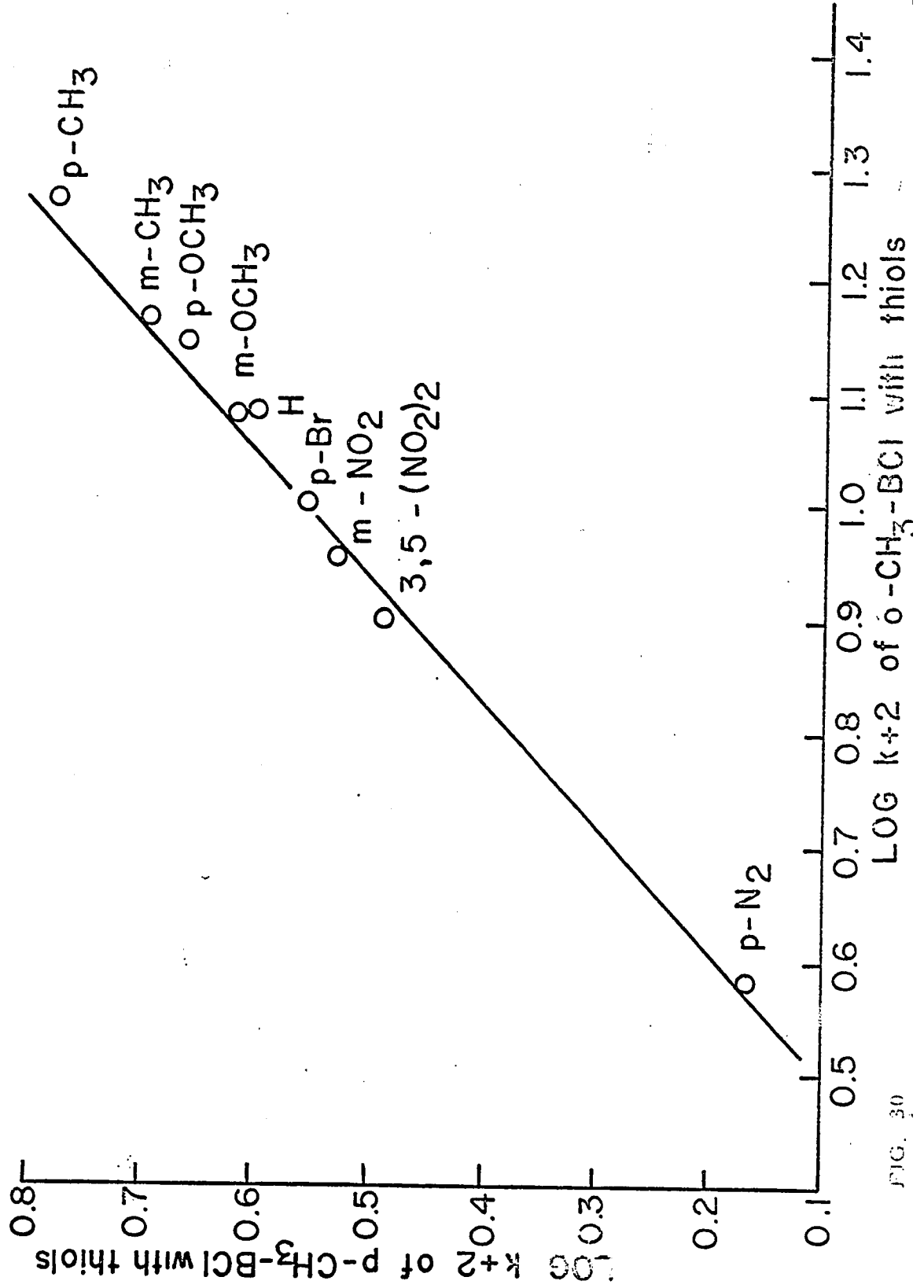


FIG. 30

FIGURE 31

Logarithms of k for the reactions of p-CH₃-benzyl chloride with substituted thiophenoxides plotted against logarithms of k for the corresponding reactions of 2,6-(CH₃)₂ benzyl chloride.

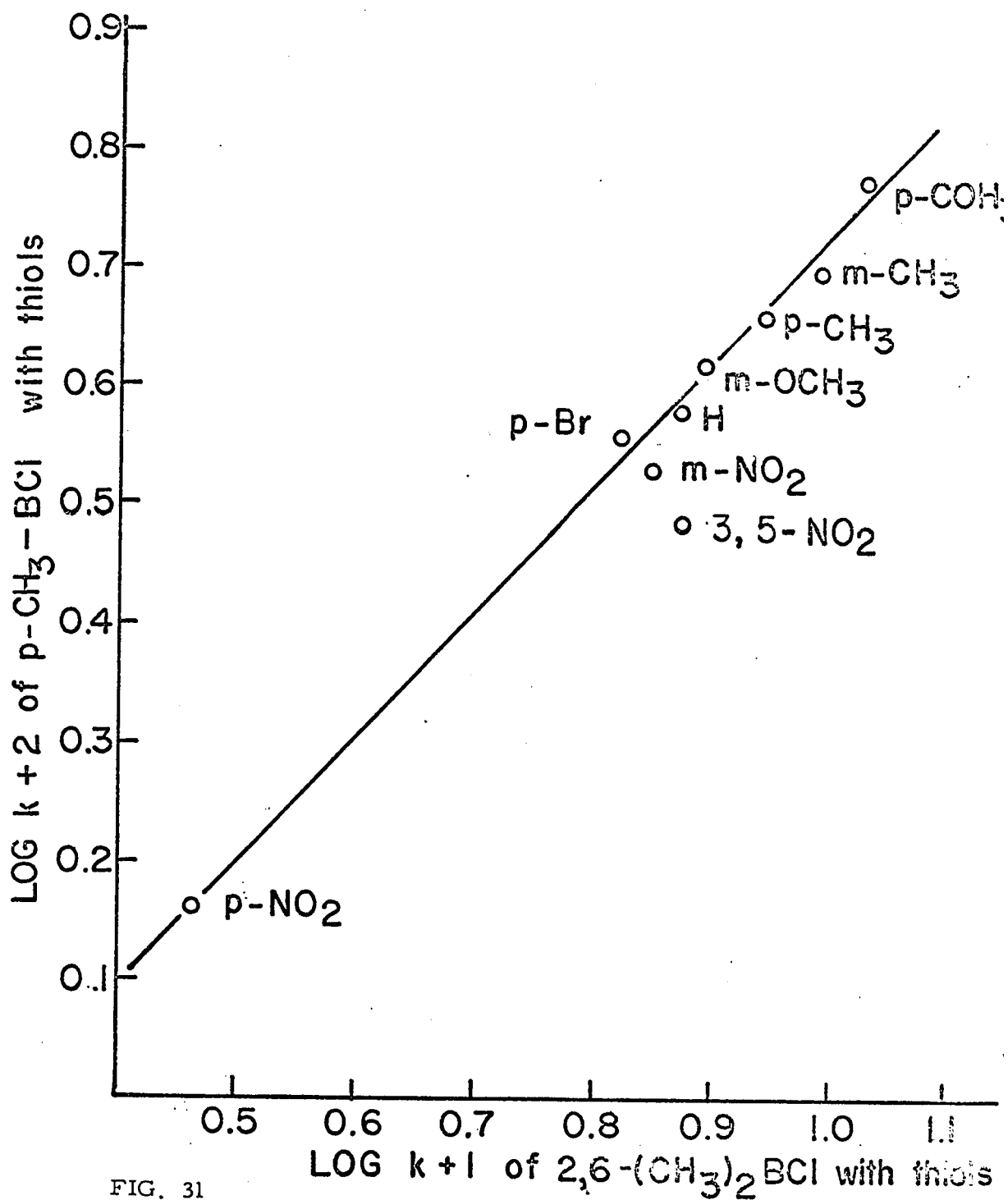


FIG. 31

$$\Delta\Delta F = -2.303RT \cdot \log k_{Y^-} / k_{CH_3O^-} = \rho \cdot \Delta N + \Delta\Delta F_L \quad (R-5)$$

where ΔN represents the nucleophilicity difference of the nucleophiles. If *o*-methylbenzyl chloride is used as a substrate, the energy difference between the nucleophiles methoxide and thiophenoxide will be:

$$\begin{aligned} \Delta\Delta F_{o-CH_3}^\ddagger &= -2.303RT \log(k_{C_6H_5S^-} / k_{CH_3O^-})_{o-CH_3} \\ &= \rho_{o-CH_3} \Delta N + \Delta\Delta F_L^H + \Delta\Delta F_L^{CH_3} \end{aligned} \quad (R-6)$$

where k is the rate constant of the reaction with methoxide or thiophenoxide as cited; ΔN the difference in nucleophilicity of the two nucleophiles; ρ_{o-CH_3} the reaction constant of the reaction; $\Delta\Delta F_L^H$ the difference in London interaction energy between two nucleophiles with the ortho hydrogen groups, and $\Delta\Delta F_L^{CH_3}$ the difference between two nucleophiles with the ortho methyl group.

Similarly, the energy difference for the reactions of *p*-methylbenzyl chloride (in which two hydrogen groups are in both ortho positions) with methoxide and thiophenoxide is:

$$\Delta\Delta F_{p-CH_3}^\ddagger = -2.303RT \log(k_{S^-} / k_{CH_3O^-}) = \rho_{p-CH_3} \Delta N + 2(\Delta\Delta F_L^H) \quad (R-7)$$

Subtracting equation (R-6) from equation (R-7) one obtains:

$$\Delta\Delta\Delta F^\ddagger = \Delta\Delta F^\ddagger_{\text{o-CH}_3} - \Delta\Delta F^\ddagger_{\text{p-CH}_3} = -2.303RT \log \left[\frac{(k_{\phi S^-} / k_{\text{CH}_3\text{O}^-})_{\text{o-CH}_3}}{(k_{\phi S^-} / k_{\text{CH}_3\text{O}^-})_{\text{p-CH}_3}} \right]$$

$$= (P_{\text{o-CH}_3} - P_{\text{p-CH}_3}) \Delta N + \Delta\Delta F_L^{\text{CH}_3} - \Delta\Delta F_L^{\text{H}} \quad (\text{R-8})$$

From Fig. 30, $P_{\text{o-CH}_3} / P_{\text{p-CH}_3} = 0.91$. This 10% difference in P_N values is not considered to be critical enough to affect evaluation of the London energy when it is neglected; equation (R-8) can then be reduced to:

$$\Delta\Delta\Delta F^\ddagger = \Delta\Delta F_L^{\text{CH}_3} - \Delta\Delta F_L^{\text{H}} = -RT \cdot 2.303 \log \left[\frac{(k_{\phi S^-} / k_{\text{CH}_3\text{O}^-})_{\text{o-CH}_3}}{(k_{\phi S^-} / k_{\text{CH}_3\text{O}^-})_{\text{p-CH}_3}} \right] \quad (\text{R-9})$$

where $\Delta\Delta\Delta F^\ddagger$ is the London energy difference for the polarizable nucleophile, thiophenoxide, relative to methoxide with p-methylbenzyl chloride relative to p-methylbenzyl chloride.

The London energies for seven substituted thiophenols relative to methoxide are given in Table 17. The variation of the London energies for these seven thiophenols is small. There are three variables that determine the magnitude of the energy; the polarizability, the ionization potentials of the two groups involved, and the distance of the ortho substituent and the incoming nucleophile in the transition state. The equation to evaluate the theoretical London energy is usually given as follows⁹⁰:

$$W_{YR} = 2.1 \frac{3\alpha_Y\alpha_R}{2r^6} \left(\frac{I_Y \cdot I_R}{I_Y + I_R} \right) \quad (R-10)$$

where W_{YR} is the energy of attraction between atoms Y and R; α_Y and α_R their polarizabilities, r their distance of separation, and I_Y and I_R their ionization potentials. Substitution in the thiophenol will change the ionization potential of the thiols, and the polarizability of the S atom may also change slightly. Even though the reactions go through the same mechanism, the London energies may not be constant due to changes in I and α .

The term of the difference in nucleophilicity in equation (R-8) can be eliminated without approximation by multiplying equation (R-6) by 0.9 ($\rho_{p-CH_3} / \rho_{o-CH_3} = 0.9$ calculated by plotting $\log k_{o-CH_3}$ vs. $\log k_{p-CH_3}$); then subtracting equation (R-7) one gets

$$\begin{aligned} \Delta\Delta F^\ddagger &= 0.9 (\Delta\Delta F_L^H + \Delta\Delta F_L^{CH_3}) - 2(\Delta\Delta F_L^H) \\ &= -2.30RT \log [0.9 (k_{\phi S^-} / k_{CH_3O^-})_{o-CH_3} / (k_{\phi S^-} / k_{CH_3O^-})_{p-CH_3}] \quad (R-11) \end{aligned}$$

This energy would be the comparison between the attraction energy for 0.9 o-methylbenzyl chloride with p-methylbenzyl chloride as shown in Table 17 under the column $E_{0.9(o-CH_3)}$. The difference between energies obtained from equation (R-9) and equation (R-11) are about 60 cal. This calculation indicates that the approximation used in deriving equation (R-9) has a small effect on the E calculated.

The values obtained from our rate ratios were compared with the calculated values derived from equation (R-10). Bunnett has a calculated value of -340 cal. for the interaction energy of thiophenoxide

relative to methoxide with a methyl benzyl chloride relative to benzyl chloride⁹¹. Reinheimer's value is 151 cal.⁹². Our experimental value is 380 cal. which is closer to Bunnett's calculated value.

There are difficulties in the calculation of the theoretical London energy in this case, inasmuch as the ionization potential of the ortho methyl substituent is not known (the value for the corresponding radical was used⁹⁰). Further, the distance between the nucleophile and the ortho substituent in the transition state is uncertain, and finally the values for the ionization potentials and the polarizabilities of the nucleophiles in the transition state were assumed to be the average of the corresponding atom and the ion. All these factors make it impossible to calculate the absolute value for these London energies.

(v) Additive London effect for the di-substitution in ortho positions

The London energy for 2,6-dimethylbenzyl chloride can be evaluated in a similar way to that of o-methylbenzyl chloride:

$$\begin{aligned}\Delta\Delta F_{2,6-(CH_3)_2}^\ddagger &= -2.303 RT \log (k_{\phi S^-} / k_{CH_3O^-})_{2,6-(CH_3)_2} \\ &= P_{2,6-(CH_3)_2} \Delta N + 2(\Delta\Delta F_L^{CH_3}) \quad (R-12)\end{aligned}$$

Subtracting equation (R-12) from equation (R-7), one obtains:

$$\Delta\Delta\Delta F^\ddagger = (\rho_{2,6-(CH_3)_2} - \rho_{p-CH_3})\Delta N + 2(\Delta\Delta F_L^{CH_3}) - 2(\Delta\Delta F_L^H)$$

Since
$$\frac{\rho_{2,6-(CH_3)_2}}{\rho_{p-CH_3}} = 1.04$$

$$\rho_{2,6-(CH_3)_2} - \rho_{p-CH_3} \approx 0$$

Therefore

$$\Delta\Delta\Delta F^\ddagger = 2(\Delta\Delta F_L^{CH_3} - \Delta\Delta F_L^H) = -2.3RT \log \frac{(k_{\phi S^-} / k_{CH_3O^-})_{2,6-(CH_3)_2}}{(k_{\phi S^-} / k_{CH_3O^-})_{p-CH_3}} \quad (R-13)$$

The London energies for 2,6-dimethylbenzyl chloride with various substituted thiophenoxides estimated from equation (R-13) are given in Table 18. If one compares equation (R-13) to equation (R-9), the energy for 2,6-dimethylbenzyl chloride $[\Delta\Delta\Delta F^\ddagger = 2(\Delta\Delta F_L^{CH_3} - \Delta\Delta F_L^H)]$ should be theoretically twice that of the o-methyl compound $[\Delta\Delta\Delta F^\ddagger = \Delta\Delta F_L^{CH_3} - \Delta\Delta F_L^H]$. Indeed, the experimental values show that the energies for diorthomethyl compound are almost double that for one methyl compound (Table 17 and 18). This implies that the effect of the London interaction of a nucleophile with an ortho methyl group is, to at least a good approximation, additive.

Sisti and Lowell⁹¹ argued that the trend in adjusted rate ratios for various nucleophiles with a given ortho substituted benzyl chloride is also consistent with decreasing steric interaction between the nucleophiles and the given ortho substituent, i. e. the rate ratios increase in the series $\text{MeO}^- < \text{C}_6\text{H}_5\text{S}^- < \text{I}^-$. They suggested that these variations of the adjusted rate ratios might be caused by the ability of the highly polarizable nucleophiles to distort their bonding electrons without bringing the rest of the molecule close enough to cause excess repulsive forces.

Our present studies of o-methylbenzyl chloride and 2,6-dimethyl benzyl chloride do not agree with Sisti's proposal. Accordingly, the 2,6-dimethyl compound should have a less favorable steric effect compared to the mono-ortho methyl compound, but the adjusted rate ratios further increase from o-methyl to 2,6-dimethylbenzyl chloride. The additive energy for the two ortho methyl groups is consistent with the presence of a London energy between the substituent and the nucleophile. The anomalous result observed by Sisti and Lowell for the adjusted ratios of o-methyl and o-bromobenzyl chloride with a given nucleophile may be due to the steric dissimilarities of the methyl and bromo substituents and the difference in the distance between the substituent and the coming nucleophile at the transition states.

TABLE 17

Adjusted Rate Ratio and London Force Energy for o-Methyl Benzyl Chloride

$$R = \frac{\left(\frac{k_{Y^-}}{k_{CH_3O^-}} \right)_{o-CH_3}}{\left(\frac{k_{Y^-}}{k_{CH_3O^-}} \right)_{p-CH_3}}$$

| Thiophenols | $\frac{k_{Y^-}}{k_{CH_3O^-}}_{p-CH_3}$ | $\frac{k_{Y^-}}{k_{CH_3O^-}}_{o-CH_3}$ | R | R x 0.9 | E_{o-CH_3} (cal/mole) | $E_{0.9(o-CH_3)}$ (cal/mole) |
|--------------------|--|--|-------|---------|----------------------------|---------------------------------|
| P-CH ₃ | 1065 | 2027.6 | 1.904 | 1.714 | 380 | 320 |
| m-CH ₃ | 1158 | 2122.2 | 1.833 | 1.65 | 360 | 300 |
| H | 880.9 | 1755.4 | 1.993 | 1.79 | 410 | 340 |
| P-OCH ₃ | 1389 | 2708.8 | 1.950 | 1.76 | 400 | 330 |
| m-OCH ₃ | 964.8 | 1749.6 | 1.813 | 1.63 | 350 | 290 |
| P-Br | 839.3 | 1455.6 | 1.74 | 1.57 | 330 | 270 |
| P-NO ₂ | 337.7 | 556.0 | 1.65 | 1.48 | 300 | 230 |

TABLE 18

Adjusted Rate Ratio and London Force Energy for 2,6-Dimethyl Benzyl Chloride

$$R = \frac{\frac{k_{y-}}{k_{CH_3O^-}}(2,6-(CH_3)_2)}{\frac{k_{y-}}{k_{CH_3O^-}}(p-CH_3)}$$

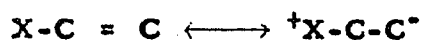
| Thiophenols | $\frac{k_{y-}}{k_{CH_3O^-}}(p-CH_3)$ | $\frac{k_{y-}}{k_{CH_3O^-}}(2,6-(CH_3)_2)$ | $R(CH_3)_2$ | cal. $E(CH_3)_2$ |
|--------------------|--------------------------------------|--|-------------|------------------|
| P-CH ₃ | 1065 | 4248.3 | 3.989 | 820 |
| m-CH ₃ | 1158 | 4646 | 4.012 | 820 |
| H | 880.9 | 3607 | 4.095 | 830 |
| P-OCH ₃ | 1389 | 5167 | 3.72 | 770 |
| m-OCH ₃ | 964.8 | 3783 | 3.921 | 810 |
| P-Br | 839.3 | 3234 | 3.853 | 800 |
| P-NO ₂ | 337.7 | 1412 | 4.1 | 830 |

IV. CHARGE TRANSFER COMPLEX FORMATION AT THE TRANSITION STATE

There appears to be abnormal reactivity of *m*-nitrothiophenoxide and 3,5-dinitrothiophenoxide. For example, there are significant deviations for *m*-NO₂ and 3,5-dinitrothiophenoxide in the plots of $\log k/k_0$ for reactions of substituted benzyl chlorides with various substituted thiophenoxides vs. $\log k/k_0$ for the corresponding reactions of benzyl chloride, as shown in Figs. 25-28. Deviation is greatest when 2,6-dimethylbenzyl chloride is used as the substrate and 3,5-dinitrothiophenoxide as the nucleophile. The rate constant of this reaction with 3,5-dinitrothiophenoxide is almost the same as that of the unsubstituted thiophenoxide, even though thiophenoxide ($pK_a = 8.65$) is a much stronger base than 3,5-dinitrothiophenoxide ($pK_a = 4.745$).

The magnitude of the observed deviation in these plots increases as more electron-withdrawing groups are added to the meta position of the thiophenoxide, or as more electron donating substituents are added to the ortho or para position of the substrate benzyl chloride. There are several possibilities that might cause these deviations:

(1) A large change in polarizability of the sulfur atom by introducing a nitro group into the benzene ring of the thiophenol. The presence of an exalted molar refraction is a common property of conjugated unsaturated compounds¹⁴⁹.



The greater the stability of the dipolar structure, the lower the level of the excited state, and the greater the exaltation of the refraction of the X atom. If the sulfur in *m*-NO₂, and 3,5-dinitrothiophenol have greater polarizabilities (by inductive effect), there will be an extra increment in the London energy due to this presumed exaltation of the molar refraction of sulfur by the substituents of *m*-NO₂ and 3,5-(NO₂)₂ as compared to the rest of the seven thiophenols. These increments will become greater as the polarizabilities of the ortho substituents of the substrate increase: the order should be 2,6-dimethyl > *o*-methyl > benzyl chloride, and the deviations observed, which are shown as the length of vertical line in Figs. 13-16 increase in the same order. This possibility is rendered less likely by the fact that there is no deviation for *m*-NO₂ and 3,5-dinitrothiophenoxide in the plot of log *k* for reactions of *o*-methylbenzyl chloride against log *k* for reactions of the *p*-methyl isomer, as shown in Fig. 30, in which the former possesses a H atom and one methyl group while the latter has two H atoms in the ortho position.

The deviation, however, is observed in the plot of log *k* of *p*-methyl vs. log *k* of benzyl chloride (Fig. 25); in this case, both substrates contain only hydrogens in the ortho positions. Here the deviations cannot be due to the large change of the polarizability of sulfur. Furthermore, if there is any large change in the polarizability of S, one would expect that the change in *p*-nitrothiophenol would be the greatest of all the thiols studied, as it is able to form structures in which the *p*-NO₂ group and the sulfur atom are directly conjugated.

One would therefore expect it to show the largest deviation in those plots of $\log k$ for a substituted benzyl chloride vs. $\log k$ for benzyl chloride. On the contrary, however, there is no deviation for *p*-NO₂-thiophenoxide.

(2) A possible explanation for the deviations involves differences in solvation of nucleophiles and ion-pair dissociation. The pK_a values for substituted thiophenols vary from 9.055 for *p*-methyl to 4.75 for the 3,5-dinitro compound. The degree of solvation for the weak base 3,5-dinitrothiophenoxide is likely to be smaller than that for a strong base such as *p*-methylthiophenoxide, which would have a more concentrated electron density on the sulfur atom. The solvated anion is usually considered to suffer a rate-diminishing influence which increases as the degree of solvation is increased^{8,9}. Thus, 3-5, dinitrothiophenoxide would on these grounds be more reactive relative to its basicity than the more basic thiophenoxides, which are more strongly solvated. It is doubtful that such an effect would so moderate nucleophilicity in a protic solvent as to overcome a difference of almost 4 pK_a units.

However, the change in nucleophilicity due to solvation cannot be responsible for the deviations of the *m*-NO₂ and 3,5-dinitrothiophenoxide, inasmuch as each point in those plots involve reactions of two different substrates with the same nucleophile (Figs. 25-28, 30). Any change in nucleophilicity will be cancelled out. For the same reason, any difference in the degree of ion-pair aggregation of the nucleophiles in methanol cannot be responsible for the observed deviations.

(3) Charge-transfer complex stabilization of the transition state for the reactions of m-nitro and 3,5-dinitrothiophenoxide with substituted benzyl chlorides: Mulliken considered the idea of transferring an electron pair from the donor to the acceptor¹⁵⁰ which involves the interaction of a non-bonded ground state $\psi(D, A)$ and a polar excited state $\psi(D^+ - A^-)$ to produce a stabilized ground state having a wave function

$$\psi_0 = \psi(D, A) + \lambda \psi(D^+ - A^-).$$

In the excited state, the charge-transfer state,

$$\psi_1 = \psi(D^+ - A^-) + \mu \psi(D, A)$$

and μ in most cases is small compared with unity. The energy of the electronic transition $(D, A) \rightarrow (D^+ - A^-)$ is given to a first approximation by the expression

$$I_D - E_A + C$$

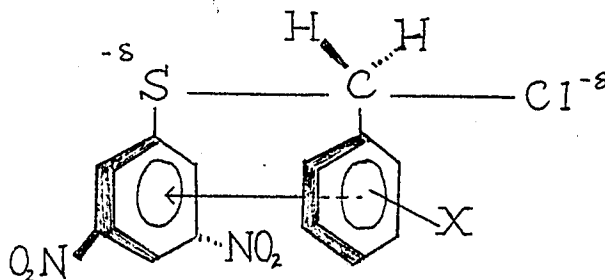
where I_D is the ionization potential of the donor, E_A the electron affinity of the acceptor and C is the mutual electrostatic energy of D^+ and A^- relative to that of D and A .

The field of organic molecular complexes of donor-acceptor type has been a very active one during the past decade^{150, 151}. Photometric absorption and n.m.r. techniques have been applied successfully to measure the association of the complex^{152, 153, 154} (and references cited therein). However, relatively little attention has been given to the effects of charge transfer complex formation in reaction kinetics.

The formation of a complex in the rate-determining step was found in the nitration of aromatic hydrocarbon and in the Friedel-Crafts alkylation of toluene with benzyl chloride and aluminum chloride^{155, 156}. The molecular complex of allyl chloride and HBr was suggested to initiate the radical chain reaction of photolytic hydrobromination¹⁵⁷. Evidence has also been reported that the reactivity of a compound can be modified through charge-transfer complexing^{158, 159, 160}. Rates of acetolysis of 2, 4, 7-trinitro-9-fluorenyl p-toluenesulfonate are increased by addition of an aromatic donor.

Swain and Taylor¹⁶¹ reported that the rate constant for sodium phenoxide with benzyldimethylsulfonium p-toluenesulfonate is faster than the corresponding reaction with the stronger base sodium hydroxide. It was attributed to the ancillary molecular bonding of the π -complex or charge transfer type in the transition state. With trimethylsulfonium perchlorate, a case in which π -complexing is impossible, hydroxide is more reactive than phenoxide.

The significant rate enhancement in the case of m-nitro and 3, 5-dinitrothiophenoxide with the methyl substituted benzyl chlorides may be explained by assuming that there is a charge transfer interaction between the electron-deficient ring of the nucleophile due to the presence of the strong electron-withdrawing nitro group and the electron rich methyl substituted benzene ring of benzyl chloride at the transition state, as shown in the following hypothetical transition state:



The following evidence is consistent with charge-transfer complex stabilization of the transition state for reactions of *m*-nitro and 3,5-dinitrothiophenoxide with substituted benzyl chlorides:

(1) Substituent effect: According to Charton^{162,163} the effect of the substituent in donors on the equilibrium constant of charge-transfer complex can be correlated by the Hammett equation:

$$Q_X = \alpha \sigma_I + \beta \sigma_R + Q_H$$

where Q_X and Q_H are the logarithm of the equilibrium constant for substituted and unsubstituted compounds respectively, σ_I and σ_R are substituent constants, and α and β are constants for the system.

The trend of the deviations (or the deviation relative to their expected nucleophilicity) for the reactions of *m*-nitro and 3,5-dinitrothiophenoxide depends upon the donor strength of the substituted benzyl chlorides. The order of the deviation estimated from Figs. 25-28 by the vertical length of the line appeared to be 2,6-dimethyl > *o*-methyl > H > *m*-nitro. This order is consistent with the predicted behaviour for a substituent in the substrate.

(2) If the degree of π -complex stabilization at the transition state is governed by the donor, this favorable effect for the rate of the two meta nitro substituted thiophenoxides should be similar for both *o*-methyl and *p*-methylbenzyl chloride. The polar effects in ortho and para positions are often considered to be similar when not complicated with steric and hydrogen bond effects, etc. Further, we have shown this to be the case for these two substrates by our determination of the ρ_N values (see Table 16).

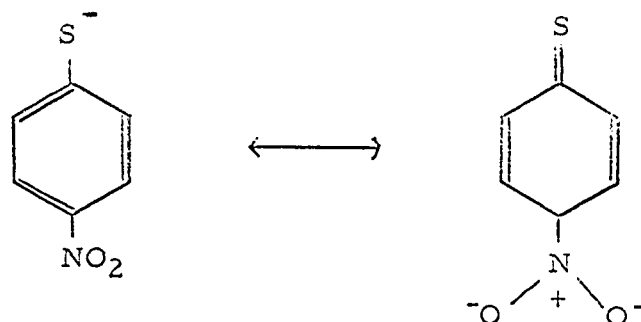
It is very interesting to observe that there is little if any deviation for the nucleophiles of *m*-NO₂ and 3,5-(NO)₂-thiophenoxide in the plot of log *k* of *o*-CH₃ vs. log *k* of *p*-CH₃ benzyl chloride (Fig. 30, p. 166), even though the individual rate for the *o*-methyl isomer is almost three times as fast as in the case of the *p*-methyl isomer.

(3) *m*-Nitrobenzyl chloride should be a weaker donor than benzyl chloride. The π -complex stabilization at the transition state should be more favorable for the latter than for the former. From Fig. 28 (the plot of log *k* for *m*-nitrobenzyl chloride vs. log *k* for benzyl chloride), the negative deviation for 3,5'-dinitrothiophenoxide is as expected. Since the point for *m*-nitrothiophenoxide is on the line in Fig. 28, it seems that *m*-NO₂-thiophenoxide is not an acceptor when it reacts with benzyl chloride or *m*-nitrobenzyl chloride, which are both relatively weak donors.

The change of the reactivity of 3,5-dinitrothiophenoxide with the change of the substrate (substituted benzyl chloride) becomes very obvious if one compares its rate constant with the corresponding rate constant for unsubstituted thiophenoxide. When m-nitrobenzyl chloride is used as a substrate, the reaction for 3,5-dinitrothiophenoxide is about seven times as slow as the thiophenoxide, but if the 2,6-dimethylbenzyl chloride is used as a substrate, the rates for both nucleophiles are almost the same.

It is therefore proposed that the anomalous behaviour exhibited by 3-nitro and 3,5-dinitrothiophenoxide can be explained by a charge-transfer complex stabilization of the transition state. An attempt was made to detect charge-transfer complex formation between 3,5-dinitrothiophenol and 2,6-dimethylbenzyl chloride by spectral means. No charge transfer band was found from 640 m μ to 220 m μ . To prevent reaction complications, the 3,5-dinitrothiophenol was used rather than its anion. It is probable that there is no charge-transfer interaction for the ground state reagents of 3,5-dinitrothiophenoxide and 2,6-dimethylbenzyl chloride, but as the reaction proceeds along the reaction coordinate, the two molecules are brought close enough to allow charge-transfer interaction in the transition state, as shown in Structure I on page 180.

The puzzling question remained as to why there is no charge-transfer stabilization for p-NO₂-thiophenoxide while there is for m-NO₂-thiophenoxide. It may be suggested (although it is not convincing) that the aromatic π -electrons in p-NO₂-thiophenoxide are not as electron-deficient as that of m-NO₂-thiophenoxide, owing to its ability to form the resonance structure



(4) Thermodynamic criteria: The rate constants for reactions of *o*-methylbenzyl chloride, 2,6-dimethylbenzyl chloride and benzyl chloride with *p*-methyl, H, *p*-nitro and 3,5-dinitrothiophenoxides measured at 25°C, 16°C and 6.8°C are shown in Tables 19, 20, 21. These thermodynamic parameters were obtained from the plots of log *k* vs. 1/*T* as given in Figs. 32-37. The Arrhenius activation energies were calculated from the slopes of these plots and the thermodynamic parameters are shown in Table 22. It is to be noted that the standard deviations of the plots are in most cases about 1%, which means that the probable errors in the activation energies are about 0.2 kcal. per mole. The activation enthalpies decrease as the 3,5-dinitro substituents are introduced into thiophenol. In order to examine the rate enhancement for 3,5-dinitrothiophenoxide, its activation enthalpy and entropy were compared with those of the nucleophiles which do not show the deviation formerly discussed. It appears that ΔS^\ddagger for 3,5-dinitrothiophenoxide is relatively more negative and ΔH^\ddagger is smaller than for the rest of the thiophenoxides. The rate decrease for the 3,5-dinitro compound is due to the decrease in ΔH^\ddagger , while the more negative entropy indicates a relatively more rigid transition state. It seems that charge-transfer interaction as shown in Structure I will stabilize the transition state and enhance the rate.

FIGURE 32

Logarithms of k for the reactions of benzyl chloride
with substituted thiophenoxides plotted against $1/T$.

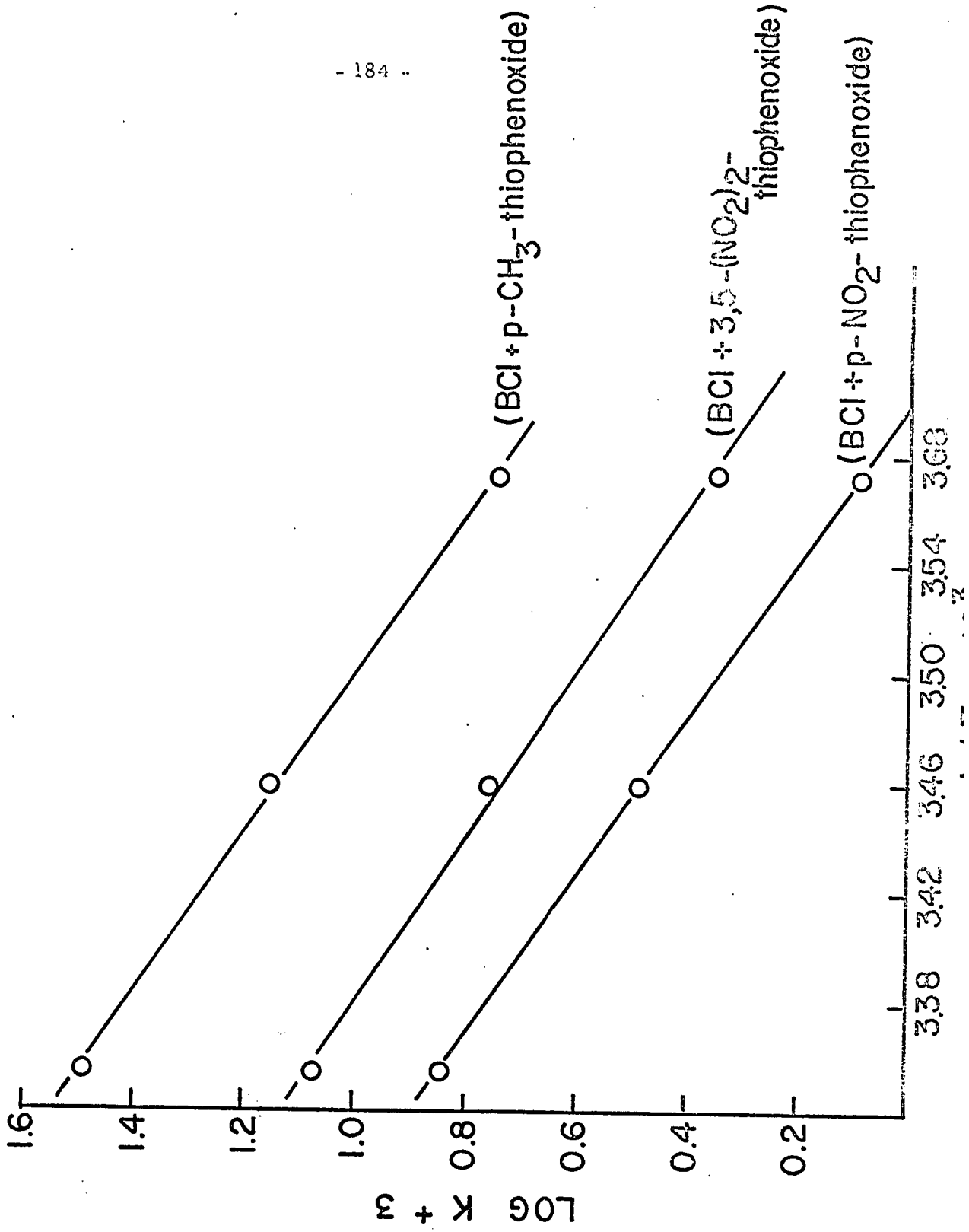


FIGURE 33

Logarithms of k for the reaction of benzyl chloride with thiophenoxide plotted against $1/T$. (The rate constant of the first point * is taken from Ref. 90)

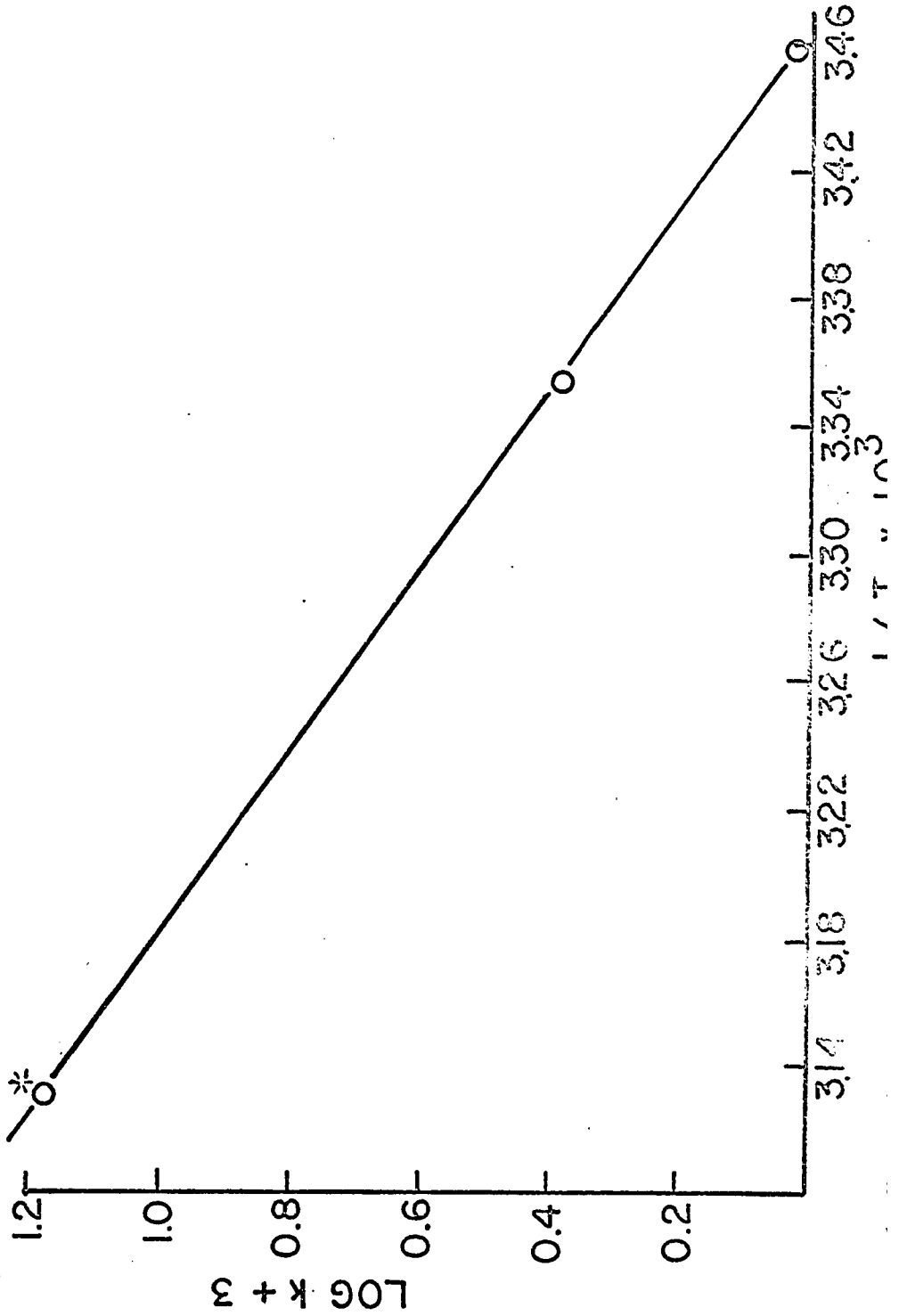


FIGURE 34

Logarithms of k for the reactions of o -CH₃-benzyl chloride with substituted thiophenoxides plotted against $1/T$.

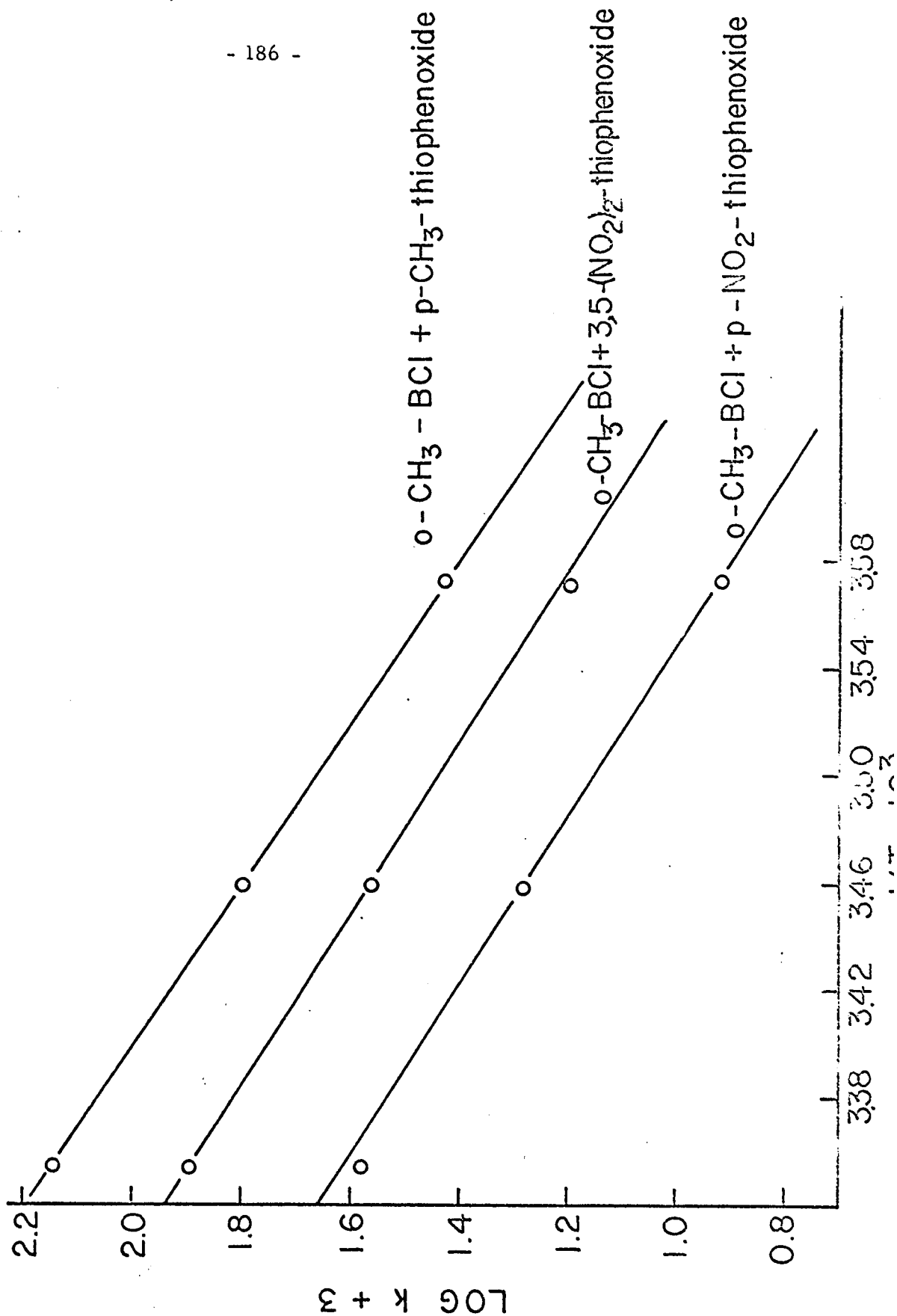


FIGURE 35

Logarithms of k for the reactions of o -CH₃-benzyl chloride with thiophenoxide against $1/T$. (The rate constant for the last point* is taken from Ref. 90).

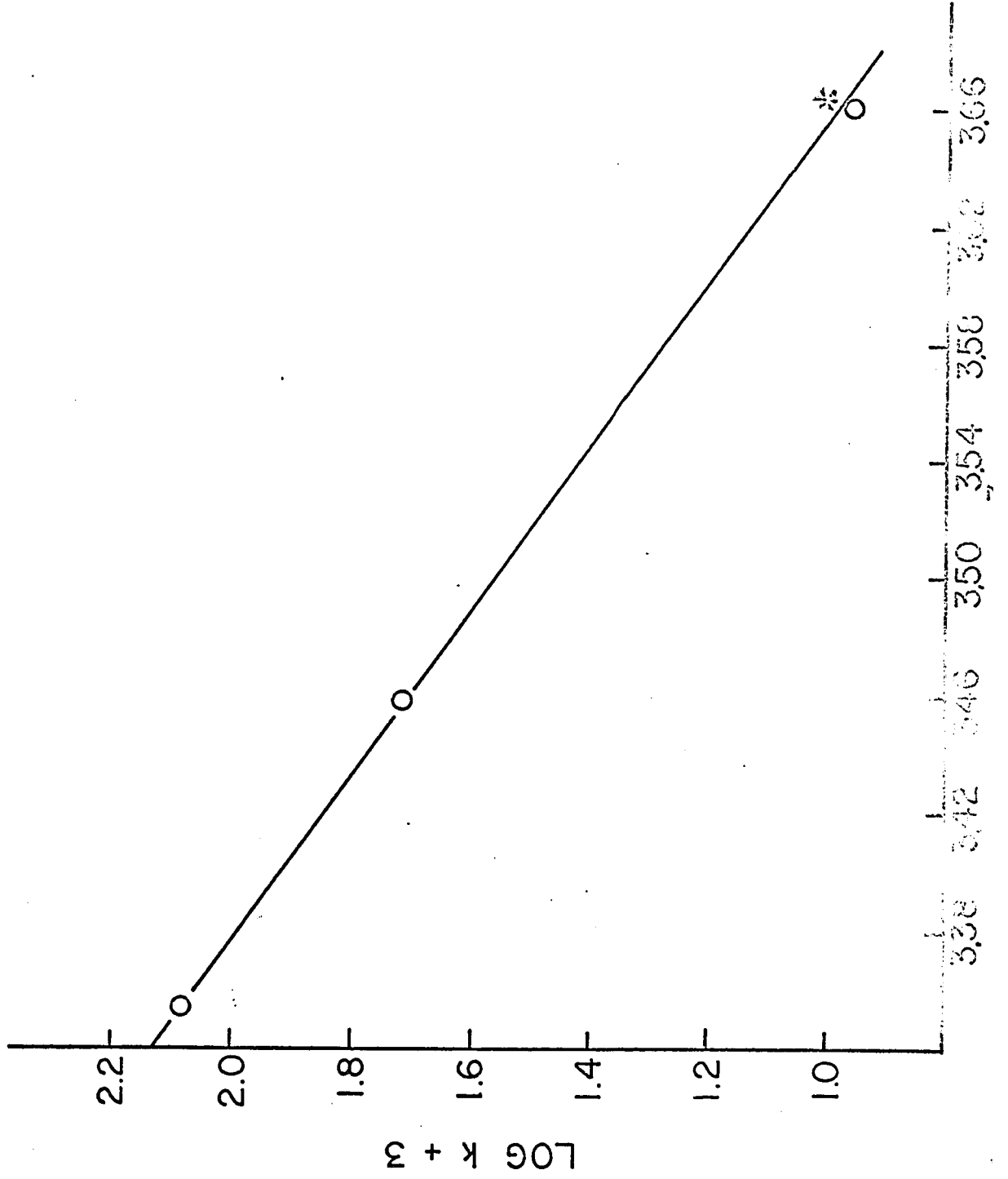


FIGURE 36

Logarithms of k for the reactions of 2,6-(CH₃)₂-benzyl chloride with substituted thiophenoxides against $1/T$.

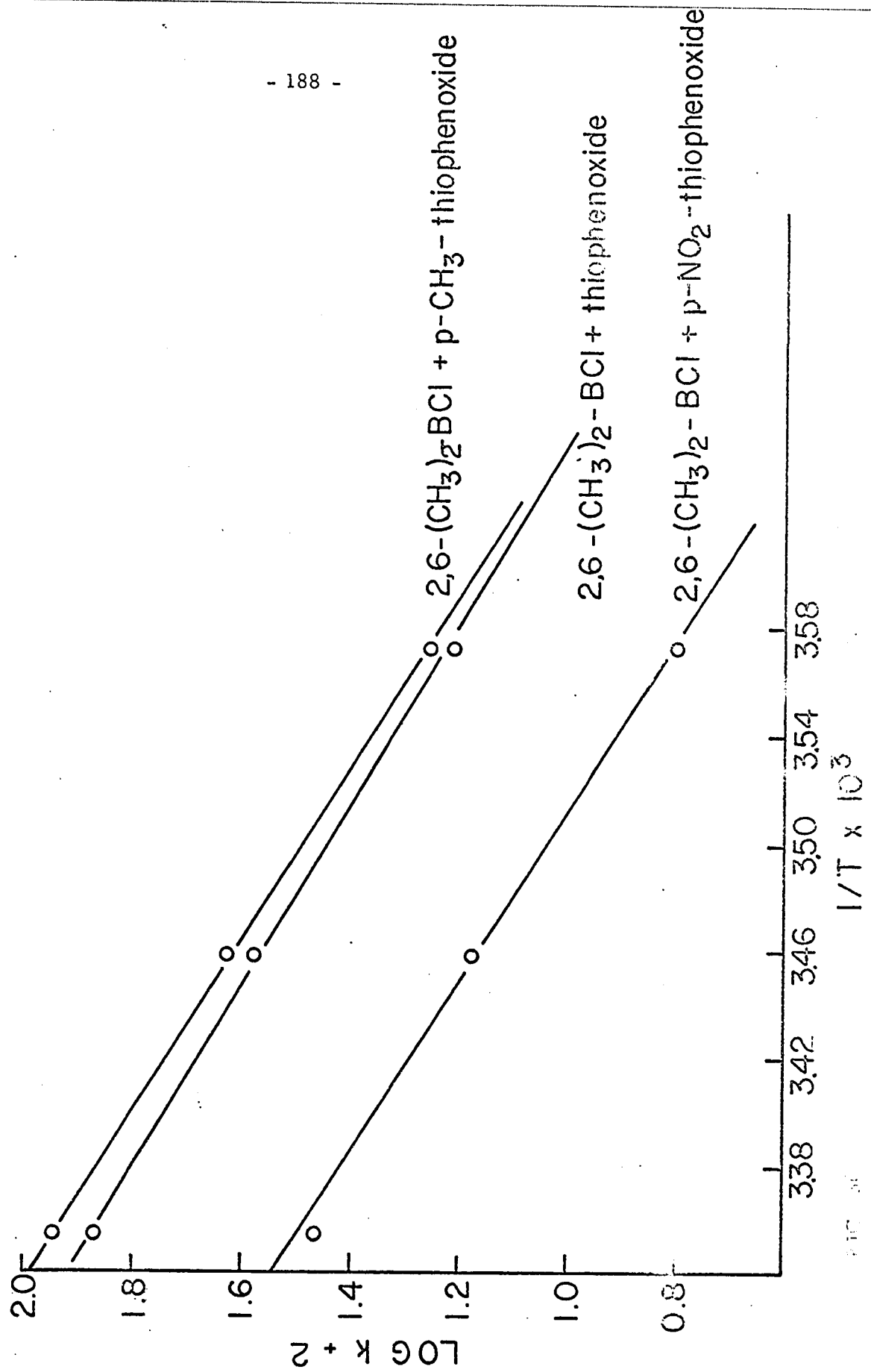


FIG. 36

FIGURE 37

Logarithms of k for the reaction of 2,6-(CH₃)₂-
benzyl chloride with 3,5-dinitrothiophenoxide
against 1/T.

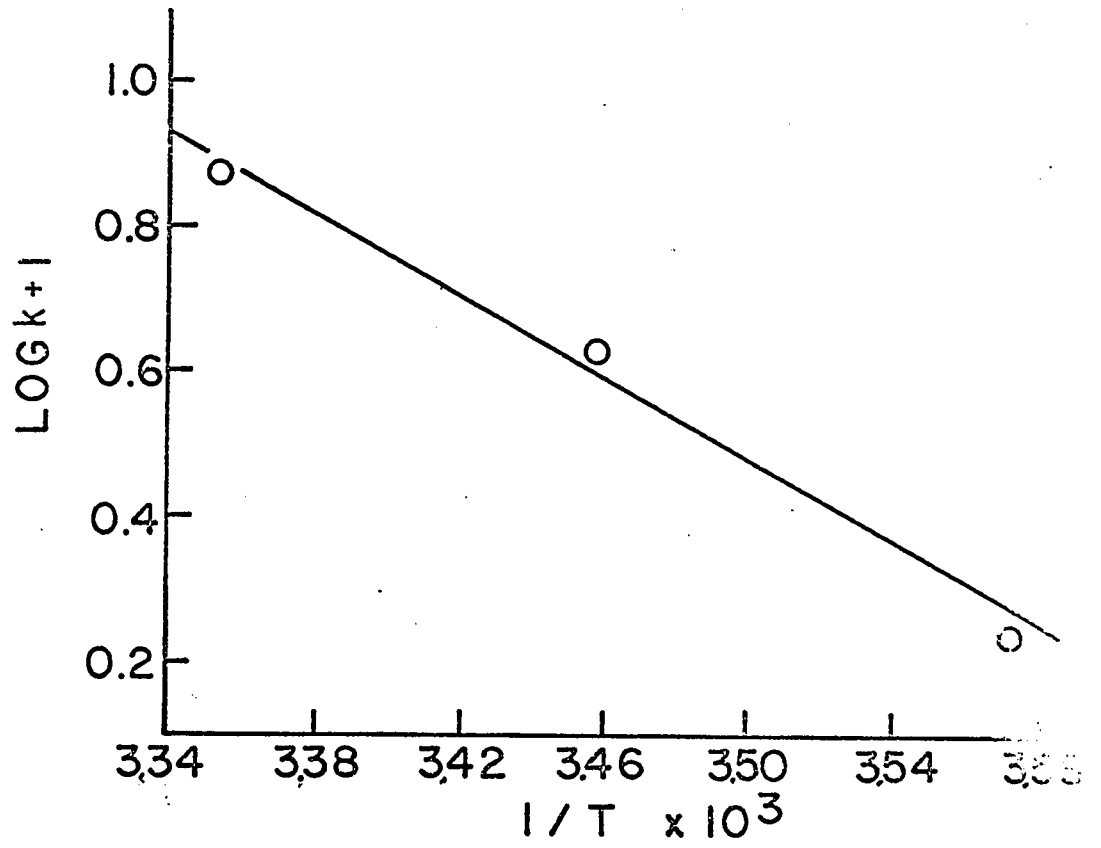


FIG. 37

TABLE 19

Reactions of Benzyl Chloride with Substituted Thiophenoxide at Various Temperatures in CH₃OH

| Nucleophiles | Temperature °C | k ₂ (l mole ⁻¹ sec ⁻¹) |
|-------------------------------------|----------------|--|
| P-CH ₃ | 16 | 1.41 x 10 ⁻² |
| H | 16 | 1.05 x 10 ⁻² |
| P-NO ₂ | 16 | 3.03 x 10 ⁻³ |
| 3,5-(NO ₂) ₂ | 16 | 5.72 x 10 ⁻³ |
| P-CH ₃ | 6.8 | 7.56 x 10 ⁻³ |
| P-NO ₂ | 6.8 | 1.23 x 10 ⁻³ |
| 3,5-(NO ₂) ₂ | 6.8 | 2.20 x 10 ⁻³ |
| P-CH ₃ | 25 | 3.04 x 10 ⁻² |
| H | 25 | 2.42 x 10 ⁻² |
| P-NO ₂ | 25 | 7.02 x 10 ⁻³ |
| 3,5-(NO ₂) ₂ | 25 | 1.17 x 10 ⁻² |

TABLE 20
Reactions of o-Methyl Benzyl Chloride with Substituted Thiophenoxide at Various Temperatures in CH₃OH

| Nucleophiles | Temperature °C | k ₂ (l mole ⁻¹ sec ⁻¹) |
|-------------------------------------|-------------------|--|
| P-CH ₃ | 16 | 6.24 × 10 ⁻² |
| H | 16 | 5.17 × 10 ⁻² |
| P-NO ₂ | 16 | 1.92 × 10 ⁻² |
| 3,5-(NO ₂) ₂ | 16 | 3.70 × 10 ⁻² |
| P-CH ₃ | 6.8 | 2.64 × 10 ⁻² |
| P-NO ₂ | 6.8 | 8.10 × 10 ⁻³ |
| 3,5-(NO ₂) ₂ | 6.8 | 1.58 × 10 ⁻² |
| P-CH ₂ | 25 | 1.39 × 10 ⁻¹ |
| H | 25 | 1.21 × 10 ⁻¹ |
| P-NO ₂ | 25 | 3.81 × 10 ⁻² |
| 3,5-(NO ₂) ₂ | 25 | 7.93 × 10 ⁻² |

TABLE 21

Reactions of 2,6-(CH₃)₂-Benzyl Chloride with Substituted Thiophenoxides at Various Temperatures in CH₃OH

| Nucleophiles | Temperature °C | k ₂ (l mole ⁻¹ sec ⁻¹) |
|-------------------------------------|-------------------|--|
| P-CH ₃ | 16 | 4.20 × 10 ⁻¹ |
| H | 16 | 3.83 × 10 ⁻¹ |
| P-NO ₂ | 16 | 1.51 × 10 ⁻¹ |
| 3,5-(NO ₂) ₂ | 16 | 4.25 × 10 ⁻¹ |
| P-CH ₃ | 6.8 | 1.81 × 10 ⁻¹ |
| H | 6.8 | 1.63 × 10 ⁻¹ |
| P-NO ₂ | 6.8 | 6.21 × 10 ⁻² |
| 3,5-(NO ₂) ₂ | 6.8 | 1.71 × 10 ⁻¹ |
| P-CH ₃ | 25 | 8.71 × 10 ⁻¹ |
| H | 25 | 7.42 × 10 ⁻¹ |
| P-NO ₂ | 25 | 2.90 × 10 ⁻¹ |
| 3,5-(NO ₂) ₂ | 25 | 7.48 × 10 ⁻¹ |

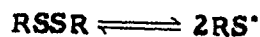
TABLE 22

Thermodynamic Parameters for Reactions of Substituted Benzyl Chloride with Substituted Thiophenoxide in Methanol at 25°C

| Nucleophile | Substrate | Slope $\times 10^3$ | Standard deviation of plots | ΔE^\ddagger (kcal /mole) | ΔH^\ddagger kcal /mole) | ΔS^\ddagger (cal/deg) |
|-------------------------------------|-------------------------------------|------------------------|-----------------------------------|-------------------------------------|------------------------------------|----------------------------------|
| P-CH ₃ | H | 3.62 | 3.8×10^{-2} | 16.6 | 16.0 | -11.9 |
| H | H | 3.67 | 2.6×10^{-2} | 16.8 | 16.2 | -11.6 |
| P-NO ₂ | H | 3.66 | 3.0×10^{-2} | 16.8 | 16.2 | -14.1 |
| 3,5-(NO ₂) ₂ | H | 3.55 | 4.5×10^{-2} | 16.3 | 15.7 | -14.7 |
| P-CH ₃ | o-CH ₃ | 3.56 | 3.7×10^{-2} | 16.3 | 15.7 | -9.8 |
| H | o-CH ₃ | 3.54 | 2.3×10^{-2} | 16.2 | 15.6 | -10.3 |
| P-NO ₂ | o-CH ₃ | 3.35 | 3.6×10^{-2} | 15.3 | 14.7 | -15.4 |
| 3,5-(NO ₂) ₂ | o-CH ₃ | 3.57 | 2.3×10^{-2} | 15.4 | 14.8 | -13.8 |
| P-CH ₃ | 2,6-(CH ₃) ₂ | 3.37 | 3.7×10^{-2} | 15.4 | 14.8 | -9.1 |
| H | 2,6-(CH ₃) ₂ | 3.24 | 4×10^{-2} | 14.8 | 14.2 | -11.4 |
| P-NO ₂ | 2,6-(CH ₃) ₂ | 3.31 | 4.4×10^{-2} | 15.2 | 14.6 | -12.1 |
| 3,5-(NO ₂) ₂ | 2,6-(CH ₃) ₂ | 3.16 | 5.8×10^{-2} | 14.4 | 13.8 | -12.6 |

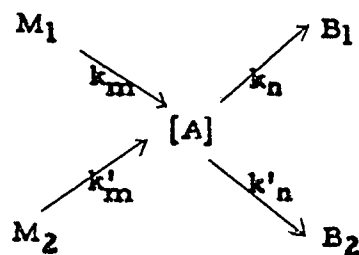
V. UNIMOLECULAR DECOMPOSITION OF DIARYLDISULFIDES BY MASS SPECTROMETRY

Much attention has been given to the scission of the sulfur-sulfur bond^{164, 165}. Light-induced homolysis of the S-S bond of disulfides has been reported in several cases^{165, 166, 167};



However, the structural effects on the homolysis of the S-S bond have not yet been investigated. Eight symmetrical bis-(substituted-phenyl)-disulfides were prepared from the oxidation of the corresponding substituted thiophenols.

Applications of the kinetic approach to mass spectra have recently been made by McLafferty^{168, 169}. A kinetic argument can be made to provide a basis for the applicability of free-energy relationships to ion abundances in mass spectra. If the formation of the fragment A has many sources and decomposes to another fragment;



the rate of the change in the concentration of A in the ion source is given by the equation:

$$\frac{d[A]}{dt} = \sum k_m[M_m] - \sum k_n[A] - \sum k_{inst}[A] = 0 \quad [A] = \frac{\sum k_m[M_m]}{\sum k_n + \sum k_{inst}} \quad (R-14)$$

where k_m is the rate constant for the formation of A; k_n is the decomposition of A, and k_{inst} represents the apparent loss of A because of an instrument parameter. If z is the concentration of the A fragment relative to the molecular ion,

$$z = (A)/(M) \quad (R-15)$$

Combining equations (R-14) and (R-15), one obtains

$$z/z_0 = \frac{[A]/[M]}{[A_0]/[M_0]} = \frac{k_1}{k_2} \frac{k_n^0 + \sum k_{inst}^0}{k_n + \sum k_{inst}} \quad (R-16)$$

where $(A)/(M)$ and $(A_0)/(M_0)$ are the ratios for substituted and unsubstituted diphenyl disulfide respectively; it was assumed that the formation of A has only one source. If the further degradation of A is small (this can be accomplished by using low electron energy), equation (R-16) is reduced to

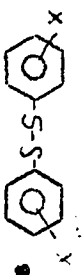
$$z/z_0 = k_1/k_0 \quad (R-17)$$

The free-energy relationship in ion intensities has been applied successfully in the form of the Hammett equation¹⁶⁸⁻¹⁷².

The mass spectra of disulfides have been reported by Williams and co-workers¹⁷³ whose attention was focused on skeletal rearrangements of the disulfides. Our attempt was to study the substituent effect on the degradation of the molecular ion $[RSSR]^+$, to the fragment ion RS^+ . The relative abundance of the molecular ion and fragment ions are given in Table 23.

TABLE 23

Mass Spectrometry of Disulfide (RSSR)⁺ → RS⁺ + RS[•]

| Disulfides |  | I _{RSSR⁺} | I _{RS⁺} | $z = \frac{I_{RS^+}}{I_{RSSR^+}}$ |
|-------------------|---|-------------------------------|-----------------------------|-----------------------------------|
| H | | 33.5 | 45.9 | 1.37 |
| m-NO ₂ | | 58.1 | 16.3 | 0.28 |
| p-NO ₂ | | 72.7 | 8.7 | 0.119 |
| m-CH ₃ | | 25.3 | 35.8 | 1.4 |
| p-Br | | 60 | 58 | 0.966 |

$$z = [\text{RS}]^+ / [\text{RSSR}]^{\cdot+}$$

A plot of $\log z$ vs. σ is shown in Fig. 38; five disulfides are on the line. The deviation for $p\text{-CH}_3$ and $p\text{-OCH}_3$ substituted diphenyl disulfide are off the scale used in graphing. From Fig. 38 it will be seen that the intensity of RS^+ will be zero when the substituent constant is greater than 1.05. There is no fragment peak of RS^+ for bis-(3,5-dinitrophenyl)disulfide as expected. It is interesting to note that the reaction constant ($\rho = -1.28$).

After electron bombardment, the disulfide gives a molecular radical ion. Following the homolytic cleavage of the S-S bond of the molecular ion, an odd electron radical and an even electron ion are formed:

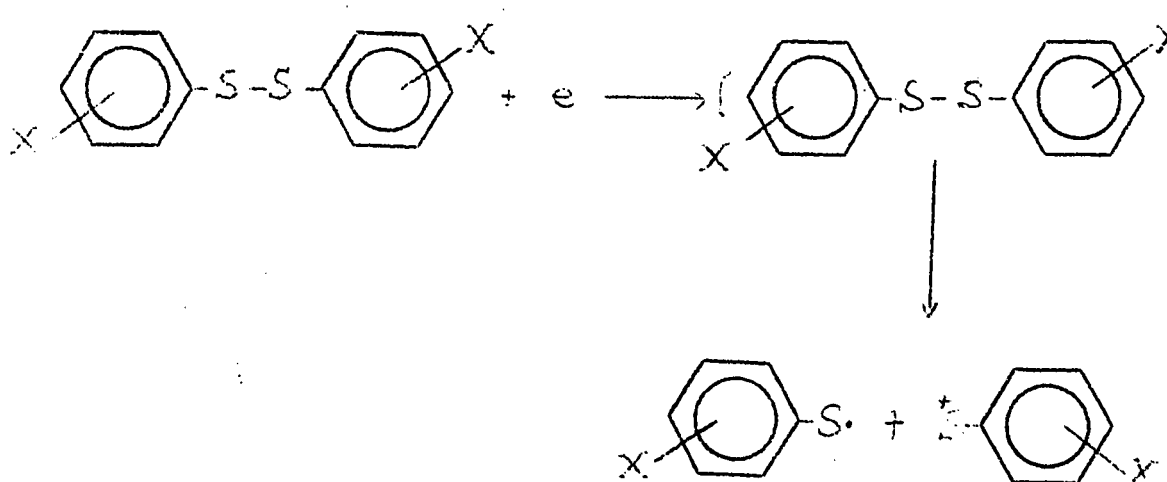


FIGURE 38

Logarithms of the ratios of fragment ion (RS^+) and
molecular ion ($RSSR^+$) plotted against substituent
constants

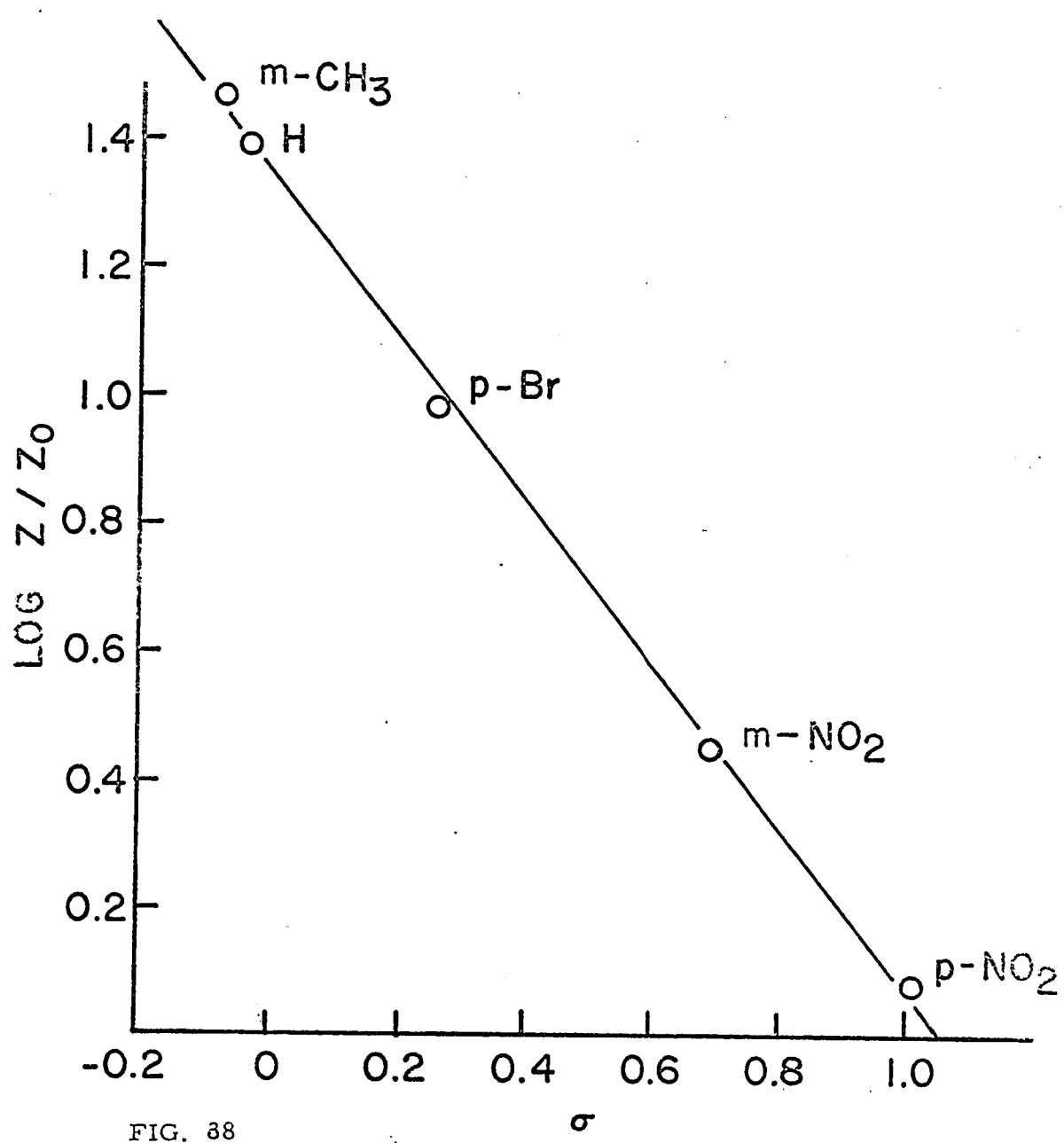


FIG. 38

Generally, the even-electron fragment¹⁷⁴, whether ion or neutral, has a much greater stability and therefore a greater influence on the course of degradation. The large negative reaction constant in this case implies that electron-donating substituents will enhance the rate of the S-S bond cleavage and this rate enhancement is due to the increase in the stability of the even electron fragment ion RS^+ , which will decidedly affect the rate, to give a subsequent increase in the abundance of the fragment peak. Product ion stability is an important driving force in ion decomposition reactions^{169, 174}.

The present results indicate that the m-nitro substituent obeys the linear substituent effects (Fig. 38). From the previous ground-state structure correlations of the nucleophiles (substituted thiophenols) there are linear relationships between the acidity constants of the thiols and their substituent constants. The chemical shifts (δ_{S-H}) of nine substituted thiophenols are linearly related to the corresponding pK_a values of the thiols. This implies that the high reactivities of m-nitro and 3,5-dinitrothiophenoxide towards benzyl chlorides (as discussed in Section IV), is not due to the ground state structures of m-nitro and 3,5-dinitrothiophenoxide. The charge-transfer complex stabilization in the transition state of substituted benzyl chlorides with m-nitro or 3,5-dinitrothiophenoxide has been discussed in Section IV.

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