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# Effect of dimethyl sulfoxide on aliphatic nucleophilic reactions and determination of organic halides in dimethyl sulfoxide

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NUCLEOPHILIC REACTIONS AND DETERMINATION  
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EFFECT OF DIMETHYL SULFOXIDE ON ALIPHATIC  
NUCLEOPHILIC REACTIONS AND DETERMINATION  
OF ORGANIC HALIDES IN DIMETHYL SULFOXIDE

by

Joe Allen Vinson

A Dissertation Submitted to the  
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1967

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**PART I. EFFECT OF DIMETHYL SULFOXIDE  
ON NUCLEOPHILIC REACTIONS**

## INTRODUCTION

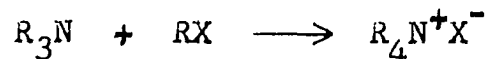
The effect of solvent on the rate of reaction of amines with alkyl halides has been extensively studied since 1890, when Menshutkin first investigated the reaction. Many theories have been advanced to explain the effect of solvent, incorporating such factors as polarity, polarizability and dielectric constant.

A recent development is the introduction of dipolar aprotic solvents such as dimethyl sulfoxide (DMSO). The mechanism of their large rate enhancing effect has been the subject of much debate. It is the purpose of this work to investigate the effect of DMSO on the rate of reaction of some aliphatic nucleophilic reactions, mainly that of amines with alkyl halides.

The interaction of DMSO with the nucleophile and substrate are investigated using the technique of nuclear magnetic resonance (NMR). Rate studies in mixtures of DMSO and hydroxylic solvents such as methanol and water should show any interaction between DMSO and these solvents. The pK values of some amines are determined in order to find a correlation between nucleophilicity and basicity. The effect of the nucleophile, leaving group and added salts are also investigated. Lastly, activation parameters are determined in order to elucidate the nature of the transition state.

## HISTORICAL

Menshutkin (1) was the first to study the solvent effect for the reaction of tertiary amines and alkyl halides:



He measured the velocity of the reaction between triethyl amine and ethyl iodide in twenty different solvents and found the velocity varied nearly a thousand fold. The order was roughly alcohols > ketones > esters > ethers > hydrocarbons.

A comparison of rates shows that for most functional groups, the use of an aromatic solvent leads to higher rates than does the use of the corresponding aliphatic derivative of similar dielectric constant. This effect is probably due to the ability of aromatic molecules to stabilize the charge separation in the transition state because of the high capacity for polarizability of the  $\pi$ -electrons. Reinheimer (2) was able to correlate the logarithm of the rates with the polarizability of the aromatic solvents iodobenzene, bromobenzene, chlorobenzene and benzene. The correlation held for different tertiary amines and different alkyl halides.

From a crude application of electrostatic theory, the free energy of activation would be expected to be inversely proportional to the dielectric constant of the medium. A plot of relative rates against the reciprocal of the di-

electric constant (3) shows a trend toward higher rates in solvents of higher dielectric constant, but the proportionality is far from exact. Kirkwood (4) has suggested the use of the following equation:

$$\ln k_2 = \ln k_0 - \frac{1}{kT} \left[ \frac{(D-1)}{(2D+1)} \left\{ \frac{\mu_A^2}{r_A^3} + \frac{\mu_B^2}{r_B^3} + \frac{\mu_{\ddagger}^2}{r_{\ddagger}^3} \right\} \right] + \frac{\sum \Phi}{kT}$$

where D is the macroscopic dielectric constant;  $k_2$  is the rate constant in the solvent;  $k_0$  is the rate constant at  $D = 1$ ;  $\mu_A$ ,  $\mu_B$ , and  $\mu_{\ddagger}$  are the dipole moments of the reagents A and B and the transition state respectively;  $r_A$ ,  $r_B$ , and  $r_{\ddagger}$  are the corresponding radii; and  $\sum \Phi$  is the contribution of all non-electrostatic forces. If the non-electrostatic term  $\sum \Phi/kT$  is small enough to be neglected, and if  $\mu_{\ddagger}^2/r_{\ddagger}^3$  is independent of the medium, the plot of  $\log k$  against  $(D-1)/(2D+1)$  should be a straight line for the same reaction carried out in different solvents. While the logarithms of the rates of some Menshutkin reactions (4) and (5), show a linear dependence on the above quantity, those in nitrobenzene-benzene mixtures give definitely curved plots, the rates being faster than theory predicts.

Laidler and Eyring (6) explained the deviation in terms of non-electrostatic contributions. The microscopic dielectric constant may differ from the measured value due to the preferential solvation or interaction of reactant or activated complex with one solvent of the mixture. Even in pure benzene, the solvent must effect some type of stabilization of



the complex, since the Menshutkin reaction will not take place in the gas phase. Stearn and Eyring (7) have shown that the activated complex in quaternary salt formations, while not completely ionic, has a large dipole moment and approaches the structure of the product salt. In benzene-nitrobenzene, the complex is selectively solvated by the highly polar component nitrobenzene. This results in a low activity coefficient for the activated complex. From transition state theory, the rate equation is as follows:

$$\text{rate} = K k^\ddagger \frac{f_A f_B}{f_{AB}^\ddagger}$$

Thus a low activity for the complex results in a high velocity of reaction.

Two other workers have also suggested that the Kirkwood equation does not have universal applicability. Watanabe and Fuoss (8) have investigated the reaction of butyl bromide with pyridine and 4-picoline in five solvents of high dielectric constant. The variable  $(D-1)/(D+1)$  which determines the magnitude of the solvent effect is found to be insensitive to  $D$  when  $D$  is large. When  $D$  is between 1 and 30, the above term increases from 0 to 0.476; further increase in  $D$  beyond 30 to infinity only causes the variable to increase to 0.50. Hence all solvents with dielectric constants greater than 30 would be expected to give the same rate. Judging from the effect of solvent on quaternization rates, the capacity to stabilize the developing charges in the transition state is a rather specific chemical property of the solvent,

and one that is at best only partially coincident with the dielectric constant.

The rate of reaction of pyridine with methyl bromide in benzene is enhanced by the addition of hydrogen bonding agents such as methanol, phenol and p-nitrophenol, the rate enhancement increasing with the acidity of the hydroxylic addend (9). The effect is not due to an increase in dielectric constant. The observed increase in polarity would only increase the rate by approximately 1%, while it is actually increased 10-100% depending on the addend. More recently it has been shown that nitrobenzene, which is neither a hydrogen bond donor or acceptor, increases the rate almost as much as methanol (10). These catalytic effects appear to be due to the stabilization of the incipient charges in the transition state by the polar addend.

In the reaction of amines with alkyl halides, the developing anion and cation require different solvating characteristics. Electrophilic solvents (water and alcohols) make good solvents for anions, while nucleophilic solvents (amines, ethers, alcohols and water) make good solvents for cations. Water and alcohols which combine both requirements, can effectively solvate both the anionic and cationic part of a dipole. The problem is further complicated by the fact that the very property which makes electrophilic substances capable of solvating anions, makes them also capable of solvating nucleophilic reagents and in particular, amines. Such

solvation, via hydrogen bonding of the solvent to the amine, would reduce both the nucleophilicity and the base strength of a given amine. Pearson and Vogelsong (11) have shown that by changing the solvent, either primary, secondary, or tertiary amine can be made the strongest base. There is, therefore, no reason why similar, though not necessary parallel effects should be observed with respect to the nucleophilicity of amines.

Hall (12) suggests that the amine basicity sequence in water, primary > secondary > tertiary reflects greater solvation requirements of charged (protonated) amine over those of the uncharged (free) amine. From a pure inductive argument, the order above should be reversed. Substitution of alkyl groups for protons in amines should result in a progressive increase in the steric hindrance to solvation and a decrease in basicity as one goes from a primary to a tertiary amine. Solvation of the ammonium ion by hydrogen bonding to an oxygen of the solvent stabilizes the ion in that solvent and thus increases the base strength of the parent amine. This latter effect accounts for the different order of basicity in solvents such as chloroform which has no basic oxygen atoms. Condon (13) has been able to correlate the basicity of all types of aliphatic amines, excluding very hindered ones, by an equation involving the Taft substituent constant and the number of hydrogens attached to the ammonium ion and parent amine.

Henderson (14) proposed that the nucleophilicity of amines should have the same order as the basicities. Rates for different amines with alkyl halides in acetone at 35° completely support this hypothesis. Hall (15) found no correlation between Taft constants and rate for several nucleophilic amine reactions, including the Menshutkin reaction. He did find fair correlation with the Swain-Scott equation (16) for the rates of selected amines with alkyl bromides in benzene. However, no good correlations were found in hydroxylic solvents.

Since the review article by Parker (17), much work has been done using dipolar aprotic solvents such as dimethyl sulfoxide and dimethylformamide for anionic  $S_N2$  reactions. Parker cites the reduced solvation of anions in dipolar aprotic solvents compared to protic solvents, as being responsible for the rate increase seen in anionic reactions. Dipole-dipole reactions such as the ones in this study are much less susceptible to changes in solvent structure, provided that the dielectric constants do not change appreciably. These observations confirm that the differential solvation of anions in the initial state, rather than in the transition state, is the major factor influencing the kinetic behavior.

Tommila and co-worker (18) have reacted triethylamine and ethyl iodide in DMSO-benzene mixtures and found a rate increase of 157 in going from pure benzene to pure DMSO. No linear correlation was found between the rate and the dielectric constant of the medium. The authors concluded that the

solvation of the transition state by DMSO caused the rate enhancement.

The rate of reaction of butyl iodide and chloride with pyridine has been studied by Parker (19). He ran the reactions at 0° in DMF and a methanol-water mixture of the same dielectric constant. The rate of reaction with butyl chloride is faster in methanol-water than in DMF but the reverse is true for butyl iodide. This is attributed to transition state solvation of the partial negative charge by hydrogen bonding with the methanol. Such stabilization is greater for less polarizable transition states such as C---Cl than for C---I. Dimethylformamide is assumed to solvate the transition state much less than methanol in these reactions.

## RESULTS AND DISCUSSION

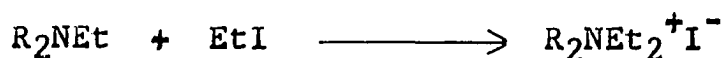
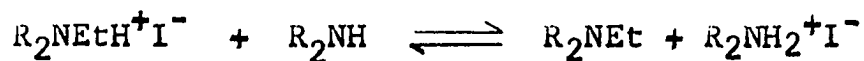
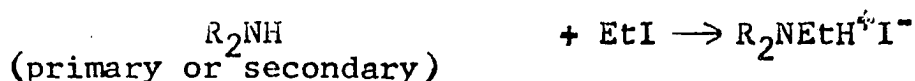
The order of reactants was checked by variation of their concentration and the effect on the second order rate constant. The results are shown in Table 1.

Table 1. Order of reactants in the reaction of di n-butyl amine and ethyl iodide in DMSO at 30.4°

Concentration amine x 10 <sup>2</sup> M	Concentration alkyl halide x 10 <sup>2</sup> M	k x 10 <sup>3</sup> (l.-m. <sup>-1</sup> -sec. <sup>-1</sup> )
4.62	2.00	1.11 ± .02
4.63	4.00	1.03 ± .05
5.92	2.00	1.09 ± .01

The consistency of the calculated second order rate constants show the reaction to be first order in both amine and alkyl halide.

Second order rate plots give straight lines from only one to three half-lives, the plots curving downward. This effect is pronounced only in the reactions of primary and secondary amines in DMSO. It is not due to destruction of reactants or product because the reaction goes to 100% completion. Henderson (14) has suggested the following scheme:



When the amine is in excess, the equilibrium for the second reaction is shifted to the right producing, in the case of an initial primary amine, a secondary amine, and a tertiary amine in the case of an initial secondary amine. In either case, an amine is produced which is less reactive than the original, hence a decrease in rate. The hypothesis was tested by adding triethylamine hydrobromide (a product-like substance) to the reaction of di n-butyl amine with ethyl iodide. As the concentration of the salt was increased, the curvature of the plot began earlier in the run. This effect tends to confirm the scheme proposed by Henderson.

In order to test the possibility of a correlation between the basicity of the amine and its nucleophilicity, non-aqueous titrations were performed in methanol and DMSO. The millivolts at half-neutralization ( $E_{\frac{1}{2}}$ ) is linearly related to the pK of the amine (20). The data are shown in Table 2.

The rate order follows basicity since the more negative  $E_{\frac{1}{2}}$  indicates the more basic amine. Plots of  $\log k$  vs.  $E_{\frac{1}{2}}$  are shown in Figures 1 and 2. In DMSO a curved line results, even with the exclusion of di-isobutyl amine which is anomalously slow. If there is any relation between nucleophilicity

Table 2. Relationship between  $E_{1/2}$  and the rate of reaction of amines with ethyl iodide at 30.4°

Amine	Solvent	k (l.-m. <sup>-1</sup> -sec. <sup>-1</sup> )	$E_{1/2}$ (mv)
n-butyl amine	DMSO	1.80 ± .07 x 10 <sup>-2</sup>	-247
di-isobutyl amine	DMSO	2.80 ± .21 x 10 <sup>-3</sup>	-211
di n-butyl amine	DMSO	1.09 ± .02 x 10 <sup>-2</sup>	-197
tri n-butyl amine	DMSO	6.65 ± .20 x 10 <sup>-4</sup>	-87
di-isobutyl amine	methanol	1.89 ± .21 x 10 <sup>-5</sup>	-99
n-butyl amine <sup>a</sup>	methanol	1.34 ± .07 x 10 <sup>-5</sup>	-85
di n-butyl amine <sup>a</sup>	methanol	1.03 ± .05 x 10 <sup>-5</sup>	-80
tri n-butyl amine <sup>a</sup>	methanol	1.94 ± .10 x 10 <sup>-6</sup>	-30

<sup>a</sup>Extrapolated from runs at higher temperatures.



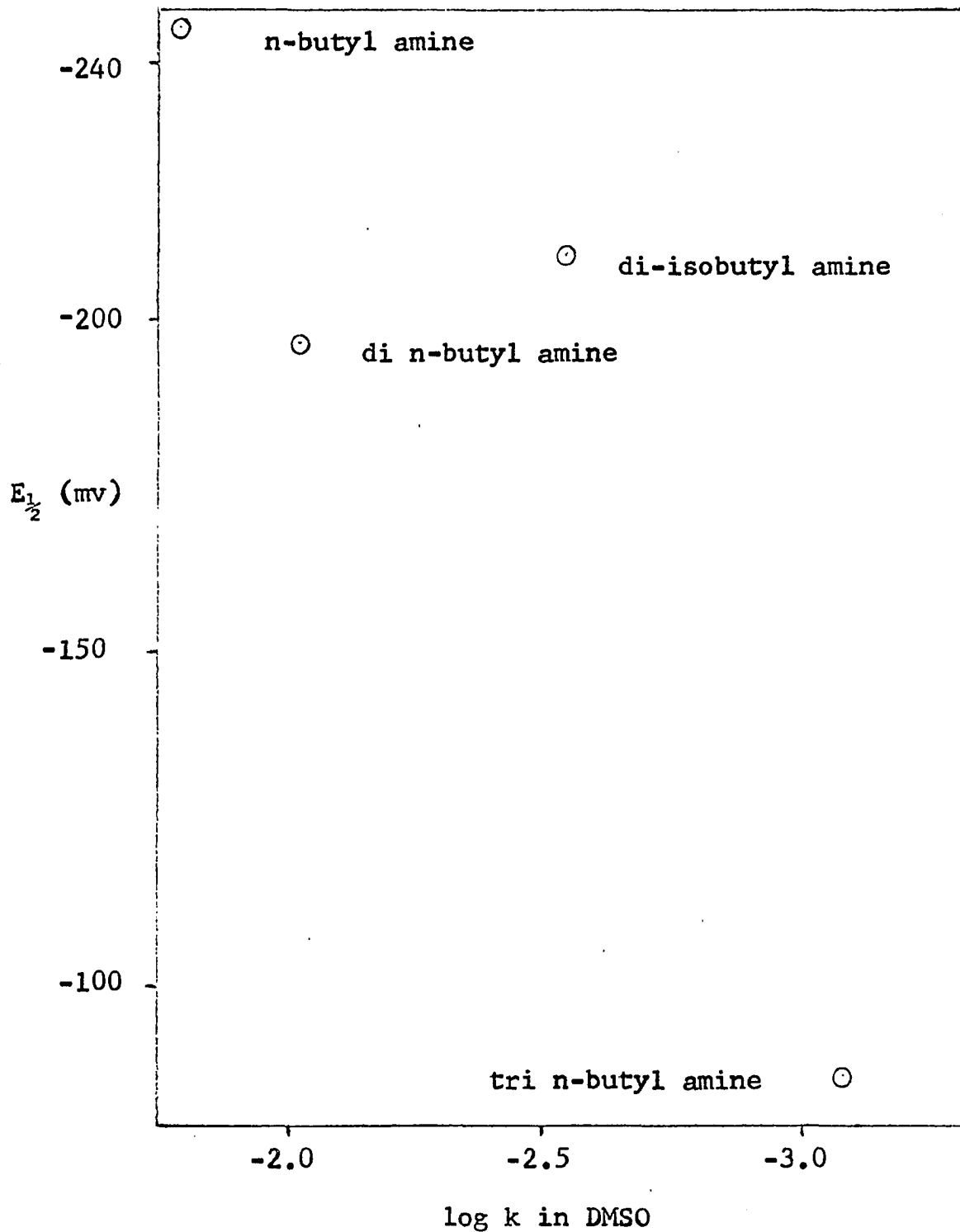


Figure 1. Plot of  $E_{1/2}$  (mv) vs.  $\log k$  of the reaction of amines with ethyl iodide in DMSO at  $30.4^\circ$

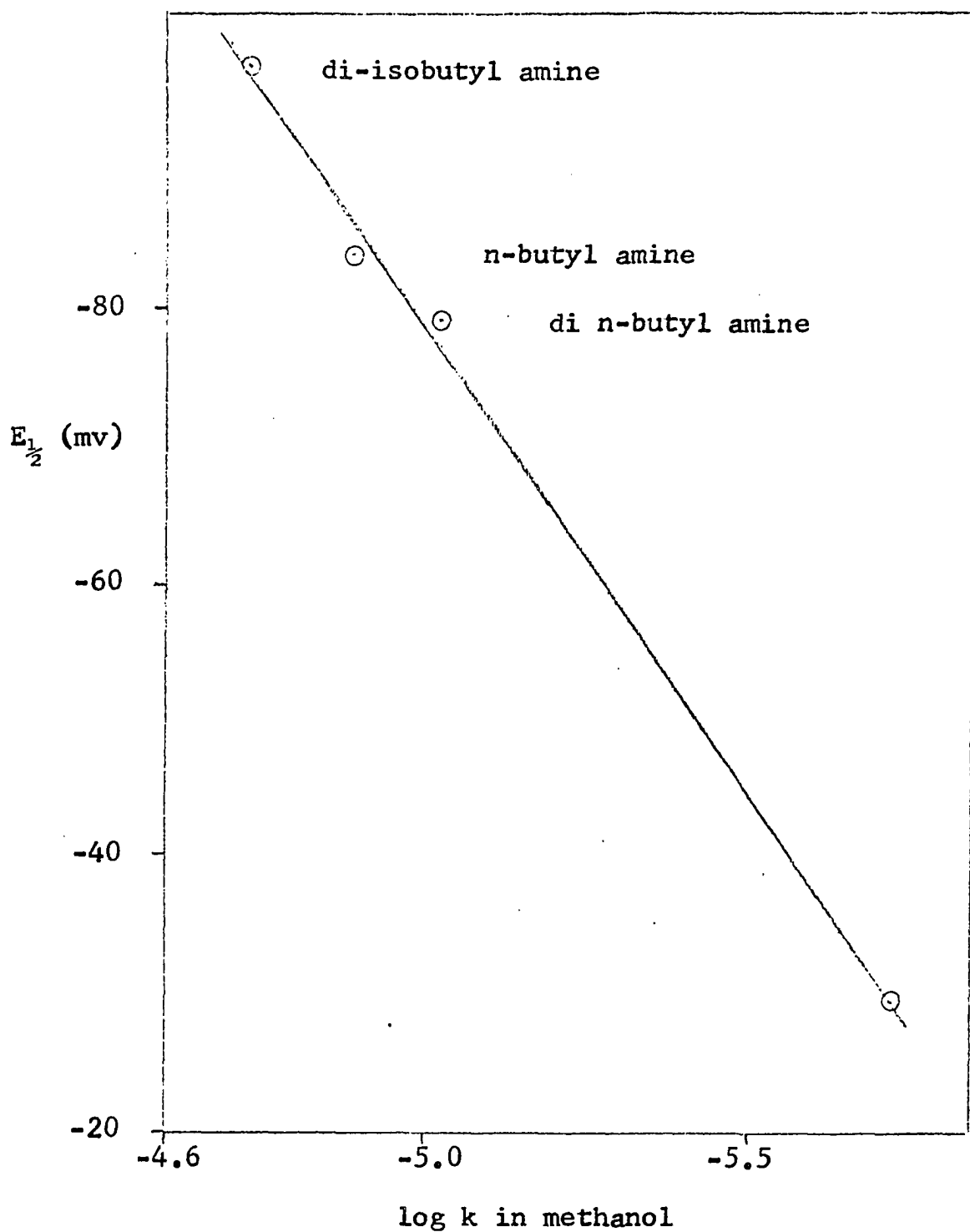


Figure 2. Plot of  $E_{1/2}$  vs.  $\log k$  of the reaction of amines with ethyl iodide in methanol at  $30.4^\circ$

and basicity, then amines would be expected to be more nucleophilic in DMSO than in methanol because amines are more basic in DMSO. The plot for methanol shows a linear correlation between rate and basicity, indicating factors which affect basicity also affect nucleophilicity in the same manner. The effect of solvent mixtures on the rate is shown in Table 3. The rate order is seen to be primary > secondary > tertiary in all mixtures as well as in pure solvents. Hall (15) found the same order for the butyl amines in the reaction with ethyl iodide in acetone at 35°. As can be seen from the table, the accelerating effect of DMSO is more pronounced in the primary and secondary amines than in the tertiary.

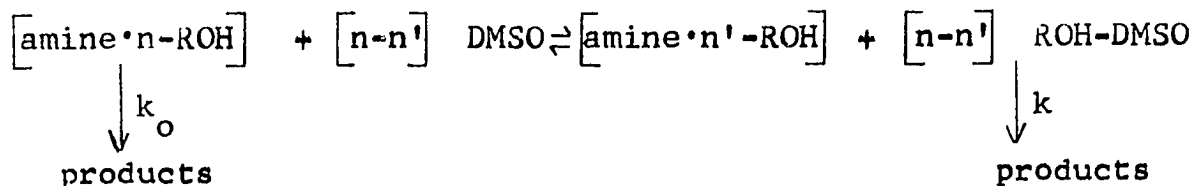
In an attempt to find a correlation between rate and the composition of the solvent mixture, the logarithm of the rate was plotted against mole fraction of DMSO and methanol, and against the molarity of DMSO and methanol. All gave curved plots, especially in the region of low DMSO concentration. Polarity differences such as dielectric constant, should not be a factor because the dielectric constants of methanol and DMSO are similar, 31.5 and 45 respectively (17).

Kingsbury (21) has derived a relationship assuming that DMSO is able to promote nucleophilic attack by removal of hydroxylic solvent species hydrogen bonded to the attacking nucleophile. An equilibrium such as the following would then exist:

Table 3. Rate of reaction of butyl amines with ethyl iodide in DMSO-methanol mixtures at 30.4°

DMSO vol. %	n-butyl	k/k <sub>0</sub>	k (l.-m. <sup>-1</sup> -sec. <sup>-1</sup> )		tri n-butyl	k/k <sub>0</sub>
			di n-butyl	k/k <sub>0</sub>		
0 <sup>a</sup>	1.34 ± .07 × 10 <sup>-5</sup>	1	1.03 ± .05 × 10 <sup>-5</sup>	1	1.94 ± .10 × 10 <sup>-6</sup>	1
40	4.97 ± .49 × 10 <sup>-4</sup>	37	2.93 ± .05 × 10 <sup>-4</sup>	28	4.72 ± .12 × 10 <sup>-5</sup>	24
50	9.33 ± .18 × 10 <sup>-4</sup>	70				
60	1.56 ± .03 × 10 <sup>-3</sup>	106	1.13 ± .01 × 10 <sup>-3</sup>	110	1.32 ± .02 × 10 <sup>-5</sup>	68
70	3.26 ± .12 × 10 <sup>-3</sup>	243				
80	7.20 ± .25 × 10 <sup>-3</sup>	537	3.50 ± .05 × 10 <sup>-3</sup>	340	2.95 ± .06 × 10 <sup>-4</sup>	152
100	1.80 ± .07 × 10 <sup>-2</sup>	1360	1.09 ± .01 × 10 <sup>-2</sup>	1060	6.65 ± .21 × 10 <sup>-4</sup>	343

<sup>a</sup>Extrapolated from data at higher temperatures.



where  $[n-n']$  is the number of hydrogen-bonded solvent molecules lost by interaction with DMSO,  $k_0$  is the rate in pure methanol and  $k$  is the rate in mixed solvents. As the amount of DMSO in the solvent mixture is increased, the equilibrium shifts to the right producing a less heavily hydrogen-bonded nucleophile which is more reactive than the original nucleophile. The above equation provides the following relationship:

$$\log [k-k_0] = [n-n'] \log (\text{ROH}) + \text{constant}$$

Plots of  $\log [k-k_0]$  vs.  $\log (\text{ROH})$  are shown in Figure 3 for the butyl amines. There is a slight curvature in all plots, possibly indicating an equilibrium relationship perturbed by other factors. Ignoring the curvature, the following slopes are obtained: n-butyl amine 2.58, di n-butyl amine 2.45, and tri n-butyl amine 1.79. These are the number of methanol molecules hydrogen bonded to the amine, which are lost by interaction with DMSO.

Condon (13) proposed that the primary shell of hydrogen-bonded water is composed of three molecules for primary amines, two for secondary, and one for tertiary. He was able to calculate  $\text{p}K_a$  values of amines by putting this assumption into an equation involving hydration energies and Taft substituent

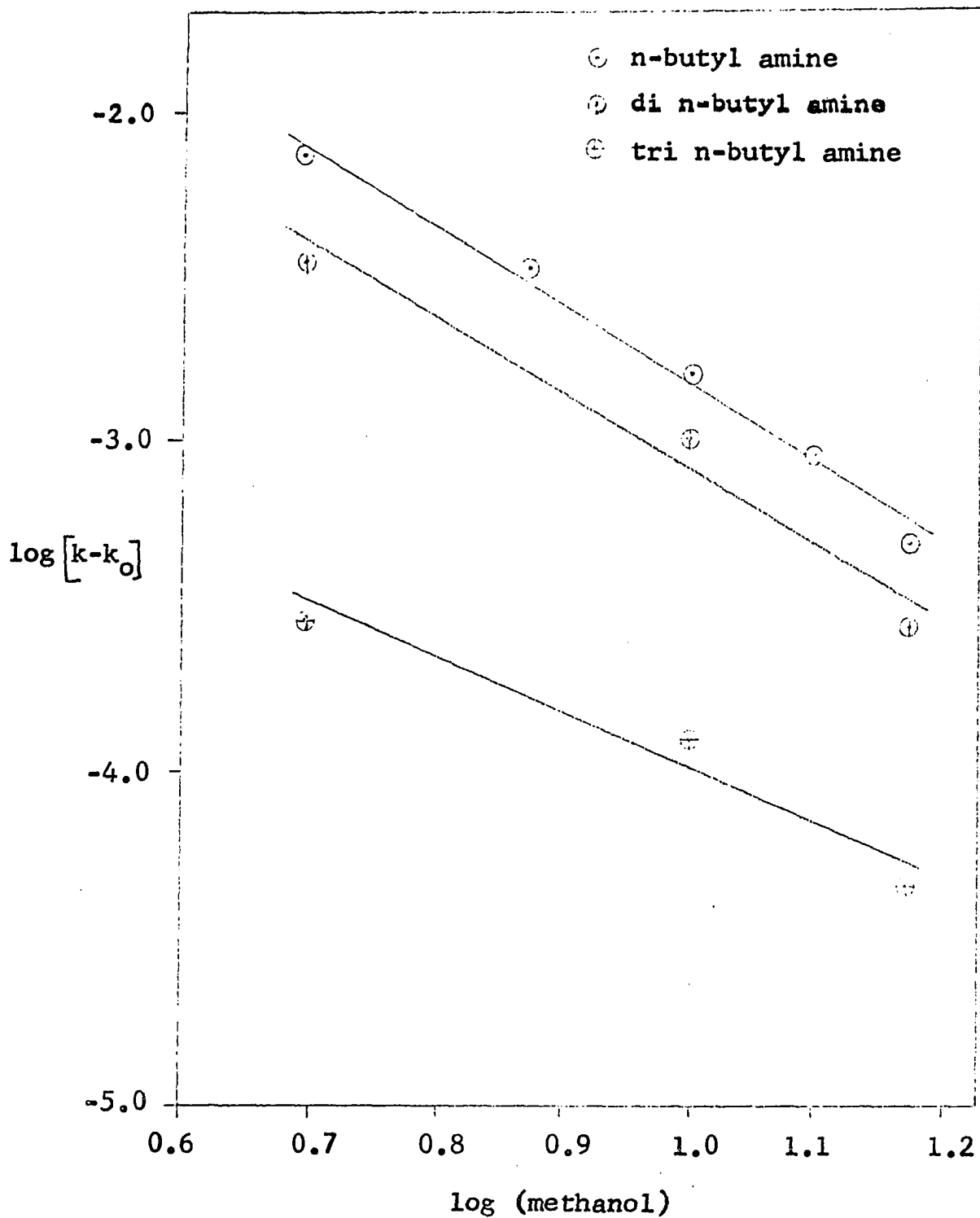


Figure 3. Plot of  $\log [k - k_0]$  vs.  $\log (\text{methanol})$  for some butyl amines reacting with ethyl iodide in DMSO-methanol mixtures at  $30.4^\circ$ .

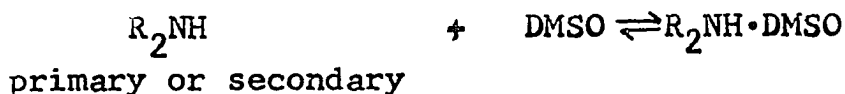
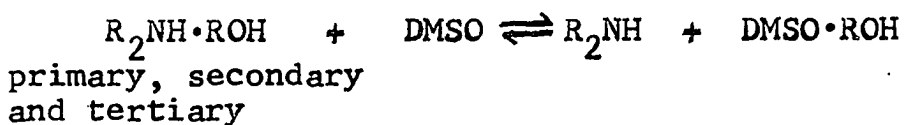
constants. The calculated pK values agreed well with the experimental, thus validating his proposal. The slopes in Figure 3 indicate the amount of hydrogen bonds lost in the reaction of secondary and primary amines are approximately equal. Tertiary amines lose approximately one less molecule.

Excellent linear plots of  $\log [k-k_0]$  vs. (DMSO) were obtained for the butyl amines, and are shown in Figure 4. This indicates that the following relationship is obeyed:

$$\log [k-k_0] = r (\text{DMSO}) + \text{constant}$$

The slope  $r$  for various amines is listed in Table 4.

The  $r$  values for primary and secondary amines are roughly the same with the exception of aniline. A tertiary amine appears to be less sensitive to DMSO than primary or secondary amines. The following scheme is proposed to account for the data:



Hydrogen bonding by methanol ( $-\overset{\cdot}{N}:--H-OR$ ) is rate decreasing for all amines because it removes electron density from the nitrogen making it less nucleophilic. DMSO strips the methanol from the amine and thus increases the rate for all amines. In addition, DMSO can hydrogen bond to primary and

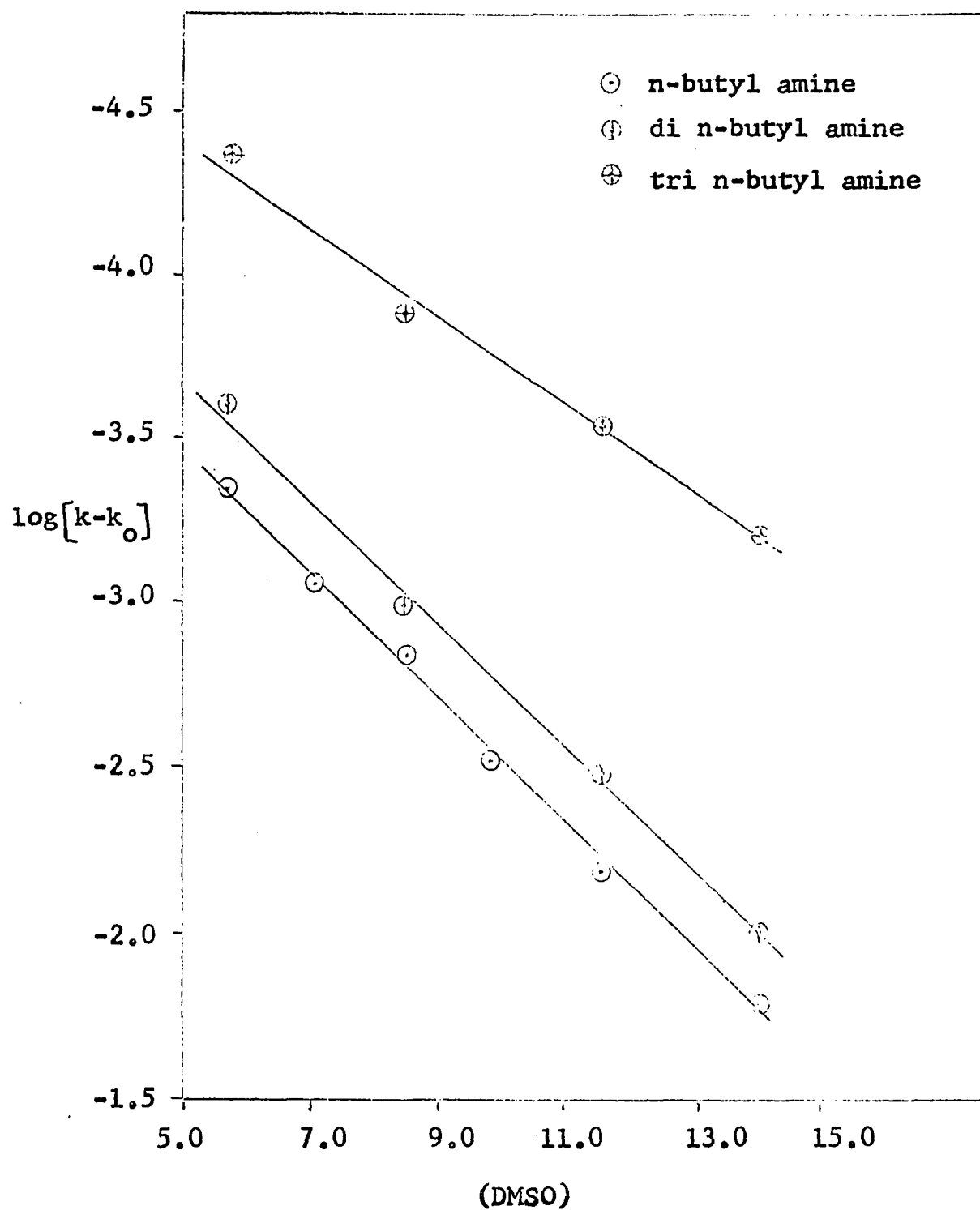


Figure 4. Plot of  $\log [k - k_0]$  vs. (DMSO) for some butyl amines reacting with ethyl iodide in DMSO-methanol mixtures at  $30.4^\circ$ .

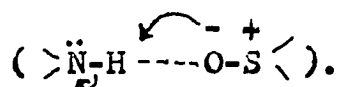


Table 4. Slope of the plot of  $\log [k-k_0]$  vs. (DMSO) in DMSO-methanol mixtures for the reaction of amines with ethyl iodide at 30.4°

Amine	Slope r
t-butyl amine	0.203
benzyl amine <sup>a</sup>	0.178
n-butyl amine	0.188
di n-butyl amine	0.183
tri n-butyl amine	0.135
aniline	0.115

<sup>a</sup>Reacted with 2,4-dinitrochlorobenzene at 25.6° (21).

secondary amines by donating the electrons from the negative oxygen



This pushes the N-H bonding electrons toward the nitrogen atom making it more nucleophilic. The effect of added DMSO on tertiary amines is less than that for primary and secondary since the latter rate increase is missing for tertiary. The lack of an interaction between tertiary amines and DMSO can also be seen in their low solubility in DMSO compared to primary and secondary amines.

Corroboration of hydrogen bonding of DMSO to amines is found in infra-red (22) and NMR (23) studies. The N-H fre-

Table 5. Effect of the addition of DMSO to the N-H resonance of amines in deuteriochloroform ( $\text{CDCl}_3$ )<sup>a</sup>

Amine	$\delta\Delta$ (ppm)	$\text{pK}_b$ in $\text{H}_2\text{O}$ (12)
aniline	0.44	9.42
t-butyl amine	0.37	3.65
n-propyl amine	0.18	3.47
diethyl amine	0.23	3.02

<sup>a</sup>One millimole of amine in one ml. of solvent. Comparison was made between  $\text{CDCl}_3$  and a mixture of 0.8 ml.  $\text{CDCl}_3$  and 0.2 ml. DMSO.

quency of primary amines in the infra-red is shifted to lower values by the addition of DMSO to a solution of the amine in carbon tetrachloride. This is due to the formation of a 1:2 or 1:1 DMSO-amine complex. The NMR study showed the down-field shift of the N-H resonance as DMSO was added to the pure amine. DMSO was found to give the greatest shift of all the oxygenated solvents in the study, while nitromethane gave the lowest.

The results of some NMR experiments in this work are shown in Table 5. The least basic amine should have the strongest hydrogen-bond donating ability since its hydrogens are more mobile and thus more readily donated. The least basic amine should also give the greatest shift on addition of DMSO. With the exception of aniline which gives a very small

shift in relation to its  $pK$ , other amines give shifts roughly in order of their basicity.

The anomalously low sensitivity of aniline to DMSO in its reaction with ethyl iodide in DMSO-methanol mixtures can now be explained. Aniline, being a very weak base, does not readily accept hydrogen bonds from methanol. Therefore, the addition of DMSO does not change its nucleophilicity to any great extent because it is already a relatively "free" nucleophile. On the other hand, the strong hydrogen-bond donation to DMSO expected from its weak basicity, does not occur as evidenced by the NMR study. Thus, the two effects combine to give a decreased sensitivity to DMSO relative to other primary amines.

Nitromethane is a poor hydrogen bond acceptor and donor and has a high dielectric constant, 39.4 (17). The results of amine reactions in this solvent are shown in Table 6. It is seen that there is a larger decrease in the rate when methanol is added to nitromethane, than when it is added to DMSO. In pure nitromethane ( $\text{CH}_3\text{NO}_2$ ), there is little hydrogen bonding with the amine. This is confirmed by the NMR measurements mentioned previously (23).

In nitromethane-methanol mixtures, the hydroxyl proton hydrogen bonds to the amine and thus the nucleophilicity is lowered. Nitromethane cannot strip off methanol from the amine as does DMSO, since it is a poor hydrogen-bond acceptor. These two effects combine to make the rate more sensi-

Table 6. Rate of reaction of n-butyl amine with ethyl iodide in various solvents at 30.4°

Solvent	k (l.-m. <sup>-1</sup> -sec. <sup>-1</sup> )	k/k <sub>0</sub>
100% CH <sub>3</sub> NO <sub>2</sub>	1.50 ± .08 x 10 <sup>-3</sup>	211
80% CH <sub>3</sub> NO <sub>2</sub> -methanol	2.05 ± .06 x 10 <sup>-4</sup>	29
40% CH <sub>3</sub> NO <sub>2</sub> -methanol	7.09 ± .14 x 10 <sup>-5</sup>	1
100% DMSO	1.80 ± .07 x 10 <sup>-2</sup>	36
80% DMSO-methanol	7.20 ± .25 x 10 <sup>-3</sup>	15
40% DMSO-methanol	4.97 ± .49 x 10 <sup>-4</sup>	1

tive to methanol in nitromethane.

In an effort to learn the effect of solvent on the leaving group, a study was performed with ethyl p-toluene-sulfonate (EtOTs). The results are shown in Table 7. The rate enhancing effect of DMSO is less for EtOTs, approximately 300-400, than for ethyl iodide, 1000-1300. This can be explained by the fact that -OTs is a poorer leaving group than iodide and hence requires more solvation. This solvation can only be provided by methanol. This difference in reactivity can also be ascribed to polarization of the ethyl iodide by the DMSO, and lack of it for EtOTs.

A stable addition compound of methyl iodide has been isolated by Winstein (24). However, its intermediacy in the reaction of methoxide ion with methyl iodide has been disproven by Murto (25). He isolated the addition compound and

Table 7. Rate of reaction of some butyl amines with ethyl p-toluenesulfonate at 30.4°

Amine	Solvent	k (l.-m. <sup>-1</sup> -sec. <sup>-1</sup> )	k/k <sub>0</sub>
n-butyl amine	100% methanol	2.99 ± .13 × 10 <sup>-6</sup>	1
n-butyl amine	100% DMSO	1.28 ± .02 × 10 <sup>-3</sup>	428
di n-butyl amine	100% methanol	1.45 ± .03 × 10 <sup>-6</sup>	1
di n-butyl amine	100% DMSO	4.23 ± .25 × 10 <sup>-4</sup>	292

ran a rate study of it with methoxide in DMSO and found the rate to be much slower than the rate of reaction of methoxide with methyl iodide. An NMR study was run on one millimole of ethyl iodide in one milliliter of carbon tetrachloride and then with one millimole of DMSO added. No shift in the methyl or methylene resonance was found. Therefore, either a complex is not present or else the complex does not involve shifted resonance absorptions compared to the parent molecule. The latter possibility is not considered likely.

The effect of solvent on the rate of a phosphine with ethyl iodide is shown in Table 8. The tertiary phosphine was found to be approximately ten times more reactive than the corresponding amine in DMSO, in spite of the lower basicity of the phosphine; pK<sub>b</sub> is 5.57 in water compared to 3.51 for the amine. Henderson (14) has ascribed this to decreased steric factors in phosphines. A plot of log [k-k<sub>0</sub>]

Table 8. Rate of reaction of tri n-butyl phosphine and amine with ethyl iodide in DMSO-methanol mixtures at 30.4°

Nucleophile	k (l.-m. <sup>-1</sup> -sec. <sup>-1</sup> )		
	100% DMSO	80% DMSO	60% DMSO
phosphine	6.28 $\pm$ .19 x 10 <sup>-3</sup>	4.36 $\pm$ .08 x 10 <sup>-3</sup>	2.84 $\pm$ .03 x 10 <sup>-3</sup>
amine	6.65 $\pm$ .20 x 10 <sup>-4</sup>	2.95 $\pm$ .06 x 10 <sup>-4</sup>	1.32 $\pm$ .02 x 10 <sup>-5</sup>

vs. (DMSO) gives a slope of 0.057, considerably less than that for the corresponding amine, 0.135. This low sensitivity of phosphine to DMSO may be the result of decreased hydrogen bonding of the methanol to the phosphine owing to its low basicity. The rate difference between methanol and DMSO would therefore be less than that of the more basic amine.

The rates and activation parameters for some triaryl metallics are shown in Table 9. The order of reactivity with ethyl iodide is found to be P > As > Sb. Triphenyl amine is a factor of a thousand less reactive than the phosphine in acetone (26). This probably puts it after antimony in the rate order in DMSO.

This nucleophilicity order may be explained using the principle of hard and soft acids and bases proposed by Pearson (27). Hard electrophilic centers (acids) react rapidly with hard nucleophiles (bases) and soft acids react rapidly with soft bases. A typical SN<sub>2</sub> reaction may be illustrated

Table 9. Rate of reaction of triphenyl metallica with ethyl iodide in DMSO at 30.4°

Nucleophile	$k \times 10^4$ (l.-m. <sup>-1</sup> -sec. <sup>-1</sup> )	$\Delta H^\ddagger a$ (kcal·m. <sup>-1</sup> )	$\Delta G^\ddagger a$ (kcal·m. <sup>-1</sup> )	$\Delta S^\ddagger a$ $\frac{\text{l. cal}}{\text{deg} \cdot \text{m.}}$
phosphine	5.47 ± .71	9.04	22.23	-40.17
arsine	1.99 ± .10	13.75	22.84	-29.95
stibine	1.05 ± .01	19.49	23.21	-12.25

<sup>a</sup>Activation parameters at 30.4°.

as follows:



The transition state is just another acid-base complex with an increased coordination number for A and somewhat longer bonds. The increased charge on A makes it a softer acid. Thus softness is more important in rate phenomena than in thermodynamics. Ethyl carbonium ion is a medium-soft acid and reacts most rapidly with soft bases. The order of soft basicity is N << P > As > Sb, the same as the rate order of Table 9 for ethyl iodide.

The high negative entropy of activation is characteristic of the high degree of organization in the transition state of the Menshutkin reaction. The change in rate is almost entirely due to entropy effects indicating a different degree of solvation in the transition state.

Table 10. Salt effects on the reaction of di n-butyl amine with ethyl iodide

Solvent	No salt	$k \times 10^3$ (l.-m. <sup>-1</sup> -sec. <sup>-1</sup> )		
		0.114 M Me <sub>4</sub> NNO <sub>3</sub>	0.114 M LiNO <sub>3</sub>	0.246 M LiNO <sub>3</sub>
DMSO 30.4°	10.9 ± .10	9.53 ± .60	9.87 ± .21	---
methanol 81.4°	1.62 ± .13	2.26 ± .02	1.94 ± .09	2.29 ± .06

The effect of added salts is shown in Table 10. As can be seen from the data, the effects are quite small, as predicted from a reaction of two uncharged species. The slight decrease in rate upon salt addition in DMSO may be due to decreased hydrogen bonding between the amine and DMSO, thus lowering the nucleophilicity of the amine. The rate increase in methanol is due to the decreased hydrogen bonding between the methanol and amine, thus increasing its nucleophilicity. The fact that tetramethyl ammonium ion causes greater changes in rate than lithium ion is inferred from data tabulated by Parker (17). He found that Me<sub>4</sub>N<sup>+</sup> is more conducting, and therefore less solvated than Li<sup>+</sup> in dipolar aprotic solvents. The former would therefore be more effective in stripping off hydrogen bonds between the amine and DMSO.

The data in Table 3 and Table 11 have a bearing on the



Table 11. Effect of water on the rate of reaction of n-butyl amine with ethyl iodide at 30.4°

Solvent	$k$ (l.-m. <sup>-1</sup> -sec. <sup>-1</sup> )
100% DMSO	$1.80 \pm .07 \times 10^{-2}$
80% DMSO-water	$5.50 \pm .14 \times 10^{-3}$
60% DMSO-water	$8.24 \pm .56 \times 10^{-4}$
50% DMSO-water	$4.26 \pm .05 \times 10^{-4}$

theory of solvent polarity effects as formulated by Ingold (28). It states that reactions in which charge is generated in the transition state should undergo a strong rate increase as the polarity of the medium is increased. The decrease in rate in methanol-DMSO mixtures as methanol is added conforms to the theory. However, the decreased rate, as water is added, violates the theory since the polarity of the medium is increased. The rate is also decreased upon water addition in the reaction of methoxide ion and methyl iodide in DMSO (25).

A plot of  $\log[k-k_0]$  vs.  $\log(\text{water})$ , assuming  $k_0$  to be negligible, gives a slope of 2.92 implying all three hydrogen bonds are removed from the amine by DMSO. The slope is slightly less, 2.45, for DMSO-methanol mixtures. The increased sensitivity to DMSO-water mixtures is explained by the increased affinity of DMSO for water compared to methanol.

This is vividly demonstrated by adding water or methanol to DMSO. Much heat is evolved when water is added and very little upon addition of methanol.

The activation parameters for the butyl amines are shown in Table 12. The very small negative entropy in pure methanol suggests that the nucleophile must be desolvated prior to the formation of the transition state. This supports the data of Parker (19) in which methanol was found not to solvate a C---I transition state. The very large negative entropy in pure DMSO indicates a high degree of solvation in the transition state. In general, the data break down into two categories primary and secondary amine, and tertiary. The less negative entropy of activation in pure DMSO for the tertiary compared to the others is due to a lesser degree of solvation, because the enthalpy data are similar. This confirms the earlier hypothesis that primary and secondary amines can hydrogen bond to DMSO but tertiary cannot. An anomalous change in  $\Delta S^\ddagger$  and  $\Delta H^\ddagger$  is seen for the tertiary amine as the solvent is changed from 100% DMSO to 80%.  $\Delta S^\ddagger$  becomes more negative as methanol is added rather than more positive as occurs for the other amines. This is due to the formation of hydrogen bonds between the tertiary amine and methanol. Primary and secondary amines have some sort of hydrogen bonding in all solvents so no such anomaly is observed.

In general, rate increases per increment of DMSO are due

Table 12. Activation parameters for the reaction of butyl amines with ethyl iodide in DMSO-methanol mixtures at 30.4°

Amine	% DMSO	$\Delta H^{\ddagger a}$ (kcal·m. <sup>-1</sup> )	$\Delta G^{\ddagger a}$ (kcal·m. <sup>-1</sup> )	$\Delta S^{\ddagger a}$ $\frac{1, \text{cal}}{\text{degree} \cdot \text{m.}}$
n-butyl	0	21.62	24.65	-9.37
n-butyl	40	13.35	22.36	-29.79
n-butyl	60	16.59	21.61	-16.50
n-butyl	80	9.87	20.71	-35.69
n-butyl	100	8.17	20.13	-39.41
di n-butyl	0	22.31	24.62	-7.62
di n-butyl	40	15.71	22.61	-22.72
di n-butyl	60	15.83	21.87	-19.87
di n-butyl	80	12.26	21.12	-29.16
di n-butyl	100	7.81	20.43	-41.59
tri n-butyl	0	26.92	25.62	-4.27
tri n-butyl	40	18.43	23.73	-17.43
tri n-butyl	60	15.32	23.09	-25.87
tri n-butyl	80	13.68	22.68	-29.37
tri n-butyl	100	15.01	22.11	-23.08

<sup>a</sup>Activation parameters at 30.4°.

to both a change in  $\Delta H^\ddagger$  and in  $\Delta S^\ddagger$ . However, the primary and secondary amine exhibit a discontinuity in  $\Delta S^\ddagger$  and  $\Delta H^\ddagger$  as DMSO changes from an important component, 60% DMSO, mole fraction 0.463, to a minor component, 40% DMSO, mole fraction 0.264. The entropy change is probably a result of a change in solvent structure. No such break is seen for the reaction of triethyl amine with ethyl iodide in DMSO-benzene (18), since benzene does not associate with DMSO as does methanol. Another study by Murto (29) invoked hydrogen bonding by DMSO to the solvent to explain the low sensitivity to DMSO in the reaction of 4-nitropyridine N-oxide with hydroxide ion in DMSO-water mixtures. A sharp break in  $\Delta S^\ddagger$  and  $\Delta H^\ddagger$  was also found as DMSO went from the major to the minor component.

## EXPERIMENTAL

## Preparation and Purification of Materials

Solvents

Dimethyl sulfoxide (Mallinckrodt) was purified by distillation from calcium hydride (Metal Hydrides) and a center cut taken at 48-50° C at a pressure of 2 millimeters (mm.). It was then stored over molecular sieve.

Methanol (Mallinckrodt) was purified according to Vogel (30), using magnesium ethoxide as the drying agent. It was distilled through a 12 cm. Vigreux column into molecular sieve. A center cut was taken at 78-79° C.

Nitromethane (Matheson, Coleman and Bell) was distilled from calcium chloride through a 12 cm. Vigreux column. A center cut was distilled into molecular sieve, boiling point 100-101° C.

Water was purified by redistillation from a small quantity of potassium permanganate. It was distilled through a 12 cm. Vigreux, boiling point 99-100° C.

Reagents

The amines were obtained from Aldrich. They were distilled from barium oxide (G. Frederick Smith Co.) through a 6 cm. Vigreux column and stored in an amber bottle in the refrigerator. The following is a list of amines and their boiling points: n-butyl, 76-77° C; di n-butyl, 90-95° C under aspirator pressure (approximately 15 mm.); tri n-butyl,

133-134° C, aspirator; di-isobutyl, 80-83° C, aspirator; aniline, 129-132° C, aspirator, stored under nitrogen; t-butyl amine, 44-46° C, n-propyl amine, 46-48° C; and diethyl amine, 54-55° C.

Ethyl iodide was obtained from Matheson, Coleman and Bell. It was distilled from copper wire through a 6 cm. Vigreux column, boiling point 71-72° C, and stored over copper wire in an amber bottle in the refrigerator. Ethyl p-toluene-sulfonate (Eastman) was distilled through a 6 cm. Vigreux column, boiling point 150-152° C at 0.4 mm.

Triphenyl phosphine (Aldrich), triphenyl stibine (Eastman) and triphenyl arsine (Aldrich) were used without further purification since their infra-red did not indicate any oxide impurity. The melting points were 78-80° C, 52-54° C, and 58-59.5° C, respectively. Tri n-butyl phosphine (Carlisle Chemical Works) was distilled through a 6 cm. Vigreux column, boiling point 86-92° C at 2 mm., and stored in an Erlenmeyer flask flushed with nitrogen and stoppered with a serum cap.

Potassium thiocyanate (Mallinckrodt), silver nitrate (Mallinckrodt), ferric nitrate (Baker), nitric acid (Fisher), 48% hydrobromic acid (Allied) and tetramethyl ammonium hydroxide (Matheson, Coleman and Bell) were used without further purification. Lithium nitrate (Baker) was dried in vacuo at 100° C for five hours.

### Preparation of salts

Triethyl amine (Eastman) and hydrobromic acid were mixed and the salt precipitated by the addition of ethanol. It was filtered, washed with ethanol and dried in vacuo at 100° C, melting point 245-248° C. Tetramethyl ammonium hydroxide (25% aqueous solution) was reacted with nitric acid and the product worked up as before. Both salts were stored in a dessicator over phosphorous pentoxide.

### Apparatus

Melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. Boiling points and bath temperatures are also uncorrected. Nuclear magnetic resonance spectra were run on a Varian A-60 instrument with tetramethyl silane (TMS) as the internal standard. Data are given in parts per million (ppm) downfield from TMS. The concentration of solute was one millimole per milliliter of solvent. A Corning 12 pH meter with an expanded scale was used for the non-aqueous titrations.

### Kinetic Procedure

#### Ethyl iodide runs

Kinetic solutions were prepared by diluting to 50 ml., a weighed amount (2-5 millimoles) of nucleophile, and 1 millimole of ethyl iodide, with solvent thermostatted in a constant temperature bath. Five ml. aliquots were taken at suitable intervals with an automatic pipet and placed in a

solution of 50 ml. of ice-cold distilled water acidified with nitric acid. In some runs the reagents were mixed with solvent at room temperature. Five ml. aliquots were then taken and placed in ampoules, sealed, and placed in a constant temperature bath. These rate constants were corrected for volume expansion on going from room temperature to that of the bath.

A Volhard titration was done to determine the amount of iodide ion produced in the reaction. Some 0.0200 M potassium thiocyanate was run in from a buret, then 5 ml. of 0.200 M silver nitrate (standardized against thiocyanate) was added from a pipet. Three drops of a 10% aqueous solution of ferric nitrate were added as an indicator. The excess silver nitrate was then titrated with thiocyanate to the light-orange endpoint. Infinity titres were taken after 20 half-lives and usually indicated greater than 99% reaction.

#### Ethyl tosylate runs

The solutions were prepared as in the iodide runs. The reaction was quenched by pipetting or transferring into 25 ml. of ice-cold distilled water and 25 ml. of 0.0227 M hydrochloric acid. The excess acid was then back-titrated to the bromocresol purple endpoint with 0.0197 M sodium hydroxide.

#### Calculations

Second order rate constants were calculated from the following equation:



$$kt = \frac{1}{(B_0 - A_0)} 2.3 \log \frac{(B_t)(A_0)}{(B_0)(A_t)}$$

where A and B are the reactants, with B being in two to five-fold excess over A. The subscripts refer to the concentrations at time zero and t seconds. The plots were linear from 1 to 3 half-lives depending on the system. Rate constants were obtained by averaging the instantaneous rate constants for each point taken. A standard deviation was calculated for each run. Duplicate runs agreed within 5%.

Mixed solvents were prepared volumetrically. Volume changes upon mixing (known from other work) were taken into consideration in calculating the molarity of each component. Some typical data and plots are given at the end of this Experimental Section. Activation parameters were calculated from data at two different temperatures.

#### Non-Aqueous Titrations

Four ml. of 37% hydrochloric acid (Baker and Adamson) were diluted to 100 ml. with either methanol or DMSO to give approximately 0.5 N hydrochloric acid solutions. The amine (4 millimoles) was dissolved in 50 ml. of the appropriate solvent and titrated with hydrochloric acid from a 25 ml. buret. The millivolts at half-neutralization were calculated from a graph of millivolts vs. milliliters of acid.

Table 13. Rate of reactions of n-butyl amine with ethyl iodide in DMSO at 30.4° a

Time (seconds)	Titre <sup>b</sup> (ml.)	Iodide ion (M x 10 <sup>2</sup> )	k x 10 <sup>2</sup> (l.-m.-l-sec.-1)
0.00	4.22	0.312	----
139	3.15	0.740	1.69
251	2.46	1.016	1.95
427	1.80	1.280	1.78
634	1.20	1.520	1.71
852	0.79	1.684	1.63
9400	4.90 <sup>c</sup>	2.040	----
average rate constant			1.80 ± .07

<sup>a</sup>Concentration of amine 0.00900 M, concentration of ethyl iodide 0.00200 M.

<sup>b</sup>Milliliters of 0.200 M potassium thiocyanate after addition of 5 ml. of 0.200 M silver nitrate.

<sup>c</sup>Milliliters of 0.200 M potassium thiocyanate after addition of 10 ml. of 0.200 M silver nitrate.

Table 14. Rate of reaction of n-butyl amine with ethyl iodide in methanol at 81.4°<sup>a</sup>

Time (seconds)	Titre (ml.)	Iodide ion (M x 10 <sup>2</sup> )	k x 10 <sup>3</sup> (l.-m.-l.-sec.-1)
0.00	4.65	0.140	----
3282	2.80	0.880	1.63
3924	2.45	1.020	1.75
4722	2.27	1.092	1.68
6486	1.60	1.360	1.83
8364	1.22	1.512	1.79
10134	0.95	1.620	1.73
128500	0.08	1.968	----
Average rate constant			1.73 ± .05

<sup>a</sup>Concentration of amine 0.00930 M, concentration of ethyl iodide 0.00200 M.

Table 15. Rate of reaction of tri n-butyl phosphine with ethyl iodide in DMSO at 44.1° a

Time (seconds)	Titre (ml.)	Iodide ion (M x 10 <sup>2</sup> )	k x 10 <sup>3</sup> (l.-m. <sup>-1</sup> -sec. <sup>-1</sup> )
0.00	4.78	0.088	----
253	3.94	0.424	1.71
553	3.16	0.736	1.74
778	2.68	0.928	1.76
905	2.56	0.976	1.63
1009	2.45	1.020	1.59
1560	1.86	1.256	1.58
64800	3.05 <sup>b</sup>	2.002	----
Average rate constant			1.68 ± .03

<sup>a</sup>Concentration of phosphine 0.00444 M, concentration of ethyl iodide 0.00200 M.

<sup>b</sup>Two milliliter aliquot of solution.

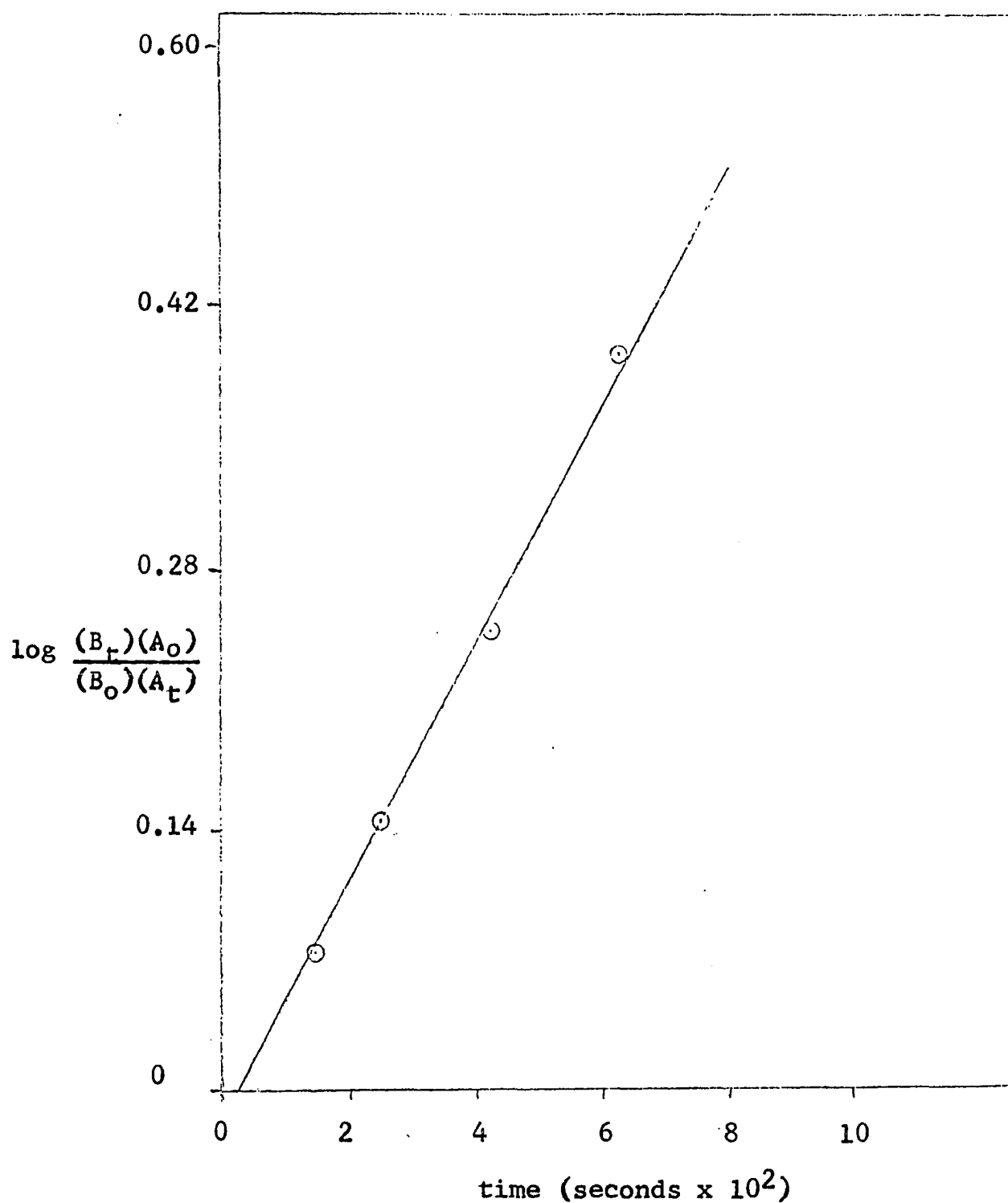


Figure 5. Plot of  $\log \frac{(B_t)(A_0)}{(B_0)(A_t)}$  vs. time in seconds for the reaction of n-butyl amine with ethyl iodide in DMSO at 30.4°.

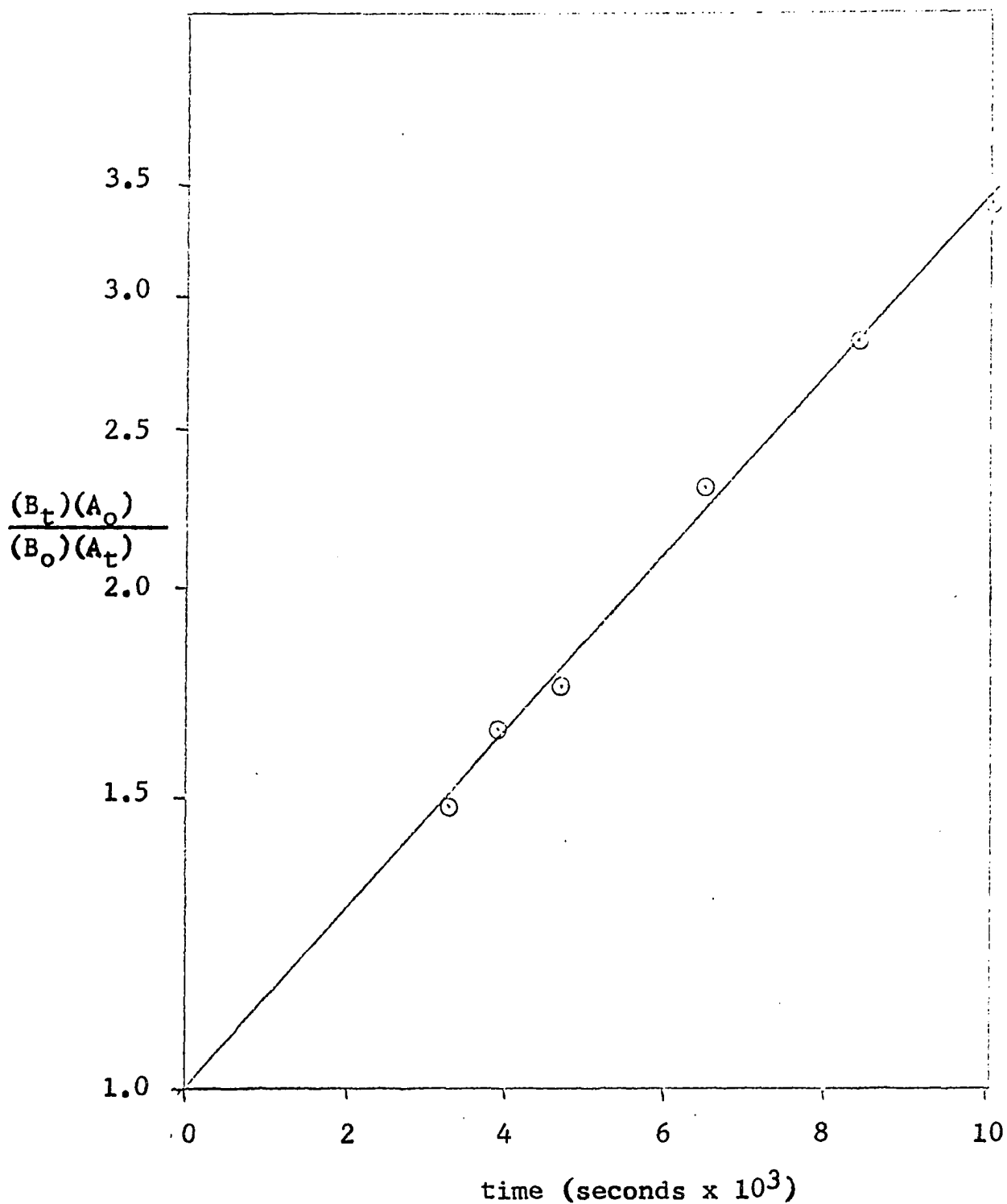


Figure 6. Semilog plot of  $\frac{(B_t)(A_0)}{(B_0)(A_t)}$  vs. time in seconds for the reaction of n-butyl amine with ethyl iodide in methanol at 81.4°.

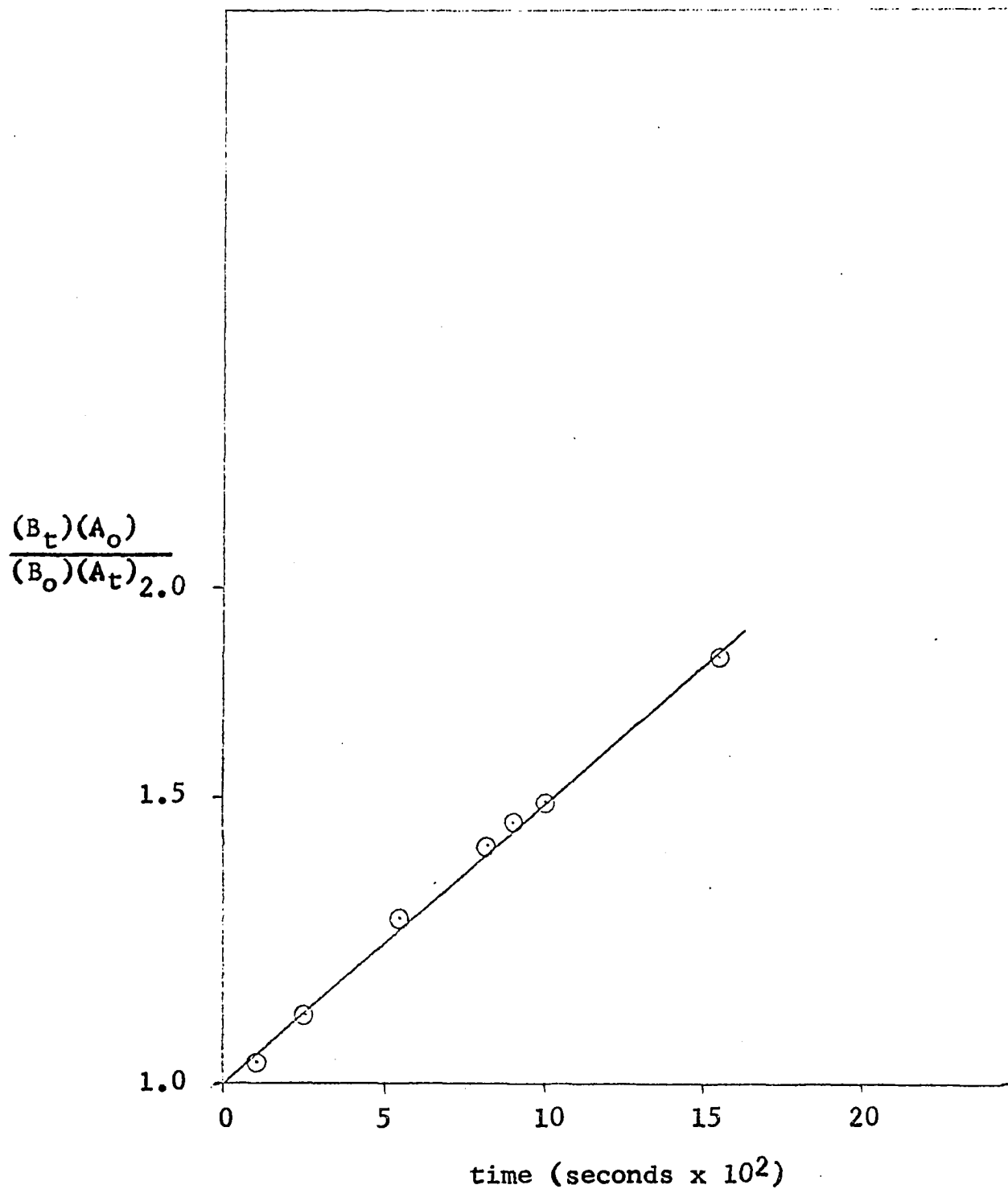


Figure 7. Semilog plot of  $\frac{(B_t)(A_0)}{(B_0)(A_t)}$  vs. time in seconds for the reaction of tri n-butyl phosphine with ethyl iodide in DMSO at 44.1°.

## SUMMARY

The effect of DMSO on some nucleophilic reactions has been studied in some detail. The rate enhancement in DMSO compared to protic solvents, in the reaction of amines with ethyl iodide is proposed to be due to three effects. First, the nucleophile is freer in DMSO compared with protic solvents, and in mixtures, DMSO is able to desolvate the solvent-amine hydrogen-bonded complex. Second, the nucleophilicity of the amine is increased by hydrogen bonding of the amine to the DMSO. Both of the above affect primary and secondary amines which are found to be equally sensitive to DMSO. Tertiary nucleophiles such as amines and phosphines, are less sensitive to DMSO due to the absence of the second effect. Third, DMSO can solvate the transition state of all amines, although it solvates least for tertiary amines, partially due to the second effect.

This hypothesis is supported by NMR data in which an interaction between DMSO and primary and secondary amines was demonstrated. Rates run in nitromethane-methanol support the proposal that DMSO can increase the rate by desolvation of the nucleophile. The rate was found to be more sensitive to methanol than in the DMSO-methanol system since nitromethane cannot accept hydrogen bonds from the methanol as readily as DMSO.

Activation parameters can also be explained on the



basis of the above proposal. The very high negative entropies of activation for nucleophiles in pure DMSO indicate that the transition state is highly solvated by DMSO. As in other data, primary and secondary amines show the same trends, with tertiary being quite different.

PART II. DETERMINATION OF ORGANIC HALIDES  
IN DIMETHYL SULFOXIDE

## INTRODUCTION

During recent years, the quantitative determination of organic compounds via their functional groups has received much attention. Excellent books of chemical analytical methods have been prepared by Siggia (31), Critchfield (32), and Cheronis and Ma (33). The analysis of organic halides by hydrolysis in dimethyl sulfoxide (DMSO) will now be considered.

Numerous methods have been proposed for the determination of organic halides. Some of the difficulties are: lack of simplicity, lengthy determination time, lack of selectivity and poor reagent stability.

The purpose of this investigation is to develop a simple and versatile method for the determination of halides. Such a method is described below.

The hydrolysis is performed in DMSO with aqueous potassium hydroxide as the reagent. Either excess base or halide ion is determined. The base is determined either by a simple acid-base titration with aqueous hydrochloric acid and phenolphthalein as the indicator, or by a potentiometric titration. The halide ion is determined by the Volhard procedure. The use of DMSO enables the determinations to be run rapidly at fairly low temperatures, usually 100° C or less.

The subsequent sections will include a review of halide procedures, discussion of the procedure for analysis and finally, a description of the experimental work.

## HISTORICAL

## Oxidation Methods

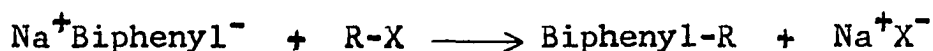
A good review of these methods is written by Schöniger (34). The oldest method is the Carius procedure (35). The organic matter is destroyed by heating with fuming nitric acid in a sealed, heavy-walled combustion tube at 250-300° C for several hours. Its disadvantages are the possibility of explosion and occasional low results. In the Parr method (36), oxidation is accomplished with sodium peroxide in a bomb. Wurzschnitt (37) introduced a modification in which ethylene glycol is introduced into the metal bomb. This reagent is oxidized at 50 to 60° C by the sodium peroxide. By this means, the decomposition can be ignited at a lower temperature. Pregl's microcombustion method (38) makes use of a stream of oxygen to burn the sample in a bead tube. The products are then passed over red-hot platinum contacts and absorbed into an aqueous solution and determined. The procedure requires 30 to 40 minutes and considerable manipulation. The most widely used oxidation method is that of Schöniger (39), in which the organic matter is combusted with oxygen in a "Schöniger Flask". A historical review of this method has been published by MacDonald (40).

## Reduction Methods

Considerable progress was achieved in this method of analysis when Burger (41, 42) found that it is possible to

use the well-known method of Vohl (43) for the detection of halogens and their quantitative determination. According to this procedure, modified later by Kainz and co-workers (44, 45, 46) for the halogens, the substance to be analyzed is fused with potassium in a sealed tube. Schöniger (47), and Radmacher and Mohrbauer (48) used magnesium and lithium, respectively, for the same purpose.

Liggett (49) introduced the use of sodium biphenyl for the determination of halides. The reagent is prepared by the reaction of sodium and biphenyl in dimethoxyethane. The reagent reacts in the following way:

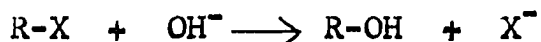


The reagent is stable for one month at room temperature and more than a year at 5° C, if air and water are excluded. The sample is dissolved in toluene and shaken with the reagent for thirty seconds in a separatory funnel. After five minutes, the extract is diluted with water, the aqueous layer withdrawn and the halide ion determined by the Volhard method. A blank must be determined for each lot of the reagent. The time for the determination is approximately twenty minutes. The disadvantages are the insolubility of some organic halides in toluene, thus requiring heating or other solvents such as ether or dioxane which rapidly decompose the reagent or precipitate it. The method is less suitable for samples containing large amounts of substances with reactive hydrogens

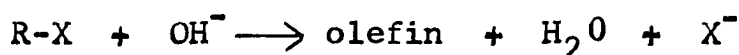
such as water, alcohols etc. Recently this method was used for the determination of fluorine in organic compounds, with good results (50).

#### Hydrolysis Methods

The general reaction is the following:



and/or:



An excellent compilation of halides determined and reaction conditions is found in a book by Ashworth (51). A good general macro and semi-micro method is proposed by Buscarons and Mir (52). Their reagent is potassium hydroxide in diethylene glycol. The sample is mixed with a two-fold excess of base in an ampoule which is then sealed. The tube is heated in an oil bath at 150-160° C for three hours. The halide ion is determined by the Volhard method. Other bases can be used, such as sodium alkoxides (53, 54, 55).

#### Summary

The methods of Schöniger and Carius are probably the most widely used procedures. The principal disadvantage of these methods is the special equipment needed. The Carius method also requires very high temperatures. The Parr method uses much lower temperatures, but also suffers from complexity. Of the reduction methods, the most widely used is the sodium

biphenyl procedure. This method suffers from reagent instability, necessity of a blank, and insolubility of some organic halides in the organic solvents used in the determination. The hydrolysis methods are blessed with simplicity, but suffer from the lengthy time required for complete reaction. All of the above methods, excluding hydrolysis, suffer from lack of selectivity in determining one halide in the presence of another.

## ANALYTICAL CONSIDERATIONS

## General Considerations

The development of an analytical method based upon a functional group reaction requires a careful consideration of several factors. The most important of these are equilibrium limitations and kinetic considerations. For the hydrolysis of organic halides, which is an irreversible reaction, only the latter need be considered. The reagent concentrations, solvent, temperature and reaction time must be investigated in order to find optimum conditions for rapid, simple analysis.

## Choice of Solvent

The solvent for the hydrolysis of organic halides should combine several features: high solubility of samples, rapid rate of reaction, absence of side reactions, and low cost. The previously used solvents were alcohols, such as ethanol and diethylene glycol. It has been found that DMSO greatly accelerates the reaction of base with organic compounds such as esters (56) and halides (18). The reaction of hydroxide ion with methyl iodide is  $5 \times 10^6$  faster in DMSO than in water. This enhanced rate, compared with protic solvents such as alcohols, is due to the decreased solvation of the hydroxide ion in DMSO. Alcohols are strong hydrogen bonding solvents and solvate anions to a great extent, thus decreas-



ing the reactivity of the anion. Other dipolar aprotic solvents such as dimethyl formamide, or dimethyl acetamide also possess rate enhancing characteristics (17). However, these are not as stable as DMSO toward base and tend to hydrolyze. Thus, DMSO appears to be the solvent of choice.

#### Reaction Time and Temperature

The choice of reaction conditions is dependent upon the reactivity of the halide with base. Increased reaction rates are observed at elevated temperatures; however, a temperature easily reached would be preferable, such as 100° C. Ideally 100% DMSO would be the best solvent composition. However, the limitation is the solubility of base in DMSO which is only  $7.6 \times 10^{-4}$  M for sodium hydroxide at 25° C (57). Owing to the decreased solvation, alkali metal hydroxides are very insoluble in pure DMSO. Therefore, some water must be present to solubilize the hydroxide.

## REAGENTS AND APPARATUS

## Reagents

Potassium hydroxide, 40%. Dissolve 470 grams of potassium hydroxide in one liter of water.

Potassium hydroxide, 0.950 N. Prepare in water and standardize against potassium acid phthalate.

Hydrochloric acid, 0.217 N. Prepare in water and standardize against potassium hydroxide.

Potassium thiocyanate, 0.400 N, primary standard.

Silver nitrate, 0.200 N. Standardize against thiocyanate.

Ferric nitrate, 10% solution in water.

Organic halides were commercially available, reagent grade samples with an estimated purity of 98-100%. They were used without further purification.

## Solvents

Dimethyl sulfoxide, reagent grade, Matheson, Coleman and Bell.

Nitrobenzene, reagent grade, Eastman Chemical.

Ethyl alcohol, reagent grade, available from the stockroom.

Propanol, reagent grade, Eastman Chemical.

## Apparatus

Corning expanded scale pH meter #12 equipped with a glass electrode and a fiber-type calomel.

Burets, 10 ml. and 25 ml. (Pyrex).

Pipets, 5, 10 and 25 ml. (Pyrex).

Culture tubes 25 x 200 and 15 x 125 cm. (Pyrex) were drawn into ampoules and sealed with an oxygen torch after addition of the reaction mixture.

Magnetic stirrer and bar.

Oil bath equipped with thermoregulator. Estimated precision about  $\pm 0.2^{\circ}$  C at  $100^{\circ}$  C.

## EXPERIMENTAL

## Procedures

Procedures for the determination of fast reacting halides

Procedure 1a: Weigh two millimoles of the sample in a weighing bottle. Transfer the sample to a 35 x 200 mm. ampoule with DMSO or to a convenient container if the halide is not volatile at 100° C. Add about 5 ml. of 1 N potassium hydroxide and DMSO to a total volume of 30 ml. Seal the ampoule and place in a steam bath or a beaker of boiling water. After the reaction is complete, remove the ampoule or flask, cool, transfer the contents into a 100 ml. beaker with distilled water and acidify with concentrated nitric acid. Pipet 20 ml. of standardized 0.20 N silver nitrate. Shake with 10 ml of nitrobenzene to coagulate the silver chloride if chloride is being determined. Add 2 ml. of 10% ferric nitrate solution and titrate with standard potassium thiocyanate (0.40 N) to the light orange endpoint.

Procedure 1b: Titrate the excess base after reaction to the phenolphthalein endpoint with 0.20 N hydrochloric acid. This method requires that the base and acid be standardized. A blank should be run under the same conditions and is usually less than 0.1 ml. of 0.20 N hydrochloric acid. The acid-base titration can also be done using a potentiometric method.

metric titration. This is especially necessary for aromatic halides, which give colored solutions with base and DMSO.

Procedure #2 for the determination of slow reacting halides

This procedure is necessary for most organic chlorides. A huge excess, 5 ml. of 40% potassium hydroxide, is mixed with two millimoles of halide and 25 ml. of DMSO in an ampoule, forming a two phase solution. The ampoule is sealed and reacted at 100° C. After completion of the reaction, the contents are diluted with water and acidified. The halide ion is then determined by the Volhard procedure.

Effect of Solvent

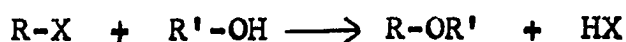
To demonstrate the superiority of DMSO as a solvent, the rates of several halides with base in DMSO were compared with the rates in alcoholic solvents under the same conditions. For these studies, one millimole of halide was reacted with 5 ml. of 0.50 N potassium hydroxide and 25 ml. of solvent in an ampoule. The ampoule was placed on a steam bath for ten minutes, cooled, diluted with distilled water, and the excess base titrated with 0.10 N hydrochloric acid. For comparison purposes, the time for the reaction to proceed ten half-lives (99.9%) was calculated from the percent reaction after ten minutes.

In general, DMSO was found to be a faster solvent for the reaction. The similar times for tert-butyl chloride in DMSO and alcoholic solvents may be due to a solvolysis

Table 16. Solvent effects in the reaction of organic chlorides with base. Time for 99.9% reaction at 100° C

Compound	<u>Solvent</u>		
	DMSO	Ethanol	n-Propanol
n-butyl chloride	96 min.	960 min.	900 min.
sec-butyl chloride	120 min.	480 min.	470 min.
tert-butyl chloride	18 min.	30 min.	28 min.

reaction with the alcohols which is not possible with DMSO:



#### Analysis of Halides

##### Aliphatic halides

The quantitative results for the analysis of some aliphatic halides are given in Table 17. The procedure refers to procedures mentioned earlier for fast and slow reacting halides. In all cases, the Volhard method is used.

In general, 30 minutes is sufficient for most aliphatic halides except extremely hindered primary and secondary halides which may require longer heating periods.

##### Polyhalides

The halides (one to two millimoles) were reacted with 5 ml. of 1 N potassium hydroxide in 25 ml. of DMSO. The halide ion formed was determined. The percent reaction in

Table 17. Hydrolysis of aliphatic halides at 100° C and analysis by the Volhard procedure

Compound	Reaction time	Procedure	Percent reaction <sup>a</sup>
n-butyl chloride	20 min.	2	98.7 ± 0.1
n-butyl bromide	10 min.	1b	99.2 ± 0.2
n-butyl iodide	5 min.	1a	98.6 ± 0.2
sec-butyl chloride	30 min.	2	96.5 ± 0.5
cyclohexyl chloride	60 min.	2	99.4 ± 0.6
benzyl chloride	10 min.	1a	100.5 ± 0.5
isopropyl bromide	10 min.	1a	99.2 ± 0.2
tert-butyl bromide	5 min.	1a	98.5 ± 0.5

<sup>a</sup>Average of two or more determinations.

Table 18. Hydrolysis of polyhalides at 100° and analysis by the Volhard procedure

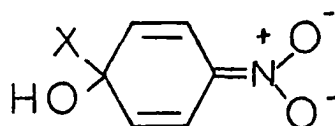
Compound	Reaction time	Percent reaction
1,3-dibromopropane	10 min.	98.7 ± 0.2
bromoform	15 min.	99.0 ± 0.3
methylene bromide	15 min.	99.2 ± 0.2
methylene iodide	5 min.	96.5 ± 0.5
1,2-dichloroethane <sup>a</sup>	30 min.	101.0 ± 0.5

<sup>a</sup>Potassium hydroxide (40%) was used.

Table 18 is based on all the halide atoms present in the molecule. As a comparison, Abdulla-Zade (58) used ethanolic potassium hydroxide at 125° C for two hours to determine dichloroethane. The present method requires only thirty minutes at 100° C.

### Aromatic halides

The unsubstituted halides; chlorobenzene, bromobenzene and iodobenzene, were treated with 5 ml. of 40% potassium hydroxide in DMSO for one hour at 120° C and no halide ion was produced. Substituted nitroaromatics reacted with base and DMSO to produce a dark color, usually orange or deep red. This is due to the formation of a Meisenheimer adduct.



This color often persisted even after acidification and made visual titrations impossible, and thus a potentiometric acid-base titration was used. The conditions were 5 ml. of 0.995 N potassium hydroxide, one millimole of halide and 25 ml of DMSO. Nitro-substituted aromatic halides can thus be determined in an hour or less. Unsubstituted halides are quite unreactive under hydrolysis conditions.

### Rate studies

In order to predict the feasibility of determining one organic halide in a mixture, rate studies were needed. Rates were run in volumetric flasks or sealed 15 x 125 mm. ampoules,



Table 19. Determination of aromatic halides after reaction at 100° C by an acid-base titration with 0.214 N hydrochloric acid (Procedure 1b)

Compound	Reaction time	Percent reaction
2,4-dinitrochlorobenzene	instantaneous	99.5 ± 0.5
p-fluoronitrobenzene	1.0 hr.	99.0 ± 1.0
p-chloronitrobenzene	45 min.	98.0 ± 1.0
o-chloronitrobenzene	1.0 hr.	99.0 ± 0.3
2-bromopyridine	6.0 hr.	95.0 ± 0.5

depending on the volatility of the halide. Four millimoles of halide were mixed with 10 ml. of 0.995 N potassium hydroxide and diluted to 50 ml. with DMSO thermostated at the temperature of the constant temperature bath. At appropriate intervals 5 ml. aliquots were taken with an automatic pipet and added to 50 ml. of cold acidified distilled water to quench the reaction. The halide ion was then determined by the Volhard procedure. A typical run is shown in Table 20.

Second order rate constants ( $k$ ) were calculated from the following equation:

$$kt = \frac{1}{(B_0 - A_0)} 2.3 \log \frac{(B_t)(A_0)}{(B_0)(A_t)}$$

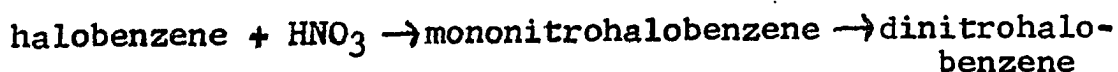
where B is hydroxide ion, A is organic halide, t is time in seconds, and the subscripts o and t correspond to the con-

Table 20. Rate of reaction of n-butyl iodide with base in DMSO at 55.5° C

Time (sec.)	Titre	Percent reaction
0.00	15.7	53.7
45	14.2	72.5
90	13.4	82.5
150	13.0	87.5
200	12.8	90.0
1200	12.2	97.5

centrations at time zero and time t. Semilogarithmic plots of the log term on the right side of the equation vs. time gave straight lines whose slopes were used to calculate the second order rate constants. Such a plot is seen in Figure 8 for n-butyl iodide. In Table 21 are listed the rate constants for some alkyl halides. From the relative rates, it should be possible to determine binary mixtures of the above compounds using differential rate methods.

Crude rate runs were done for some nitro-substituted aromatic halides at 55.5° C. The results are described in Table 22. From these data, the following reaction mixture can be completely analyzed:



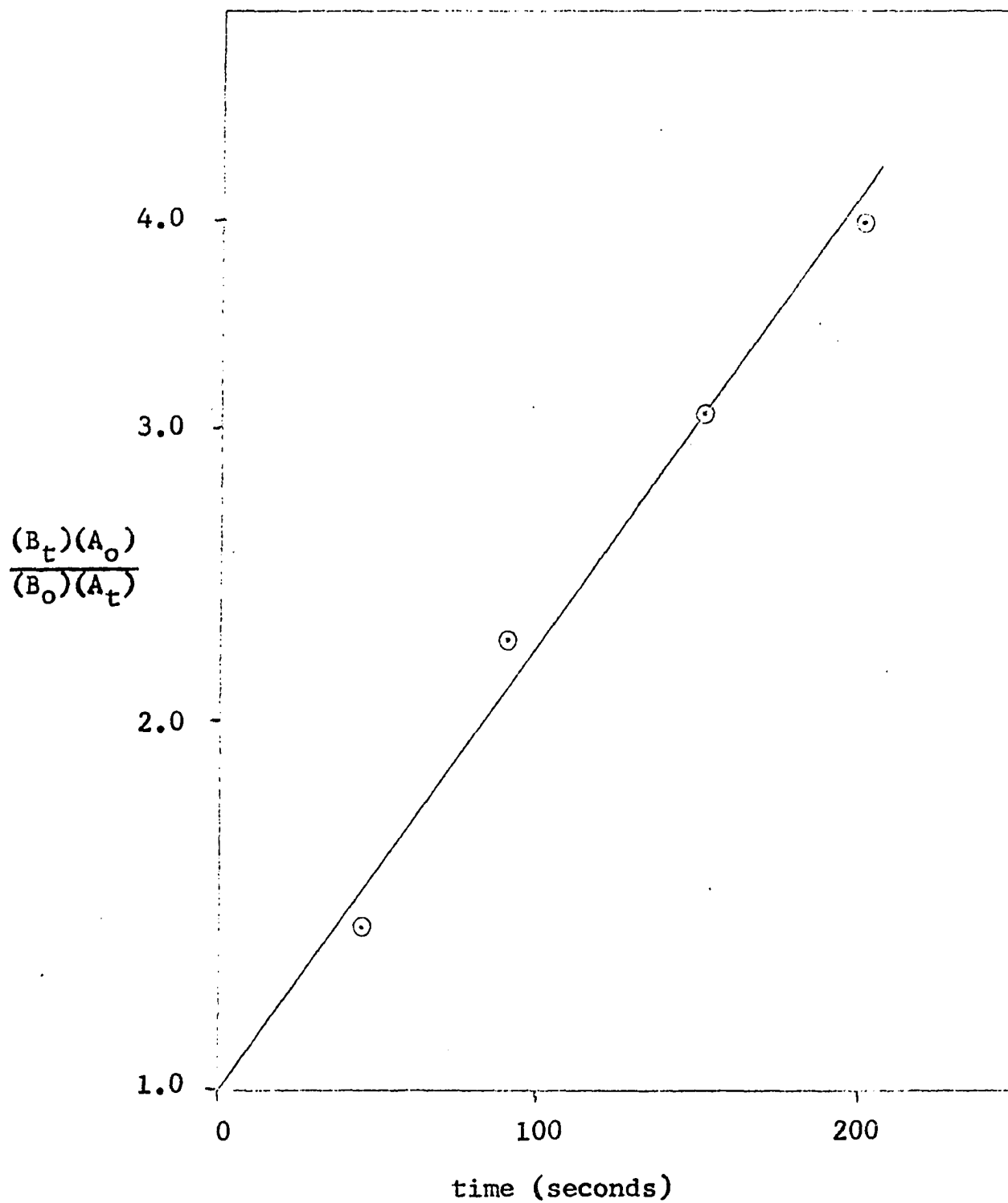


Figure 8. Semilog plot of  $\frac{(B_t)(A_o)}{(B_o)(A_t)}$  vs. time in seconds for the reaction of hydroxide ion with n-butyl iodide in a mixture of DMSO and water at 55.5° C.

Table 21. Second order rate constants for the reaction of base with butyl halides in DMSO at 55.5° C

Compound	k (l.-m. <sup>-1</sup> -sec. <sup>-1</sup> )	Relative rates
n-butyl chloride	1.68 x 10 <sup>-5</sup>	1
n-butyl bromide	1.44 x 10 <sup>-4</sup>	38.4
n-butyl iodide	3.94 x 10 <sup>-3</sup>	235

Table 22. Times for complete reaction of some nitro-substituted aromatic halides as determined by potentiometric acid-base titration

Compound	Time for complete reaction	Percent reaction
p-nitrochlorobenzene	4 hr.	97.7
p-nitrofluorobenzene	1 hr.	98.5
2,4-dinitrochlorobenzene	instantaneous	100.0

The mononitrohalobenzene can be analyzed in the presence of halobenzene because the latter does not react with base in DMSO. Dinitrohalobenzene can be analyzed in the presence of the mono-nitro compound because the former reacts much faster than the latter.

#### Analysis of mixtures

Synthetic binary mixtures were made from one millimole

Table 23. Analysis of binary mixtures after reaction with base in DMSO

Compounds	Reaction conditions and procedure	Percent reaction
chlorobenzene p-nitrochlorobenzene	45 min. at 100° C Procedure 2	99.2 of nitro
p-nitrochlorobenzene 2,4-dinitrochlorobenzene	room temperature Procedure 1b	100.7 ± 0.1 <sup>a</sup> of dinitro
1-bromo ethylbenzene 2-bromo ethylbenzene	ice temperature 1 min. Procedure 1a	98.0 ± 0.5 <sup>a</sup> of benzylic bromide

<sup>a</sup>Average of two determinations.

of each compound. The results are recorded in Table 23.

### Interferences

Any functional group that reacts rapidly with base in DMSO will interfere in the procedure which titrates the excess base. From a previous study (59), the following were found to react with base in DMSO: esters and aldehydes with alpha-hydrogens. Also any acidic compounds will react with the base. However, if the Volhard procedure is used, there are no interferences except with mixtures of halides.

## SUMMARY

The hydrolysis of organic halides with base in the solvent DMSO has been studied. The superiority of DMSO over alcoholic solvents has been demonstrated by rate studies. Two procedures have been developed for the analysis of halides. Halides which rapidly react such as bromides and iodides, as well as polyhalides, can be conveniently analyzed in thirty minutes or less using 1 N base and DMSO at 100° C. The halide ion produced is then titrated using the Volhard method. Slow reacting halides such as chlorides, can be analyzed by reaction with 40% potassium hydroxide in DMSO and use of the Volhard method. Aromatic halides substituted with nitro groups may be analyzed by reaction with standard 1 N base in an hour or less at 100° C. The excess base is titrated potentiometrically with standard acid.

Rate studies showed the feasibility of determining mixtures either by differential kinetics or by the complete reaction of one halide in the presence of another. This last method proved successful with three synthetic mixtures.

In summary, the method described has been shown to be a simple, fast, widely applicable, selective method for the determination of organic halides.

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