The Relative Nucleophilicities Of Several Sodium Alkoxides.

Citation

PETFIELD, ROBERT JOSEPH. *The Relative Nucleophilicities Of Several Sodium Alkoxides.* 1959, https://preserve.lehigh.edu/lehigh-scholarship/graduate-publications-theses-dissertations/theses-dissertations/relative-4.

PETFIELD, Robert Joseph. THE RELATIVE
NUCLEOPHILICITIES OF SEVERAL SODIUM
ALKOXIDES.

Lehigh University, Ph.D., 1959
Chemistry, organic

University Microfilms, Inc., Ann Arbor, Michigan

THE RELATIVE NUCLEOPHILICITIES
OF SEVERAL SODIUM ALKOXIDES

By

Robert Joseph Petfield

A DISSERTATION
Presented to the Graduate Faculty
of Lehigh University
in Candidacy for the Degree of
Doctor of Philosophy

Lehigh University
1959

This dissertation is respectfully submitted to the Graduate Faculty of Lehigh University, in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

Robert Joseph Petfield
Robert Joseph Petfield

Approved and recommended for acceptance as a dissertation in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

May 28, 1959
Date

E D Amstutz
Professor in Charge

Accepted May 19, 1959
Date

Special committee directing the doctoral work of Mr. Robert Joseph Petfield

E D Amstutz Chairman

Delmer B. Fish

James E. Sturm

Thomas E. Young

ACKNOWLEDGEMENTS

The author wishes to express his appreciation for the assistance given him in the preparation of this dissertation. For every contribution he is sincerely grateful.

He is indebted to Dr. E. D. Amstutz for his proposal of the original problem, for his judicious advice, and for his constructive criticism of the present results. He is also appreciative of the help afforded by the members of his Special Committee and several members of the Graduate Faculty. He is indebted to the Althouse Chemical Company and the Armstrong Cork Company for their financial aid in sponsoring this academic research.

He is deeply grateful to his loving and devoted wife, to the members of his family, to his instructors, friends, and fellow graduate students for their encouragement and unabated interest while pursuing his education.

Table of Contents

Table of Contents

List of Figures

Page

List of Tables

INTRODUCTION

The Usefulness of Nucleophilic Substitution
in
Organic Chemistry

Aromatic nucleophilic substitution has been known since 1854 (1). This type of reaction has found general utility in synthetic organic chemistry. Prior to the present decade only scattered attention has been devoted to relating structure to mechanisms and reactivity. Since 1949, in this laboratory, Amstutz et.al., (2-9) have worked on the measurements of the rates of nucleophilic substitution employing heterocyclic aromatic halides as substrates. About 1950 active research was initiated in several laboratories inorder to provide the necessary data for theoretical interpretation. In 1951 Bunnett and Zahler (10) undertook a comprehensive review of existing kinetic data on nucleophilic reactions. In the same year a shorter review was published by Miller (11). Recently a second review article by Bunnett (12) was published which is primarily concerned with the mechanisms of nucleophilic substitution in benzenoid substrates.

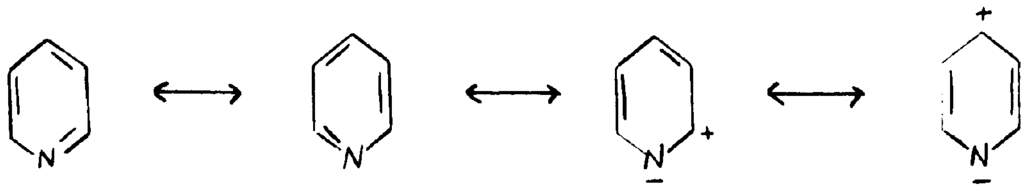
Selectivity is probably the greatest single advantage of nucleophilic reagents. The effective form of the reagents is generally obvious. Anions or un-charged basic molecules are employed. The groups readily displaced are those which can depart with the bonding electron pair as stable anions or neutral molecules. These leaving groups may be located at virtually any position on an aromatic nucleus limited, or course, by the synthetic art of the chemist. With few exceptions reaction is confined to only one position.

Nucleophilic substitution reactions are strongly dependent on the assistance of activating groups. As a result much attention is devoted to establishing the relative activating power of substituent groups. These effects are measured by observing changes in the reaction rates as the groups are varied.

Nucleophilic substitution reactions have a practical advantage in that well known analytical methods are available for estimating quantitatively the group being displaced. For example, if the group is halogen, the reaction can be followed by titrating the halide ion with standard silver nitrate. Almost without exception is it necessary to choose a substituent yielding an anion for which well-defined analytical methods are not available.

Structural Analysis of Pyridine

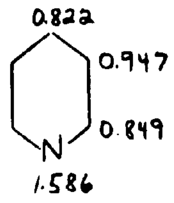
For a detailed review of the classical structural assignments employed for pyridine the reader is referred to the treatment given by Mosher (13). The existence of only one known isomer of any α-substituted pyridine derivative is accomodated by the theory of resonance. This theory also rationalizes a much broader field, that of the differences in chemical behavior of the 2-and 4-positions compared to the 3-position in pyridine. The major contributing states, structures I and II and the activated states, structures III and IV sufficiently explain the reactions of pyridine.



I   II   III   IV

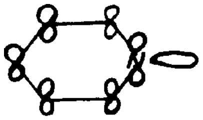
There is evidence for the existence of the polar forms III and IV since pyridine has been shown to have a large dipole moment, 2.20D(14).

A more modern interpretation for the behavior of pyridine is offered by the Molecular Orbital Theory. This theory has led to the calculation of the π electron density distributions (15) given in structure V.



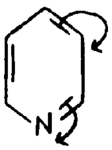
V

The sum of the electron densities equals the total number of π electrons in the molecule. Thus the greater electron density at the 3-position compared to the 2-and 4-positions accounts for the observed orientations in substitution reactions in general. The orbital picture of pyridine is produced in structure VI.

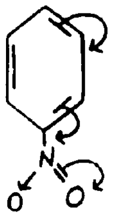


VI

The above discussion leads to an interesting analogy of pyridine to nitrobenzene pointed out by Sidgwick (16). This resemblance is obvious by inspecting their respective structural formulae VII and VIII.



VII



VIII

The strong mesomeric attraction of electrons by the nitro group causes a displacement of the π electrons so as to make the ortho-and para-positions centers of partial positive charge. For pyridine the nitrogen atom in the ring is responsible for a similar withdraw from the π electrons. This causes partial positive centers to be located at the α and γ positions. This useful concept serves to accomodate many of the observed reactivity characteristics of both nitrobenzene and pyridine. As an example, nitrobenzene when fused with potassium hydroxide at 60-70° gives up to 50% of ortho-nitrophenol (17). Pyridine when heated at 300-320° with potassium or barium hydroxide yields 2-hydroxypyridine (18), more appropriately called 2-pyridone.

This analogy appears to have certain limitations since Bergstrom (19) reports an unsuccessful attempt to prepare ortho-nitroaniline by reaction of nitrobenzene with sodium amide whereas 2-aminopyridine is prepared by the above reaction (20). In this present work it was observed that concurrent with replacement of halide by sodium propoxide and allyloxide that reduction of the nitro group was taking place which was reflected in a very sharp decrease in reaction rate.

At this point it may be understood why 2-bromopyridine was chosen as the electrophilic substrate for studying the relative reactivities of some sodium alkoxides. If the analogy given above be true then one would expect 2-bromopyridine to have halogen reactivity similar to ortho-nitrobromobenzene. The literature available records the validity of this statement (10). The bromine atom in ortho-nitrobromobenzene is vinylogous with the acid bromide of nitric acid which accounts for its reactivity with electron donating reagents.

In the case of 2-bromopyridine the carbon atom to which the bromine atom is attached is isoelectronic with the carbon atom of an acyl bromide. This system also imparts a high degree of reactivity towards reagents bearing a formal negative charge or having an unshared electron pair as in neutral molecules such as piperidine or ammonia.

Some Uses of Alkoxide Ions in Nucleophilic Reactions

Alkali metal alkoxides have long been employed in the preparation of aryl or alkyl ethers in synthetic organic chemistry. Phenoxide ion in replacing chloride ion in chlorobenzene gives rise to a side reaction product, diphenyl ether, in a commercial synthesis of phenol. When an unactivated aromatic halide is employed in conjunction with an alkoxide ion the reaction is often accompanied by a reductive removal of halogen. Thus, bromobenzene and sodium methoxide in methanol react incompletely at 200° forming anisole, phenol, and benzene (21). Paradibromobenzene with sodium ethoxide affords benzene, bromobenzene, and phenetol (22). If an activating substituent is present as in the cases of ortho-and para-nitrobromobenzenes they react smoothly with sodium alkoxides even though water is present as the solvent. Bevan (23) has employed p-halonitrobenzenes with ethoxide for a kinetic investigation.

When several activating groups are present in the ortho and para position of an aryl halide reaction may occur with the alcohol itself. This usually requires the presence of a mild basic catalyst such as pyridine or triethylamine and somewhat on the nature of the halogen atom. For example, 2,4-dinitrofluorobenzene has been recommended as a reagent for the preparation of crystalline ethers to serve as derivatives for the alcohols employed (24).

In the heterocyclic aromatic series, 2-bromopyridine has been employed in the preparation of 2-benzyloxypyridine (25) and 2-propoxypyridine (26) by reaction with the appropriate alkoxide.

Several alkoxides have been employed with the more reactive compound 2-chloro-5-nitropyridine (27). Ethers from 2-and 4-chloroquinoline have also been similarly prepared (28,29). In this laboratory several ethers of furan have been prepared (8,9) which have led to some interesting deductions concerning the reactivities of halo-furan. Sice' has also reported the preparation of 2-methoxythiophene (30).

The Nature of the Transition State

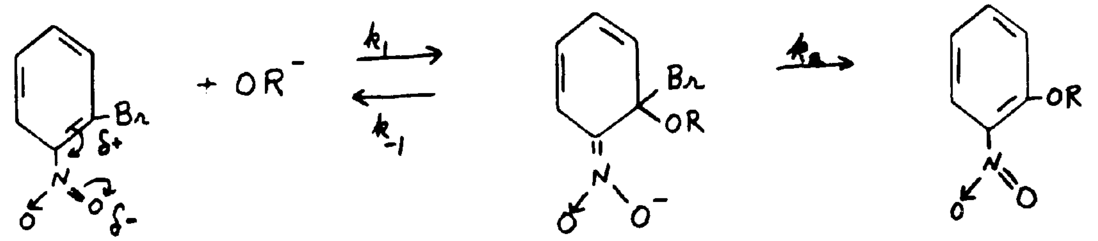
The great majority of aromatic nucleophilic **substitution reactions** which have been made the object of kinetic investigations generally fit the second order rate equation. This is evident due to the strong dependence of reactivity on the nature of the nucleophilic reagent while the solvent and general character of the environment remain the same. The substituents which facilitate the reaction are of such a nature that they withdraw electrons from the site of reaction. Reactions which are explained by the SN_1 mechanism generally require a displacement of electrons to the site of the leaving group inorder to proceed.

It should be pointed out that the SN_1 mechanism is applicable in some instances of aromatic nucleophilic substitution. For example, it is well established in the case of the thermal decomposition of aromatic diazonium cations in aqueous solution. Mechanistically, this ion splits out a molecule of nitrogen yielding an aryl cation which can react with solvent or anions present in solution. A necessary but not sufficient argument for the SN_1 mechanism in this example is the fact that the reaction is kinetically first order. More decisive is the fact that the rate of the reaction is independent of the nature or concentration of metal halide salts (31). At high concentrations of such salts the product is to a large extent the aryl halide (32).

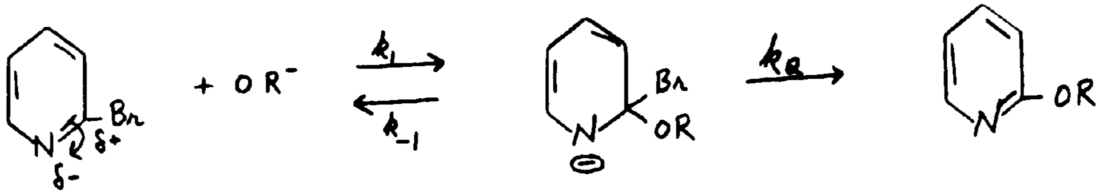
After the establishment of the SN_2 mechanism of substitution at saturated carbon atoms by Hughes, Ingold, and their co-workers (33) it was frequently assumed that bimolecular aromatic nucleophilic substitution occurs by an analogous one-step mechanism of synchronous bond-formation and bond-breaking.

An alternative two-step, intermediate complex mechanism was first forcefully advocated by Bunnett and Zahler (10). They showed that one-step, SN_2 like substitution at an aromatic carbon atom was quantum mechanically improbable, while the intermediate complex mechanism was not only acceptable in this regard but was supported by significant analogies with other phenomena. The formation of isolable adducts by interaction of nucleophilic reagents with highly activated aromatic electrophilic substrates supports the intermediate complex theory. **Meisenheimer** (34) showed that the addition of methoxide ion to 2,4,6-trinitrophenetole gave the same adduct as the addition of ethoxide ion to 2,4,6-trinitroanisole. For unactivated aromatic systems the complex might only have a transitory existence and hence defy isolation.

Ortho-nitrobromobenzene and 2-bromopyridine have similar reactivity characteristics. The permanent polarization existing in the ground states are less important than the electromeric displacements in the transition states. The transition states as well as a mechanism are presented by the following structures:



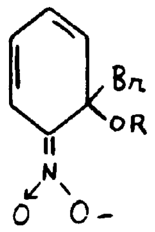
IX X XI



XII XIII XIV

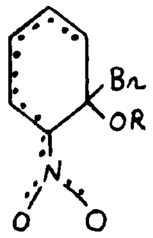
This mechanism accomodates several facts concerning aromatic nucleophilic substitution whereby an activating structural feature or substituent is present. The molecularity of the reaction is consistent with the proposed mechanism in that the reactants combine in a stoichiometric ratio of one to one. This accounts for a bimolecular reaction and following the second order rate equation. The mechanism accomodates the proposal that an equilibrium exists between reacting molecules and the activated complex. This activated complex may then pass on to an intermediate state often times depicted as a "saddle" on an energy versus reaction coordinate diagram. Since the present work gives no evidence for an isolable adduct involving the coordination of reactants, the transition state is only capable to transient existence. The mechanism says nothing about the relative magnitudes of k_1, k_{-1}, and k_2 and is not intended to do so. The only statements which are justifiable are that if $k_2 \gg k_{-1}$ then the rate of the formation of the transition state complex is rate determining whereas if $k_{-1} \gg k_2$ then the rate is dependent upon the equilibrium concentration of the complex and on k_2.

The manner in which the transition state is shown reveals that in one case that the negative charge is borne exclusively by oxygen of the nitro group and in the other case by the nitrogen atom of the pyridine ring. This treatment may be inadequate. Therefore, other canonical forms of resonating anions can be drawn to minimize this apparent over-emphais on the part of the theorist.

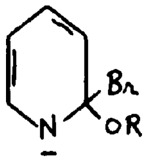


XV

⟷

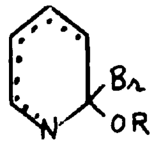


XVI



XVII

⟷



XVIII

The apparent over-emphasis may be warranted. In the case of ortho-nitro-bromobenzene the bulk of the negative charge is probably borne by the two oxygen atoms of the nitro group due to their electron attracting power. For 2-bromopyridine, the ring nitrogen acts analogously. Thus the mechanism accounts for the activating effect by electron withdrawing groups. Since the relative contributions of several possible resonating anions are not known quantitatively they all may be said to contribute to one structure, that of a hybrid.

DISCUSSION OF RESULTS

The Relative Nucleophilicities of Several Sodium Alkoxides

Introductory Remarks

The purpose of the research described herein has been to measure the rates of nucleophilic substitution reactions of a variety of sodium alkoxides with 2-bromopyridine. Recently, Manly and Amstutz (35) reported the preparation of several 2-furyl ethers. An example of the reaction sequence employed was to react an alkyl 5-bromo-2-furoate with the corresponding sodium alkoxide in the presence of the same alcohol as solvent. Saponification of the alkyl 5-alkoxy-2-furoate followed by decarboxylation afforded the 2-alkoxyfuran. When sodium allyloxide in allyl alcohol was employed under similar conditions, there was no replacement of the halogen by allyloxide ion. Sodium 5-bromo-2-furoate was identified as the reaction product. It has since been shown that under anhydrous conditions in an inert atmosphere the same product is obtained (36). Mere traces of water detected when anhydrous allyl alcohol is treated with sodium and then recovered could not account for this apparent saponification.

It has been proposed by Seubold (37), on the basis of the infrared spectra of several alkoxide ions, that these ions may be resonance stabilized, i.e., their nucleophilicity reduced, by a process termed hydride-ion hyperconjugation.

It seemed to us that, if such an effect be real, it should be particularly noticeable in the case of the allyloxide ion. Thus this effect might serve to explain its failure to act as a nucleophilic reagent in the reaction with bromofuroic esters.

Therefore the purpose of the present work has been to systematically study the nucleophilicities of a sufficiently large group of alkoxide ions so that some conclusions may be drawn as to the extent and importance of hydride-ion hyperconjugation.

Saturated Alcohols and Their Corresponding Sodium Alkoxides.

There are several factors which influence the rate of a given reaction. Among these are temperature, concentration, catalysts, steric factors, solvation of all reacting species, and activating or deactivating effects in either or both of the reacting moieties. To compare the results obtained from a series of related compounds, some control over these variables must be exercised. All of the reactions studied were designed to have the same concentration within experimental error. Only one electrophilic substrate was employed i.e., 2-bromopyridine. Catalysis by the salt produced in these reactions can be ruled out since the second order rate constants are linear over the range employed in a given run within experimental error.

As a further simplification to the above factors the rates of reaction were calculated at one temperature, 100°C. The rates have all been measured in this vicinity. The calculated rate constants for the homologous series of alkoxides from methoxide to amyloxide and also for the alkoxide of cyclohexylcarbinal are produced in Table 1.

Table 1

RATE CONSTANTS FOR SATURATED ALKOXIDES

Parent Alcohol	k (1/m-hr)	Δ k (1/m-hr)
Methanol	0.1694	0.0
Ethanol	0.2238	0.0544
Propanol	0.3483	0.1245
Butanol	0.4153	0.0670
Pentanol	0.4878	0.0725
Cyclohexylcarbinol	0.5535	

Although the differences in the rate constants are within the same order of magnitude, the trend towards higher reactivity follows an increase in the molecular weight of the straight alkyl chain. Methoxide ion in methanol solution provides a less reactive nucleophilic reagent system then all its homologs. Cyclohexylcarbinol provides a nucleophilic reagent superior to all of the alcohols employed in this present work. Qualitatively, it has been observed that the alcohols which react most readily with sodium metal provide the least reactive alkoxide ions. This suggests a correlation of the above measured reactivity characteristics to the relative acidities of the alcohols.

Relative Acidities of Some Weak Acids.

The rate of the basic hydrolysis of chloroform is much slower in methanol than in water (38). This is also true for the formation of ethylene oxide from ethylene halohydrins (39) and the reverse aldolization of diacetone alcohol (40).

To accomodate these observations it was proposed by Hine and Hine (41) that methanol is more acidic than water. Hine and Hine measured the acidities of several weak acids using isopropoxide as the base and isopropyl alcohol as a point of reference. Their data are recorded in part in Table 2.

Table 2

RELATIVE ACIDTY OF SOME WEAK ACIDS

Compound	$K_e = \frac{[A^-]}{[HA][\text{i-propoxide}]}$
Isopropyl alcohol	0.076
Propanol	ca. 0.5
Butanol	ca. 0.6
Ethanol	0.95
Water	1.20
Allyl alcohol	2.7
Benzyl alcohol	3.8
Methanol	4.0

From these measurements methanol is seen to be slightly more than three times as acidic as water. This is in agreement with the data of Unmack (42) who concludes that methanol is three times as strong an acid as water measured cryoscopically and twice as strong from potentiometric measurements.

The observed decrease in acidity from methanol to propanol means that their conjugate bases, the alkoxide ions, become stronger anions. It would then be expected, to a first approximation, that the nucleophilic reactivity would increase in the same order.

This is the observation from the present work. Therefore both sets of data i.e., acidities of alcohols and nucleophilicities of alkoxide ions have some degree of correlation.

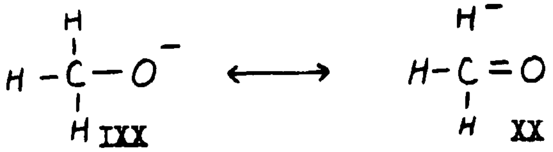
Solvent Participation in Nucleophilic Reactions.

It is a known fact that the reactivity of 2-bromopyridine is greatly enhanced by quaternization (43). Protonation has an analogous effect (44). The above data on relative acidities were determined with respect to a single strong base, iso-propoxide ion. The data presented herein were determined using the parent alcohol as the solvent for its corresponding sodium alkoxide. Therefore the presence and nature of the alcohol superimposes a variable on the present work. The measured reactivities result from the combined effects of the nucleophilic power of an alkoxide ion i.e. its basicity plus the acidic nature of the solvent. In other terms, a variable amphoteric system is present in the measurements in this work. Due to the insolubility of sodium methoxide in a non-participating solvent such as dioxane, the acid catalytic effect of added solvent could not be assayed. Inorder to test the possible participation of solvent, it is hoped that an alkoxide from a longer alkyl chain alcohol can be found whose solubility in dioxane is sufficient to permit its use in kinetic studies.

The Hydride-Ion Hyperconjugation Hypothesis

As a possible interpretation of the greater acidity of methanol compared to several other alcohols, it was proposed by Hine and Hine (41) that a type of resonance stabilization involving the hyperconjugation of a hydride-ion might be important.

This resonance stabilization is depicted in the following structures:



IXX XX

Inorder to put this proposed type of resonance stabilization on a firmer basis by means of a formal measurement, Seubold (37) undertook an investigation of the infrared spectra of several sodium alkoxides. These were compared with the spectra of the corresponding alcohols. The reasoning was that if an alkoxide ion could be stabilized by hyperconjugating a hydride ion then in the C-H stretching region a shift to lower frequency should be observed for the ion compared to its parent alcohol. Examination of the spectra for the two systems reveals that the predicted frequency shift does occur.

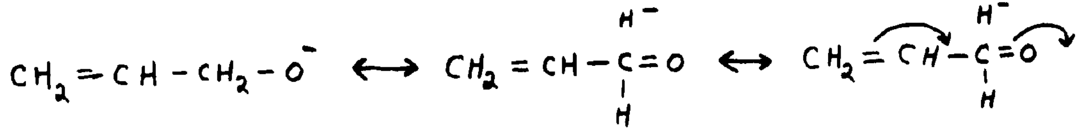
It was also predicted that a strengthening of the C-O bond should occur for the alkoxide ion relative to its parent alcohol. This latter effect would be manifested by a shift to higher frequency in the skeletal region, 1100-900 cms^{-1}. This was also found to be the case. It is necessary that the negatively charged ion be employed inorder to provide the necessary driving force for the above effects. The neutral alcohol would not be expected to produce this effect.

The hydride-ion hyperconjugation hypothesis accounts for the observed greater acidity of methanol compared to ethanol. Statistically, the methoxide ion can hyperconjugate three hydrogens as hydride ions whereas ethoxide is limited to only two such hydrogens.

In other words, methoxide ion has three equal resonance forms. Ethoxide has only two related forms. Therefore, methoxide ion should be less nucleophilic than ethoxide ion. This is supported by the present work. The above hypothesis cannot account for the decrease in acidity from ethanol to propanol. In the homologous series of saturated alcohols, with the exception of methanol, the alkoxide ions have the same number of resonance-stabilized forms. It would be expected that these alcohols should have equal acidities. It follows that the alkoxide ions should have equal nucleophilic power. Since the acidities are observed to decrease with molecular weight and the rates of nucleophilic substitution increase, the proposed hydride-ion hyperconjugation theory has severe limitations in applicability.

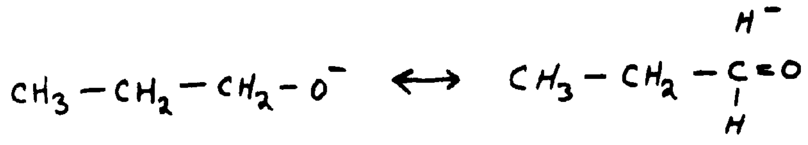
Unsaturated Alcohols and Their Sodium Alkoxides.

A priori it was expected that if the hydride ion hyperconjugation hypothesis be true and applicable then the allyoxide ion should be less reactive than the propoxide ion. The reason for this is that the hyperconjugated allyloxide ion contains an electronic system favorable for added resonance stabilization. This is shown in the following structures:



$$CH_2=CH-CH_2-O^- \longleftrightarrow CH_2=CH-\overset{H^-}{\underset{H}{C}}=O \longleftrightarrow CH_2=CH-\overset{H^-}{\underset{H}{C}}=O$$

XXI XXII XXIII



$$CH_3-CH_2-CH_2-O^- \longleftrightarrow CH_3-CH_2-\overset{H^-}{\underset{H}{C}}=O$$

XXIV XXV

A table of rate constants calculated for 100°C. for the various unsaturated alcohols is given below:

Table 3

RATE CONSTANTS FOR UNSATURATED ALKOXIDES

Parent Alcohol	k (1/m-hr)
Allyl	0.1071
Crotyl (trans)	0.2578
Benzyl	0.1310
3-Buten-1-ol	0.2356
4-Penten-1-ol	0.3574
2-Butyn-1-ol	0.0511

To facilitate comparisons, the rate constants have been divided by the value of k for allyloxide ion at 100°C. The values obtained are tabulated along with the various "thermodynamic" and kinetic functions calculable by the measurement of reaction rates over a range in temperature. These are all summarized in Table 4.

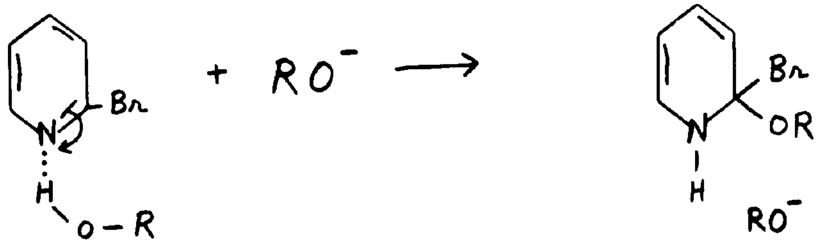
Table 4

REDUCED RATES, KINETIC AND "THERMODYNAMIC" PARAMETERS

Parent Alcohol	Reduced Rate	ΔE^* (K cals.)^1	ΔS^* (e.u.)^1	$\rho Z \times 10^{-14}$ (1/m-hr)
Methanol	1.58	26.5 ± .05	-9.76 ± .14	5.61
Ethanol	2.09	26.6 ± .15	-8.94 ± .40	8.48
Propanol	3.25	26.4 ± .2	-8.59 ± .55	10.1
Butanol	3.88	26.4 ± .15	-8.24 ± .40	12.0
Pentanol	4.56	26.5 ± .1	-7.66 ± .27	16.2
Cyclohexylcarbinol	5.17	26.0 ± .15	-8.74 ± .40	9.34
Allyl alcohol	1.0	27.6 ± .2	-7.72 ± .55	15.6
3-Buten-1-ol	2.10	27.5 ± .05	-6.42 ± .14	30.1
4-Penten-1-ol	3.33	26.8 ± .15	-7.47 ± .40	17.7
Crotyl alcohol	2.41	27.2 ± .2	-7.05 ± .55	22.0
Benzyl alcohol	1.23	28.6 ± .15	-4.91 ± .40	64.4
2-Butyn-1-ol	0.48	28.5 ± .15	-6.51 ± .40	28.7

1. Reported deviations are standard deviations.

The present work thus seems to be consistent with the prediction on the previous page, regarding the reactivities of allyloxide compared to propoxide. The difference in rate between allyloxide and propoxide is shown in Table 4 to be a factor of 3.25. The difference might be greater if both alcohols had equal acidities. By refering to Table 2 allyl alcohol is about 5.4 times as acidic as propanol. Acid catalysis by solvent could be more important for allyl alcohol than propanol. This effect can be shown by the following structures.



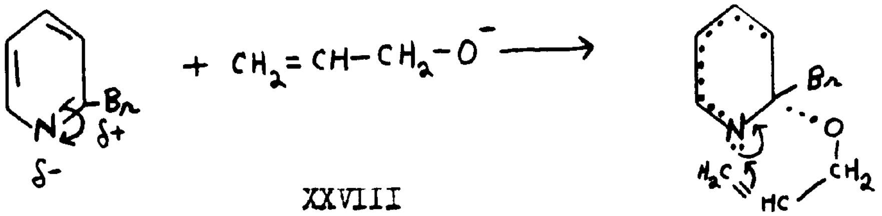
XXVI XXVII

Base-Catalyzed Deactivation

With reference to Table 4, it can be seen that each unsaturated alcohol is less reactive than its saturated counterpart. This has been pointed out for allyl alcohol versus propanol. Crotyl alcohol, 3-buten-1-ol, and 2-butyn-1-ol are less reactive than butanol. Benzyl alcohol is considerably slower in reaction than cyclohexylcarbinol and 4-penten-1-ol is slower than pentanol.

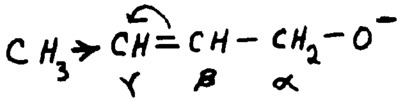
It is a known fact that a double bond is an electron donating system i.e. it is a basic center. This effect would be a deactivating influence for nucleophilic substitution.

The mechanism whereby this effect operates can be shown by examining the following structures.



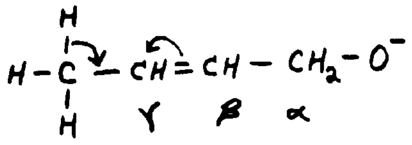
XXVIII

Thus, as the allyloxide ion approaches the polarized molecule of 2-bromopyridine, the double bond is polarized in such a way as to diminish the reactivity of 2-bromopyridine. This effect would be termed base-catalyzed deactivation which is the reverse of acid-catalyzed activation caused by the protonation by solvent. This deactivating effect would be most significant in the cases where the unsaturated linkage is located β - γ and in structures which permit the accumulation of electrons at the γ -carbon. The reason for this is that the geometry is favorable for the formation of a quasi six-membered ring. Crotyl alcohol would be expected to function similarly. Since crotyl alcohol is more than twice as reactive as allyl alcohol, this suggests that the terminal methyl group opposes the base-catalyzed deactivation. This is apparent when the following structures are examined.



$$CH_3 \rightarrow \underset{\gamma}{\overset{\curvearrowleft}{CH}} = \underset{\beta}{CH} - \underset{\alpha}{CH_2} - O^-$$

XXIX

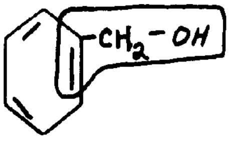


$$H-\overset{H}{\underset{H}{C}} \rightarrow \underset{\gamma}{\overset{\curvearrowleft}{CH}} = \underset{\beta}{CH} - \underset{\alpha}{CH_2} - O^-$$

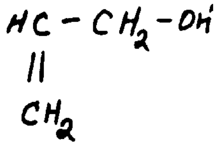
XXX

Thus, the methyl group, by inductive displacement and/or proton hyperconjugation, counteracts the polarization of the double bond towards the γ -carbon.

Benzyl alcohol, in which the β-γ unsaturated linkage is part of a resonating system, is much slower in rate than cyclohexylcarbinol. Benzyl alcohol has an electronic system related to allyl alcohol. This can be shown by the following structures.



XXXI



$$\begin{array}{l} HC-CH_2-OH \\ \| \\ CH_2 \end{array}$$

XXXII

Therefore benzyl alcohol would also be expected to participate in the base-catalyzed deactivation. The alcohol having the lowest nucleophilicity of those measured is 2-butyn-1-ol. The presence of the triple bond located in the β-γ position suggests a strong base-catalyzed deactivation.

Additional support for the deactivation mentioned above comes from a consideration of the values of k obtained from the alcohols whose multiple link is located more remote than β-γ . Two such cases were investigated, 3-buten-1-ol where the multiple linkage is γ-δ and 4-penten-1-ol where the double bond is δ-ϵ . It is observed that these alcohols are slower in rate than their saturated counterparts. Thus, when the unsaturated linkage is located beyond the point where a quasi six-membered ring can be established, the effectiveness of base-catalyzed deactivation diminishes.

From Table 2 the relative acidities are in the order methanol > benzyl alcohol > allyl alcohol.

Their conjugate bases would then have the following order of basicity: allyloxide > benzyloxide > methoxide. The observed range in nucleophilicities, although small in extent, is the reverse of this latter sequence. As mentioned above with variable amphoteric systems, the basicity of the anion coupled with solvent acid-catalysis could contribute to different degrees of reactivity. In the above series, it appears that acid catalysis is important.

"Thermodynamic" and Kinetic Parameters.

With reference to Table 4 the limits of standard deviation for several of the values of ΔE^* restrict the discussion of this parameter to groups of alcohols. Thus, ΔE^* is essentially constant for the alcohols methanol to pentanol. Consequently, an energy barrier of equal magnitude exists for these reactions. This does not imply that the reactions are proceeding from identical ground states to identical activated states but only that the energy difference between the two states is equal. For the same group of alcohols, the general trend towards a higher positive entropy of activation as well as the increase in the pZ factor indicates that with constant ΔE^*, the rate increase, with molecular weight, is caused by a more favorable activated complex. As the alkoxide ions become larger in chain length their corresponding alcohols, by steric interaction, become less efficient in solvating the ionic species. This decreasing solvating ability of the alcohols then makes their alkoxide ions more efficient nucleophilic reagents.

In other words, the methanol solvent "cage" surrounding the methoxide ion is more effective in diminishing its reactivity than that of pentanol solvating the pentanoxide ion. Table 4 shows cyclohexylcarbinol to have the lowest ΔE^* value which can account for its having the fastest rate of the saturated alcohols.

As a generalization, the unsaturated alkoxides yield higher ΔE^* values than their corresponding saturated counterparts. Allyloxide ion as stated above is less reactive than propoxide. Table 4 shows that the ΔE^* is about 1 K cal. higher for allyloxide compared to propoxide. The ΔS^* values for this same pair are nearly the same due to the limits of precision. Therefore the faster rate for propoxide is dependent upon ΔE^*. Base-catalyzed deactivation in allyloxide could account for this result, since each ion could be solvated to essentially the same degree.

Three of the unsaturated alcohols have terminal double bonds. These are allyl alcohol, 3-buten-1-ol, and 4-penten-1-ol. The ΔE^* values obtained from the first two alcohols are equal. The rate increase from allyl alcohol to 3-buten-1-ol is ΔS^* dependent since the latter has the more positive value. The third member in this series has the fastest rate but a lower ΔE^* value. Since ΔS^* obtained from 4-penten-1-ol shows a trend towards a less probable activated state, the rate increase is ΔE^* dependent. It can also be seen that 4-penten-1-ol has a ΔS^* value almost equal to its saturated counterpart, pentanol. These same two alcohols are related also in the values for ΔE^*. It is not apparent why the rates for these same two alcohols are different although the slight difference in the most probable values for ΔE^* can account for this discrepancy.

Table 4 reveals that crotyl alcohol is about 2.4 times as reactive as allyl alcohol. Here again the slight difference in the most probable value for ΔE^* can account for the difference in rate since the ΔS^* values overlap in precision.

Cyclohexylcarbinol and benzyl alcohol might be expected to be solvated to the same degree due to their approximately equal size although cyclohexylcarbinol is slightly larger. Since ΔE^* is about 2.5 K cals. higher for benzyl alcohol and the ΔS^* value is more positive, the rate of reaction is ΔE^* dependent. The possibility remains that benzyl alcohol is the less solvated of the two. The possibility also remains that the rigidly planar structure of the benzyl alcohol provides a more efficient structural feature which enhances its reactivity compared to cyclohexylcarbinol which can pass through different conformations.

The least reactive alcohol 2-butyn-1-ol has an ΔE^* value equal to benzyl alcohol. This aliphatic alcohol should be capable of solvating more so than benzyl alcohol. Therefore the lower reactivity and the lower i.e. more negative ΔS^* value are accomodated.

As a further test of the hydride-ion hyperconjugation hypothesis an experiment of a totally different kind was attempted. Aluminum allyloxide in allyl alcohol was employed in the Meerweim - Ponndorf-Verley reduction. Benzophenone was used as the oxidizing agent sinceit is known to participate in this carbinol-carbonyl equilibrium reaction (45). It was hoped that this might afford a chemical means whereby the hyperconjugated hydride-ion might be trapped.

Under conditions more forcing than that generally employed, there was no acrolein formed. Necessary and sufficient for the non-participation of allyloxide ion was the observation that benzophenone was recovered nearly quantitatively.

Conclusions

The hydride-ion hyperconjugation hypothesis appears to offer an explanation for the frequency shifts observed in the infrared spectra of some alkoxide ions. The theory accounts for the greater acidity of methanol versus ethanol since the methoxide ion can statistically hyperconjugate three hydride ions whereas ethoxide is limited to two hydrogens capable of being hyperconjugated. The theory does not explain the decrease in acidity to ethanol to propanol since the same number of resonance forms can be written for both their alkoxide ions. For the unsaturated alcohols, the same number of hyperconjugated resonance forms can be written. Inorder to explain the lower reactivities of the unsaturated alkoxides compared to their saturated counterparts, two possible explanations are offered. First, either the β-γ multiple bond interacts with the polarized molecule of 2-bromopyridine so as to diminish the ground state activation or, second, an electronically favorable system is present in the hydride-ion hyperconjugated resonance forms. With the multiple bond more remote on the alkyl chain than β-γ, both of the above effects would be expected to diminish.

An additional effect which diminishes reactivity is the extent of solvation of alkoxide ions. As the molecular weight of the alkyl chain increases, the alkoxide ions are less effectively screened by the solvent "cage". This may be due to steric interaction of the solvating alcohols. The homologous series of saturated alcohols as their alkoxide ions show a general trend towards faster rate as the alkyl chain is lengthened. With constant activation energy, the rate increase is reflected in a more positive entropy of activation. Certain analogous effects are noted with the unsaturated alcohols but it must be realized that in these cases the activation energy is generally higher than their saturated counterparts. The higher ΔE^{*} values would then be significant in determining reactivity.

The negative result obtained in the attempted reduction of benzophenone by allyloxide provides additional evidence which detracts from the credibility of the hydride-ion hyperconjugation hypothesis.

APPENDIX A

Measurements and Calculations

Calculation of Energies and Entropies of Activation

Activation energies have been calculated by means of the Arrhenius equation: (46)

(1) $$k = A e^{-\Delta E^*/RT}$$

(2) $$-\Delta E^*/R = d \ln k / d(1/T)$$

The logarithms of the experimentally determined rate constants when plotted against the reciprocal of the absolute temperature should, according to the above equation, furnish a straight line. Examination of these plots for the reactions studied indeed correspond to this requirement. Once having established this linearity either the slope, as measured graphically or arithmetically from the data themselves furnishes the value of ΔE^*. It is true that the various theories for calculating reaction rates connote a temperature dependency of some form to A in the above equation, but for the sake of agreement with prior reports, and realizing the empirical nature of the Arrhenius Equation itself, this temperature dependency has been omitted.

By employing the Eyring Equation (47) for the prediction of Absolute Reaction Rates, the entropies of activation, ΔS^*, can be calculated:

(3) $$k = e \frac{kT}{h} e^{-\Delta E^*/RT} e^{\Delta S^*/R}$$

A triviality arises upon inspection of the units in the Eyring equation i.e., k has the dimensions of reciprocal time which is the dimension applied to a first order rate constant. In this work, the units of k are those of a second order rate constant. The answer to this dilemma is that the units ascribed to k define the standard state concentration chosen. Upon inspection of the literature, the method most commonly employed and generally accepted is to express k in the dimensions of liters/mole· sec., the use of the appropriate conversion factor of hours to seconds adjusts the data to that adopted by many others.

Calculation of Second order rate constants.

Second order reactions can be expressed by the following differential equation: (4)

$d(x)/_{dt} = -k(x)(y)$ in which x and y are expressed in concentration units and represent the concentrations at any time t. Inorder to simplify the above equation by integration, there must be a relation between x and y which comes from examining the stoichiometry of the reaction. The reaction employed is as follows:

$$\text{RONa} + \text{RX} \rightarrow \text{ROR} + \text{NaX} \qquad (5)$$

Inspection of this equation reveals that x and y react in a one to one correspondence therefore the original rate expression reduces to the following:

$$\frac{d\,(x)}{d\ \ t} = -k\,(x)^2 \qquad (6)$$

which may be integrated to the following:

(7) $$\frac{1}{x} - \frac{1}{x_o} = k\ (t-t_o)$$

This general expression has been readjusted to yield the following:

(8) $$\frac{1}{a-x} - \frac{1}{a-x_o} = k\ \ t$$

where a = the amount of halide ion which could be produced at quantitative reaction in terms of the number of ccs. of standard silver nitrate solution necessary to titrate the sample, x = the number of ccs. of silver nitrate to titrate the sample at t_o which is commonly called the temperature equilibrium sample. Now from the general expression so derived the following equation can be set up:

(9) $$\frac{1}{.2\left[\frac{40-x}{40}\right]} - \frac{1}{.2\left[\frac{40-x_o}{40}\right]} = k\Delta t$$

Where .2 = the initial molar concentration of both the aromatic halide and sodium alkoxide, 40 = the number of ccs. of a 0.0250 N $AgNO_3$ solution to titrate any given 5 cc. sample at 100% reaction provided that this sample come from 0.01 mole of halide weighed out and diluted to a total volume of 50 ccs. In this way, the concentration of the halide is 0.2 molar. Of course the sodium alkoxide solution is so arranged that it has a concentration of 0.2 molar also.

Further simplification of the last equation shown affords the final expression very similar in numerical value to that which was employed in this work:

(10) $$\frac{200}{40-x} - \frac{200}{40-x_o} = k\Delta t$$

The value of k is then obtained in the units of liters/mole-hour so long as t is expressed in hours.

The data used in a representative calculation are given below:

2 - bromopyridine, Sodium pentanoxide in pentanol, 0.2 molar in each.

T = 83.65 ± .05° C.

Table 5

Example of Reaction Rate Data

Sample	Time (hr.)	$\frac{202.45}{40.49-X}$	$\frac{202.45}{40.49-X_0}$	k (lit./mole-hr.)
1	0	-	5.0461	-
2	2.0	5.2380	"	.0959
3	4.0	5.4233	"	.0943
4	5.0	5.5179	"	.0944
5	6.0	5.6127	"	.0944
6	7.0	5.7092	"	.0947
7	7.5	5.7612	"	.0953
8	8.0	5.8059	"	.0950

k = 0.0949 ± .0005 l./mole-hr.

Estimation of error in the rate constant.

Errors in the rate measurements could arise from some or all of the following causes: (1) impurities, (2) weighings, (3) dilutions or pipetting, (4) standardizations of solutions, (5) thermometry, (6) temperature fluctuations, (7) time variations, (8) titration of sample, (9) non-quantitative transfer of solutions and materials, (10) undetermined causes. Causes (2), (3), (4), (7), and (9) may be dismissed as being relatively unimportant in comparison with the others. Their combined magnitude could account for relative errors of only a few tenths of a percent. Errors caused by impurities have been minimized by careful purification of reagents; for example, those alcohols purchased from commercial suppliers were fractionated before use, those alcohols prepared in the present work were all fractionally distilled on a Todd Fractionation Assembly whose rated efficiency is of the order of fifty theoretical plates and operating at a ninety percent reflux. The prepared 2-bromopyridine was also purified by fractional distillation prior to use. The temperature fluctuations have been reduced to ± .05° in all cases which is probably the best that can be done without greatly increasing the investment in equipment.

The average difference in titrations of identical samples has been determined to be 0.072 ml. which corresponds to a deviation in the second order rate constant of about 0.0094 units. In general every second order rate determination which has been made in the course of this work has resulted in deviations in k of less than the above value so that the error involved in the rate constants is quite probably due to errors in titration.

Any purely systematic error may effect the true value of k but will not effect any of the energies of activation since it is constant throughout the titration procedure employed.

The use of the method of least squares for averaging rate constants is considered unrealistic for the present purposes. The chief reason is that the data does not have equal weight; for example, the percentage reaction at zero time can be determined with much greater absolute accuracy than is possible near the end of a "run." This is due to the fact that competing side reactions of the sodium alkoxides become increasingly important with time. Thus in a given run it was apparent, from the developing color of the sample, that a side reaction involving the sodium alkoxides was taking place but not at a sufficiently large rate so as to affect the linearity of the rate constant when measured through about twenty five percent reaction. Consequently, by attaching no special importance to the first point at zero time, the method of least squares has been known to fix the intercept at some positive value of time. This result is physically absurd.

Estimation of error in the activation energies.

In all cases it was found possible to construct the slopes of the Arrhenius plots in such a way that no point was removed from the line by an amount greater than the independently estimated limits of precision. The latter were graphed as lines since the deviation in the values of $1/_T$ is negligible due to a negligible temperature variation. The limits of precision of the activation energy were obtained arithmetically from the extremes of the empirically determined values of the rate constants themselves.

Thus, the only function of the Arrhenius plots was to establish the agreement to linearity of the plotted data.

The calculation of ΔE^* from the extremes of the experimental values affords the maximum error. Making the reasonable assumption that the activation energies show a normal distribution about the best straight line, ΔE^*, it is possible to apply a few of the principles of statistics (48). Since the above limits of precision afford the maximum values, the area under the normal curve corresponding to these limits is at least $\pm 3.9\sigma$ where σ is the standard deviation from the mean. From the value of σ, it is possible to calculate $\pm 1.96\sigma$ which represents the error including at least 95% of all values of ΔE^* and the most probable error, $\pm .97\sigma$, which includes two-thirds of all values of ΔE^*. These statistical values show that the most probable error is approximately one-half of the error which includes 95% of all ΔE^* values which is in turn one-half of the maximum error.

The reliability of the activation energies is not affected by systematic errors which alter all the rate constants for a given reaction by the same fractional amount. Possible sources of such errors are: inert impurities (rigorously true only at certain limits, but sufficiently valid over the experimental ranges used), constant thermometer error, proportional timing error, error in the standardization of solutions, and error in the calibration of volumetric apparatus.

Measurement of Second Order reaction rates.

An accurately weighed sample of 2-bromopyridine (0.01 mole) was dissolved in the appropriate amount of a 0.3 - 0.4 molar solution (by titration with standard acid) of the sodium alkoxide in its corresponding alcohol was then diluted to 50 ml. with the same alcohol. The resulting solution was shaken vigorously to insure homogeneity and then pipetted into 5 inch tests tubes, the open ends of which were partially constricted. These tubes were all washed thoroughly and rinsed with distilled water, oven-dried overnight then allowed to cool in a desiccator over P_2O_5 prior to use. Each tube was flushed with nitrogen prior to admitting a sample and then flushed again prior to sealing. Small corks were placed in the construction to prevent undue contact with the atmosphere while the tubes with their contents were chilled in an ice bath prior to sealing. A total of 32 tubes were made up at one time and they were stored under refrigeration until used in rate measurements. A total of 8 tubes were used in each run, each tube being placed in a cylindrical aluminum jacket having a metal rod fitted through a supporting cork for fitting to a piece of hard pressed paper having numerous holes for samples, thermometer and thermoregulator support. The tubes were immersed in an oil-filled cylindrical thermostated bath which was previously heated about 0.3° above the temperature desired since this generally offset the initial absorption of heat by the cold sample tubes. After attaining thermostatic equilibrium, usually within 5 minutes, the first sample tube was withdrawn, the timing device was started and the tube was immediately chilled to about 10°C. by cold water.

The sample tubes were opened by means of a file scratch touched with a hot glass rod. The contents of the tubes were poured into a small beaker, rinsed with 2 portions of about 5 cc. of distilled water, 3 ccs. of a 3 M nitric acid solution, then with 3 portions of 8 ccs. each of acetone. This solution was then titrated electrometrically with 0.025 N silver nitrate solution delivered from a 10cc. burette calibrated in .05 cc. increments. At appropriate intervals of time the remaining samples were removed and treated as described.

Analytical apparatus and procedure.

The titrimeter consisted of a Beckman pH meter adjusted to function as a potentiometer and was equipped with a silver electrode and a non-standard reference electrode. The latter was adapted from a calomel electrode by replacement of the potassium chloride solution with saturated potassium sulfate solution. The end-points were detected by observing the changes in electrical potential caused by the addition of 0.03 ml. increments of the silver nitrate solution. The increment which produced the greatest change in the value of the scale deflection was considered to be the end-point. By titration of three samples of standard sodium bromide solution, the end-points were all essentially identical. Thus, any error in evaluating the end-points would be attributed to the zero setting and final readings of the burette. Their combined magnitudes are about 0.072 mls. For standby and emergency purposes a stock solution of potassium thiocyanate was available for estimation of halide end-points by the Volhard procedure.

Thermometry. Since all the kinetic runs were measured in the range from about 85° to 120° C., one thermometer was employed which had been calibrated by the Bureau of Standards. This thermometer is calibrated in 0.2° units. An ice-point determination was made to insure that the calibrations had not changed. As a further precaution, since the temperature ranges were in the vicinity of 100°, a steam point was determined to insure the validity of the calibration for 100°C.

Thermostat bath. For all runs, an unenclosed cylindrical sheet metal tank was filled with several gallons of light lubricating oil. It was determined that a centrifugal pump did not give sufficient agitation throughout the bath while the heaters were operating i.e., the temperature varied from one place to another in the bath. To insure more adequate circulation, a blade stirrer fashioned from a sheet of aluminum measuring approximately 2 by 5 inches was employed. The corners of the sheeting were bent almost at right angles to the plane of the sheet.

This sheet was then fastened to a metal shaft which was seated into a Mix-Master type motor of variable speed. By operating at approximately 2/3 maxiumum speed, it was determined that the temperature was reproducible at almost any spot within the bath. It is to be noted that the use of a thermoregular sensitive to ± 0.05° C. would not be warrented unless the agitation within the bath was rapid enough to dissipate the heat from the heaters employed. Since the radiant heat loss from this bath is rather large, it was necessary to use three heaters of 500 watt capacity.

For fine temperature control, a blade heater of 125 watt output was connected to a Thyration relay which in turn was connected to the mercury thermoregulator.

Sample tubes: Although the temperature ranges employed in measuring the rates were for the most cases below the boiling points of the alcohols employed it was deemed advisable to use sealed test tubes. These tubes were all 5 inches long and when charged with a 5 ml. sample, were less than half filled. It can be interjected that the entire tube was placed below the surface of the oil so that at most the free space within the tube was composed of nitrogen and the alcohol vapor. In almost all cases observed, there was no condensate on the upper walls of the tubes. These tubes also are sufficiently strong to withhold the pressure of the most volatile alcohol, methanol, at temperatures of the order of 50° above the boiling point.

APPENDIX B

Preparation of Reagents

2-Bromopyridine (49). In a 5 liter three necked flask fitted with a stirrer, dropping funnel and thermometer were placed 635 mls. of 48% Hydrobromic acid solution. This was chilled in an ice-water bath to 3°C. and 120 grams of 2-aminopyridine was added in portions with stirring. The resulting solution was cooled below 0° with an ice-salt bath and 192 mls. of Bromine was added dropwise. To this well cooled suspension, a solution of 220 grams of sodium nitrite in 320 mls. of water was added dropwise over a 2 hour period while the temperature was kept at -5°. The solution was then stirred for 1/2 hour. To this, 480 grams of sodium hydroxide in 480 mls. of water was added slowly while the temperature was kept at 20-25°. The resulting solution was then extracted with four 220 ml. portions of ether, the combined ethereal extracts were dried over anhydrous sodium sulfate, distilled, and the product collected at 84-6°/18 mm. From this 141 gms. of 2-bromopyridine was obtained which is 70% of the theoretical.

Absolute Methanol supplied by the Brothers Chemical Company was treated with magnesium and a crystal of iodine then refluxed overnight followed by distillation. It was then redistilled for rate measurements collecting about 500 ml. of a middle fraction B.P. 64.5°C.

Absolute Ethanol supplied by U.S.I. was distilled from magnesium ethoxide then redistilled prior to rate measurements. B.P. 78.5°C.

Absolute n-Propyl alcohol supplied by Mathieson Coleman and Bell was distilled from aluminum propoxide then redistilled. B.P. 97-8°C.

Absolute n-Butyl alcohol supplied by J.T. Baker was treated with freshly cut sodium, refluxed several hours, distilled and then redistilled. B.P. 117-7.5°C.

Absolute n-Amyl alcohol supplied by J.T. Baker was fractionally distilled using benzene to remove water by azeotropic distillation. B.P. 137.5-138°C. using a 20 cm. Vigreaux head.

Absolute Allyl alcohol supplied by the Brothers Chemical Company was treated with sodium metal, refluxed several hours, distilled, then redistilled from amalgamated aluminum. B.P. 96.5-97.5°C.

Allyl carbinol (50). To 50 grams of magnesium turnings (oven dried at 100° overnight) in 2 liters of absolute ether, a solution of 172 grams of allylchloride in 600 mls. of absolute ether was added dropwise with stirring while the temperature was kept at 0°C. The addition of the etheral allyl chloride required about 10 hours. The milky white suspension was covered with nitrogen allowing it to stand overnight at 0°.

This suspension was treated with the gaseous depolymerizate from 100 grams of dried paraformaldehyde while being stirred rapidly at 0°. A slow stream of nitrogen was used as the carrier gas.

The suspension was then poured into 600 mls. of saturated ammonium chloride solution in a large separatory funnel. The mixture was treated with 20 mls. of concentrated ammonium hydroxide and let stand, after swirrling, for several hours. The layers were separated the aqueous phase was extracted with several small portions of ether and the etheral extracts were all combined, dried over magnesium sulfate, concentrated by flash distillation and the product collected. B.P. 112-15°C. A total of 75 grams, 51% was obtained.

The crude product from several runs of the above preparation was combined and treated with sodium metal to remove halogen shown to be present. About 600ccs. of a crude product B.P. 112-5° free of halogen was obtained. This was treated with 50 ccs. of anhydrous benzene and 50ccs. of mineral oil and fractionated on a Todd Column. This afforded about 500 ccs. of a middle cut B.P. 114.5-5°C. A 3,5-dinitrobenzoate derivative was prepared in the usual manner (51) and on recrystallization from 60-110° Petroleum ether gave a m.p. 50.5-51° C. (lit.50.5°(52)).

Tetrahydrofurfuryl chloride (53) In a 5 liter three necked flask fitted with a stirrer, dropping funnel, and thermometer, 900 grams of tetrahydrofurfuryl alcohol (B.P. 81-2°/18 mm.) and 755 grams of pyridine were placed. This solution was cooled to 3-4° by means of an ice-water bath. To this, a total of 675 ccs. of thionyl chloride was added at a rate of 3-4 drops per second; after about one third of the thionyl chloride was added a thick pale brown slurry is produced. The thionyl chloride is then added more slowly while stirring more rapidly. The temperature rises but can be kept at 40-5° by adjusting the rate of addition of thionyl chloride.

After all the thionyl chloride was added, the thick dark mass was stirred for several hours then let stand overnight at room temperature. The resulting black suspension was then extracted eight times with one liter of ether each time, the etheral extracts were then concentrated to a total volume of 1500 mls. then extracted with 250 mls. of cold water three times. The ethereal layer was then dried over magnesium sulfate, filtered, and then distilled. The product was collected at 51-4°/ 18 mm. to afford 714 grams or 67% crude product.

4-Penten-1-ol (53) In a 5 liter three necked flask filled with a condenser, stirrer, and dropping funnel, 224 grams of powdered sodium was placed and covered with 1.4 lit.of absolute ether. This was stirred rapidly and was treated with about 6 mls. of a solution of 600 grams of tetrahydrofurfuryl chloride in 600 mls. of absolute ether. After about ten minutes the reaction appeared to be well under way and then the flask was surrounded with an ice-water bath and the ethereal halide was added dropwise. A blue color appears in the solution and towards the end of the addition (5-6 hours) the suspension became creamy yellow. This was stirred an additional hour then let stand overnight. The entire slurry was poured into a large separating funnel, treated with 50 mls. of ethanol and swirled. When it appeared that any residual sodium had all been consumed, the product was decomposed by the addition of sufficient ice-water so as to yield two distinct layers. The layers were separated, the aqueous phase was extracted with two 500 ml. portions of ether, and the combined ether layers were dried over magnesium sulfate, concentrated by distillation and the product collected B.P. 132-140 °C. A total of 337 grams of this crude distillate was obtained which is 79% of theory.

In order to remove contaminating halide, the crude product was treated with sodium as described on the previous page for allyl carbinol and the final fractional distillation was done on a Todd Column collecting the material B.P. 138.5-9° C. for use in the rate runs.

3-chloro-2-buten-1-ol (54) In a five liter three necked flask fitted for stirring and reflux were placed 2500 mls. of ten percent sodium carbonate solution and 500 grams of 1,3-dichloro-2-butene. This was stirred under reflux for five hours, cooled, then poured into a separatory funnel. The aqueous phase was extracted with three 600 ml. portions of ether and combined with the original non-aqueous phase, dired over magnesium sulfate, filtered, concentrated by flash distillation and the product collected at 68-75° C/21-16 mm. The major portion was observed to boil at 72-4 °C/16 mm. A total of 317 grams were obtained which is 74% of theory.

2-Butyn-1-ol (54) A solution of sodium amide in liquid ammonia was prepared by charging a four liter Dewar flask with three liters of anhydrous ammonia, adding 1.5 gram of hydrated ferric nitrate followed by 65 grams of freshly cut sodium cubes, while being stirred. To this, 134 grams of 3-chloro-2-buten-1-ol (B.P. 66-8°/14 mm.) was added dropwise over about one hour. This was then stirred overnight. To the solution 148 grams of solid ammonium chloride was added in small portions. The entire contents of the flask were then poured into a stainless steel bucket and allowed to evaporate to dryness in the Hood. The solid was then extracted with five 250 ml. portions of ether, these were combined, distilled and the product collected at 47-55°/14 mm.

From several runs of the above preparation, a total of 550 grams of pure product fractionated in a Todd Column was obtained B.P. 142.5-44° C. Average yield is 70% based on these several runs. The major fraction collected and employed had a B.P. 143.5-144° C.

Benzyl alcohol was distilled two times under reduced pressure collecting and employing that fraction whose B.P. was 93-4°/12 mm. Supplied by Eastman Kodak, White Lable Grade.

Crotyl alcohol supplied by the Chemical Intermediates and Research Laboratories Inc. was fractionally distilled on the Todd Column using benzene to remove traces of water collecting and employing the fraction B.P. 120-121.2° C. The trans isomer content is 98-99%.

Methyl cyclohexanecarboxylate Into each of two one liter round bottom flasks were placed 320 grams of cyclohexanecarboxylic acid, 500 mls. of absolute methanol and 50 mls. of concentrated sulfuric acid. The solutions were then refluxed two days. The flasks were chilled in ice-water and the contents poured into two liters of ice chips then neutralized by adding sodium carbonate. The entire mixture was then extracted with four 500 ml. portions of ether, the ethereal extracts were dried over magnesium sulfate, filtered, then distilled. The product B.P. 83-5°/29 mm. was collected weighing 642 grams which is 92% of theory.

Cyclohexyl carbinol In a two liter three necked flask fitted with a stirrer, condenser (protected by a calcium chloride tube) and a dropping funnel with a nitrogen inlet, were placed 600 mls. of absolute ether and 21.3 grams of lithium aluminum hydride.

To this was added 140 grams of methyl cyclohexanecarboxylate in 200 mls. of absolute ether at such a rate so as to maintain gentle reflux. After adding about 75% of the ethereal ester, the reaction mixture thickens to a white pasty mass hence, an additional 200 mls. of absolute ether was added before adding more of the ethereal ester. After all of the ester had been added, the flask was surrounded with a warm water bath and refluxed with stirring for one hour. To the white suspension, 50 mls. of ethyl acetate was added with vigorous stirring this was then followed after about fifteen minutes with 600 ccs. of ice cold 6 N Hydrochloric acid addedwith caution while surrounding the flask with an ice-cold water bath. By extracting the aqueous phase with three portions of 250 mls. of ether and combining the ethereal extracts and drying over magnesium sulfate, a total of 458 grams of crude alcohol B.P. 91-3°/24 mm. was obtained from 642 grams of the above ester which is an average of 90% of theory. This alcohol was then distilled on the Todd Fractionation Assembly and the portion boiling at 185-6°C. was collected and used for the kinetic measurements.

<u>The 2-pyridyl ethers</u> were prepared in the following general procedure: To ca. 100 ccs. of the alcohol, 6 grams of freshly cut sodium was added and then heated if necessary to get the last bits of metal into solution. The solution was then cooled to ca. 50° and 15.8 grams (1 mole) of 2-bromopyridine was added. This was then swirled to obtain a homogeneous solution more of the corresponding alcohol being added if necessary and then the reactants were heated at 100° in an oil bath for 1 week.

The precipitated sodium bromide can be removed either by filtration or by extracting the entire reaction mixture with water. The extraction with cold water is convenient for those alcohols which are sparingly soluble in water. For the water soluble alcohols, filtration of the sodium bromide followed by removal of the excess alcohol by distillation under reduced pressure was found convenient. In either case, the excess sodium alkoxide was decomposed with ca. 30 ccs. of cold water and extracted with ether 3 to 4 times using ca. 50ccs. each time. The ethereal extracts were combined, dried with anhydrous magnesium sulfate, filtered, concentrated by flash distillation and then fractionation of the residue under reduced pressure using a 20 cm. Vigreaux head afforded the corresponding 2-pyridyl ethers. Only those ethers which have not been previously reported in the literature are reported here. The boiling points, analyses and picrate derivatives are reported in Tables 6 and 7 .

It has been shown (26) that when a solution of sodium n-propoxide and 2-bromopyridine is heated for several hours, extracted with ether and distilled that 2 n-propxypyridine is the product isolated since cleavage with 48% hydrobromic acid affords 2-pyridone indentified by its m.p. and mixed m.p. I.R. with 2-pyridone prepared by an independent route. This then proves that the reaction has led to the substitution of an alkoxide ion for bromide and also that the reaction is solely centered about the 2-position which originally bears the halogen.

Attempted Reduction of Benzophenone using Aluminum Allyloxide.

To one hundred mls. of allyl alcohol B.P. 97-8° C., a total of 2.7 grams, (.1mole) of Aluminum metal was added which had been freshly amalgamated (55).

To the gray suspension so obtained, 15 grams of benzophenone was added. The solution was then heated at reflux in an oil bath for two days. Tests on the distillate B.P. 96 - 8°C. gave no precipitate with 2,4-dinitrophenylhydrazine solution. The excess allyl alcohol was distilled and replaced by Xylene. Upon several hours refluxing no positive test for acrolein was obtained on the distillate. The xylene was then distilled off under reduced pressure, the residue was poured onto an ice-cold solution of 35 mls. of concentrated hydrochloric acid in 175 mls. of water. The oily product was taken up in ether, dried over magnesium sulfate, then distilled to yield an oily residue. To this, aqueous ethanol was added so as to precipitate the solid. The melting point, mixed melting point and 2,4-dinitrophenylhydrazone proved the solid to be recovered benzophenone. A total of 14.7 grams was obtained.

Table 6

		Analytical					
		Calculated			Found		
2-Pyridyl ether	B.P.[b]	C	H	N	C	H	N
allyl C_8H_9NO	178-180°	71.08	6.72	10.36	69.00	7.13	9.50
3-butenyl [a]	40-60°C/1mm.						
4-pentenyl $C_{10}H_{13}NO$	109-11°/18mm.	73.59	8.03	8.58	73.80	8.43	8.38
n-butyl $C_9H_{13}NO$	92-4°/20mm.	71.49	8.66	9.27	73.30	9.18	8.05
n-amyl $C_{10}H_{15}NO$	109-11/20mm.	72.69	9.15	8.48	73.00	9.50	7.60
2-butynyl [a]	40-60°/1 mm.						
crotyl $C_9H_{11}NO$	205-7° C.	72.45	7.43		71.10	8.89	

Table 7

		Analytical					
		Calculated			Found		
2-Pyridyl ether(Picrates)	M.P.[c]	C	H	N	C	H	N
allyl $C_{14}H_{12}N_4O_8$	105.5-106.5°C	46.16	3.32	15.38	46.45	3.60	15.32
3-Butenyl $C_{15}H_{14}N_4O_8$	81-2°	47.62	3.73	14.81	47.84	3.67	14.48
4-Pentenyl $C_{16}H_{16}N_4O_8$	84-5°C	48.98	4.11	14.28	49.05	4.33	14.08
n-Butyl $C_{15}H_{16}N_4O_8$	70.5-71.5°C	47.37	4.24	14.74	47.50	4.28	14.80
n-Amyl $C_{16}H_{18}N_4O_8$	83-4°C	48.73	4.60	14.21	48.52	4.66	14.10
2-Butynyl $C_{15}H_{12}N_4O_8$	140-1°C	47.88	3.22	14.89	47.73	3.38	14.83
Crotyl $C_{15}H_{14}N_4O_8$	99-100°C	47.62	3.73	14.81	47.59	3.77	14.95

a - analyzed only as the picrate derivatives
b - uncorrected values
c - all taken on Anshutz Thermometers

APPENDIX C

Table 8

Tabulated Reaction Rate Constants and Arrhenius Plots

Parent Alcohol	T°C ± .05°	k (1/m-hr)
Methanol	87.05	0.0470 ± .0003
	98.25	0.1442 ± .0015
	110.65	0.4563 ± .0014
Ethanol	85.45	0.0523 ± .0004
	96.55	0.1554 ± .0015
	107.85	0.4682 ± .0061
Propanol	81.60	0.0551 ± .0011
	92.0	0.1533 ± .0011
	100.50	0.3558 ± .0043
	107.30	0.6857 ± .0089
Butanol	83.20	0.0772 ± .0010
	92.15	0.1943 ± .0036
	105.45	0.6942 ± .0100
Pentanol	83.65	0.0949 ± .0005
	95.05	0.3047 ± .0065
	105.45	0.8162 ± .0063
Allyl alcohol	100.75	0.1155 ± .0018
	115.40	0.4710 ± .0096
	121.70	0.8310 ± .0055
3-Buten-1-ol	85.30	0.0514 ± .0002
	95.70	0.1519 ± .0018
	108.70	0.5493 ± .0039
4-Penten-1-ol	85.40	0.0788 ± .0011
	95.10	0.2177 ± .0018
	107.20	0.7084 ± .0054
Benzyl alcohol	85.00	0.0262 ± .0004
	96.40	0.0896 ± .0010
	109.95	0.3553 ± .0039
2-Butyn-1-ol	94.60	0.0290 ± .0003
	106.20	0.0934 ± .0006
	117.70	0.2940 ± .0021
Crotyl alcohol	85.80	0.0603 ± .0012
	96.10	0.1690 ± .0022
	108.55	0.5869 ± .0079

Reaction Rate Constants (cont'd)

Parent Alcohol	T°C + .05°	k (1/m-hr)
Cyclohexylcarbinol	83.30	0.1072 ± .0021
	91.90	0.2582 ± .0058
	105.30	0.9040 ± .0061

FIGURE I

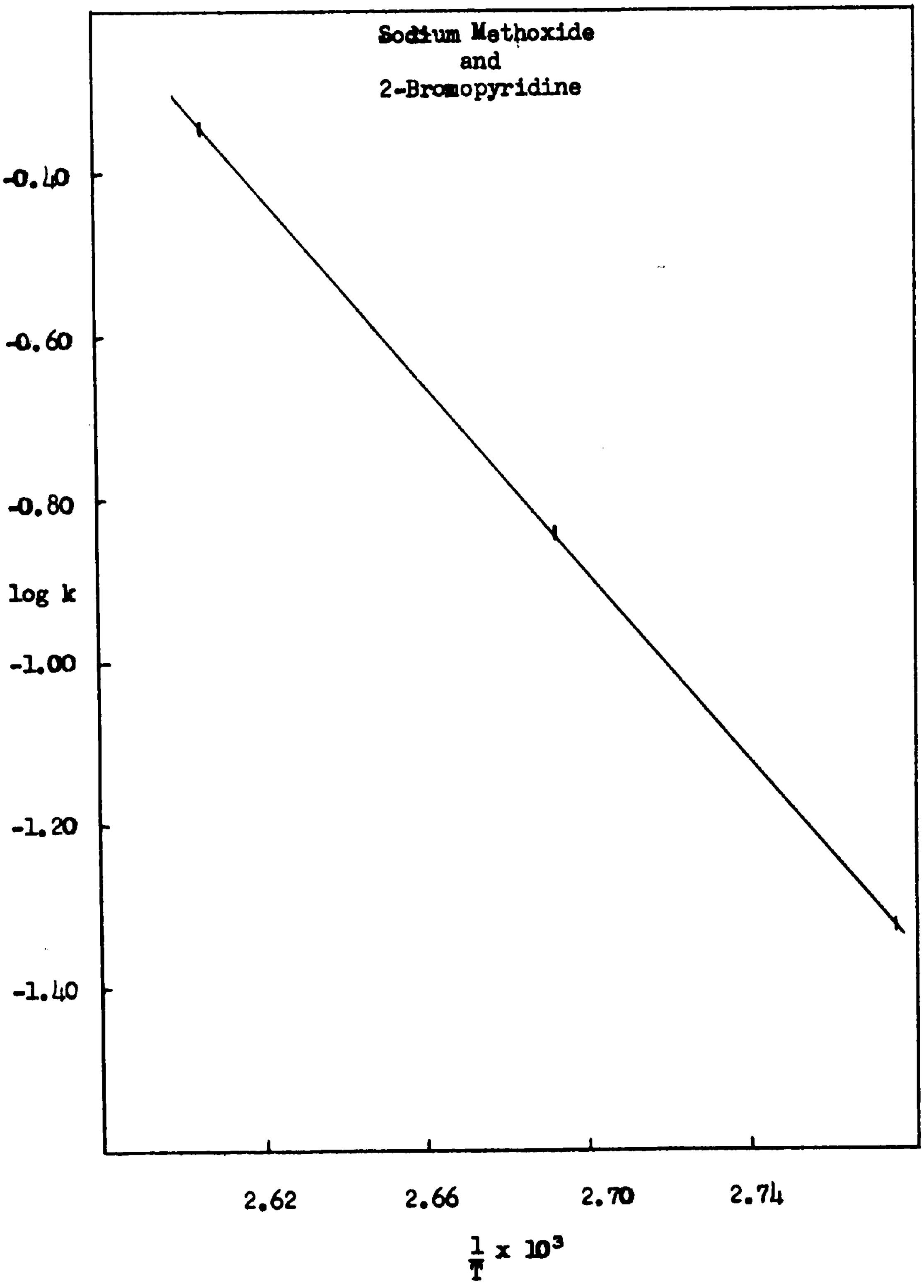

Sodium Methoxide
and
2-Bromopyridine
-0.40
-0.60
-0.80
log k
-1.00
-1.20
-1.40
2.62
2.66
2.70
2.74
$\frac{1}{T} \times 10^3$

FIGURE 2

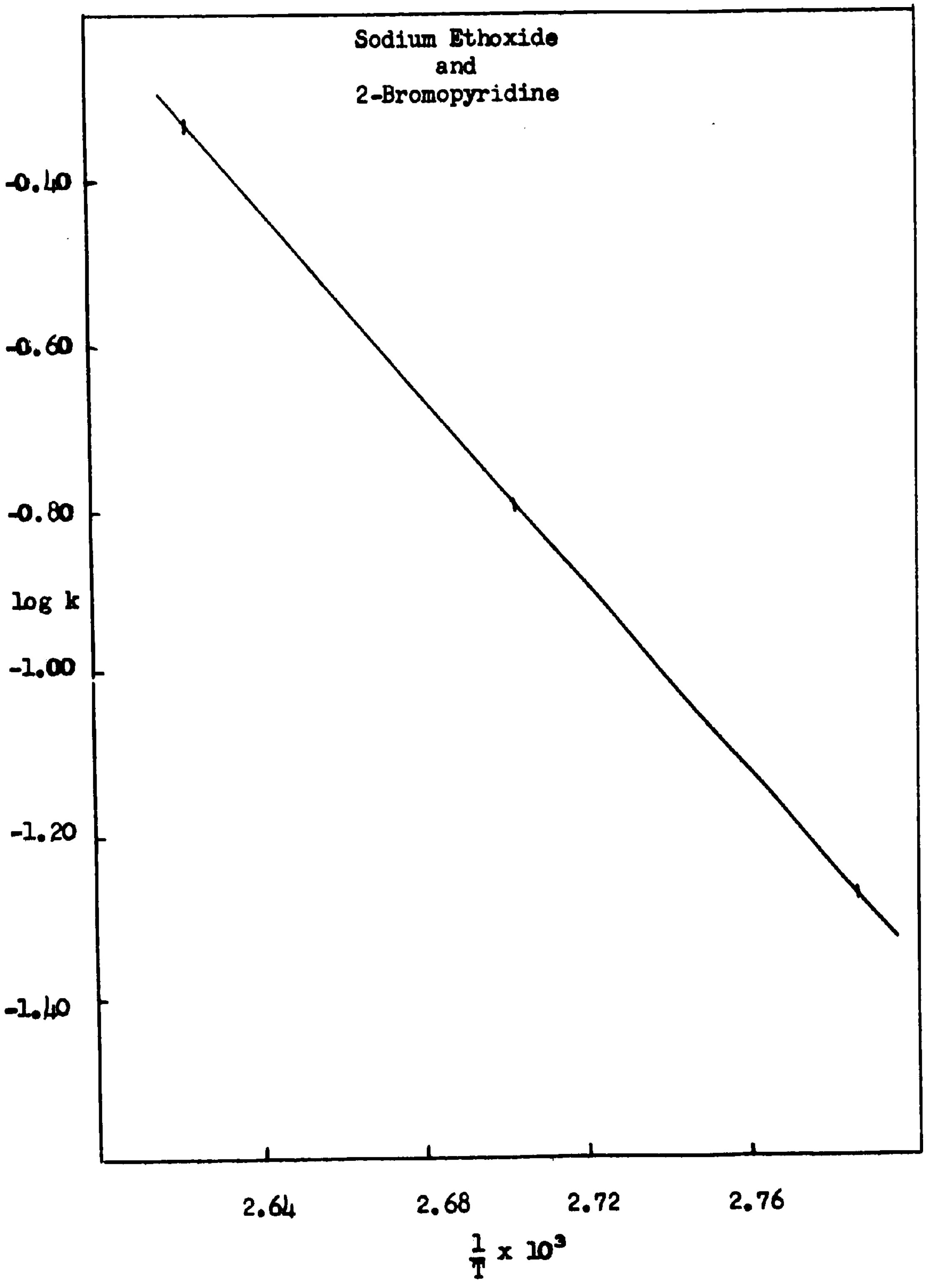

Sodium Ethoxide
and
2-Bromopyridine
-0.40
-0.60
-0.80
log k
-1.00
-1.20
-1.40
2.64
2.68
2.72
2.76
$\frac{1}{T} \times 10^3$

FIGURE 3

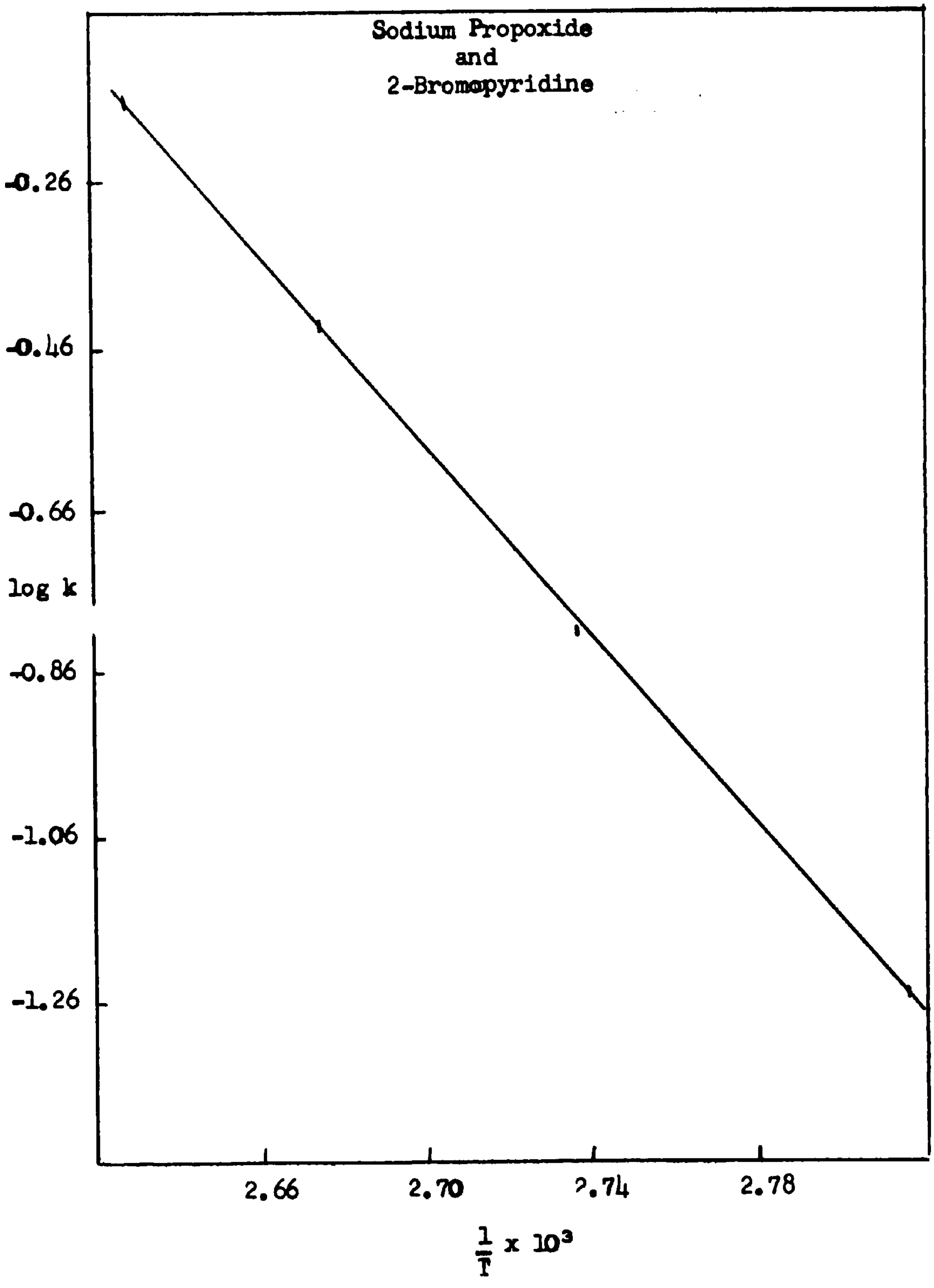

Sodium Propoxide
and
2-Bromopyridine
-0.26
-0.46
-0.66
log k
-0.86
-1.06
-1.26
2.66
2.70
2.74
2.78
$\frac{1}{T} \times 10^3$

FIGURE 4

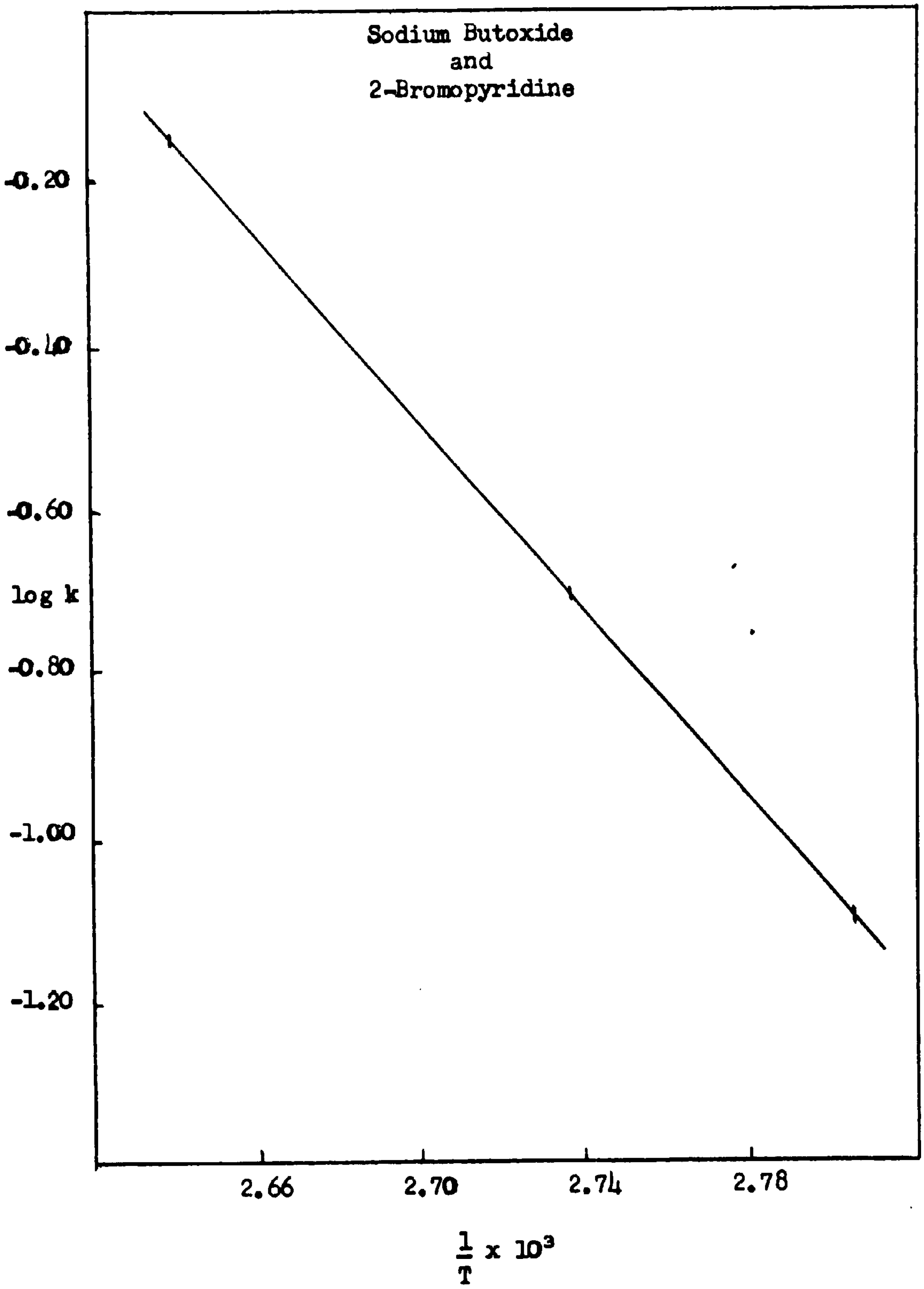

Sodium Butoxide
and
2-Bromopyridine
-0.20
-0.40
-0.60
log k
-0.80
-1.00
-1.20
2.66
2.70
2.74
2.78
$\frac{1}{T} \times 10^3$

FIGURE 5

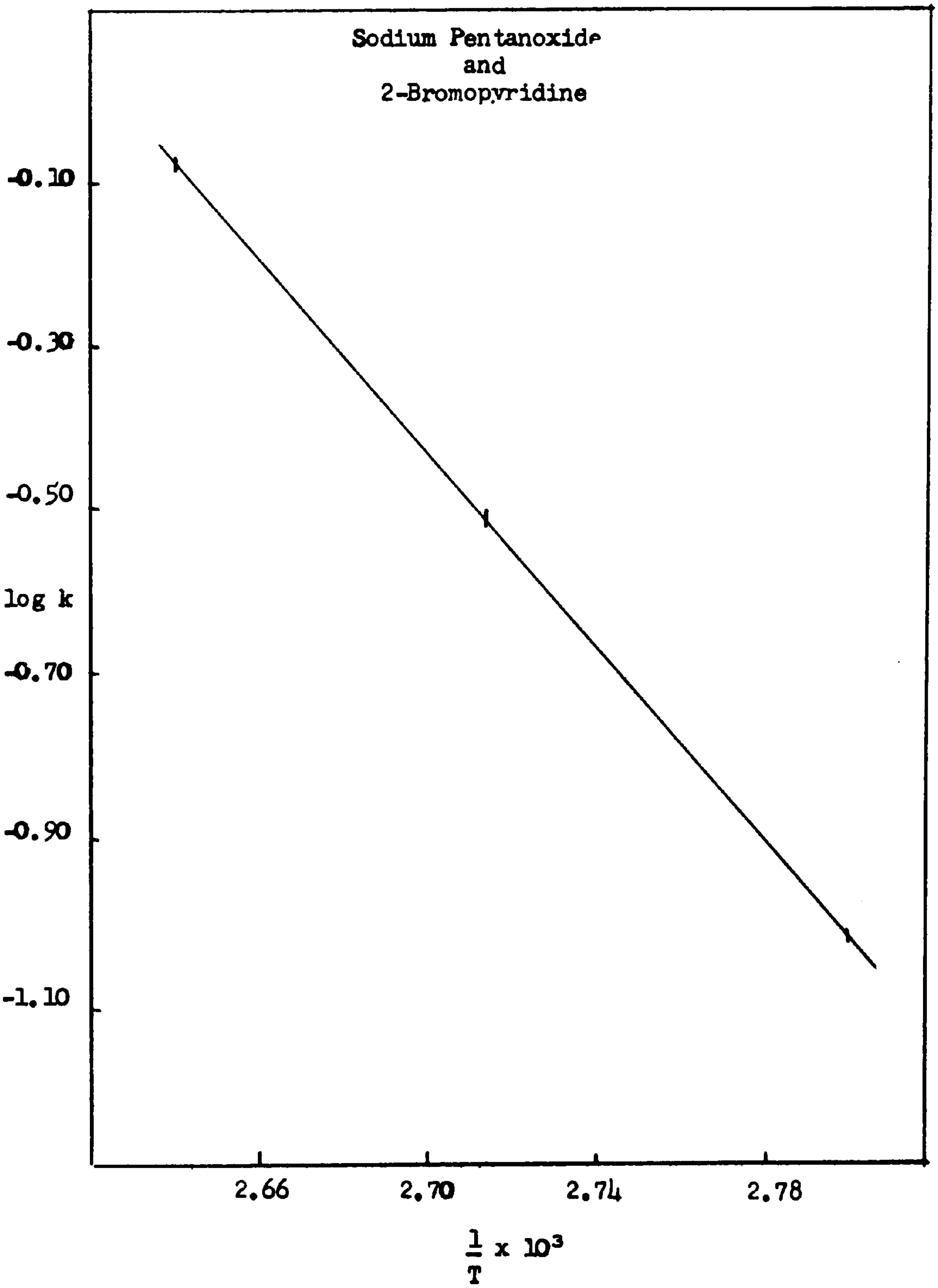

Sodium Pentanoxide
and
2-Bromopyridine
-0.10
-0.30
-0.50
log k
-0.70
-0.90
-1.10
2.66
2.70
2.74
2.78
$\frac{1}{T} \times 10^3$

FIGURE 6

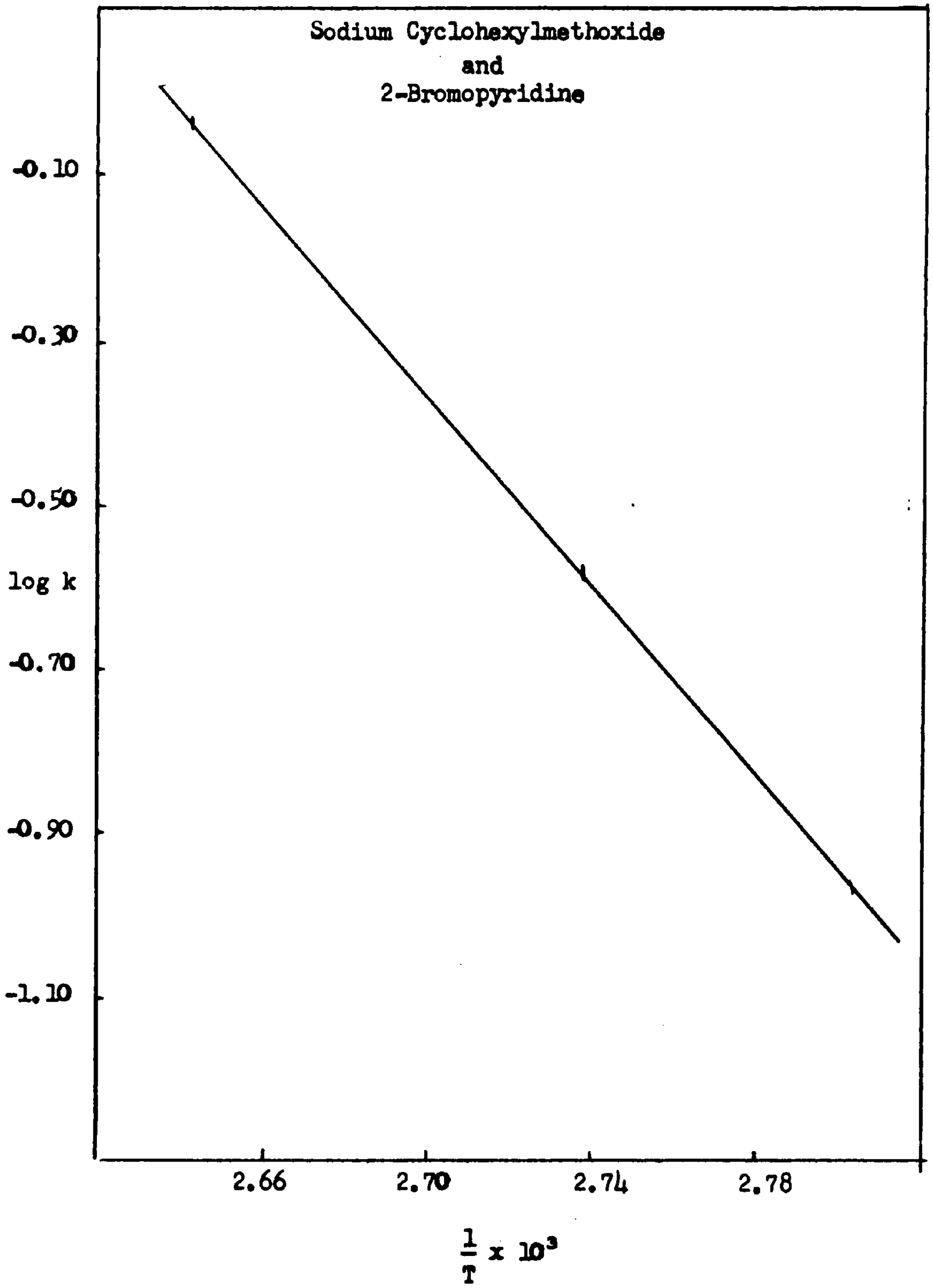

Sodium Cyclohexylmethoxide
and
2-Bromopyridine
-0.10
-0.30
-0.50
log k
-0.70
-0.90
-1.10
2.66
2.70
2.74
2.78
$\frac{1}{T} \times 10^3$

FIGURE 7

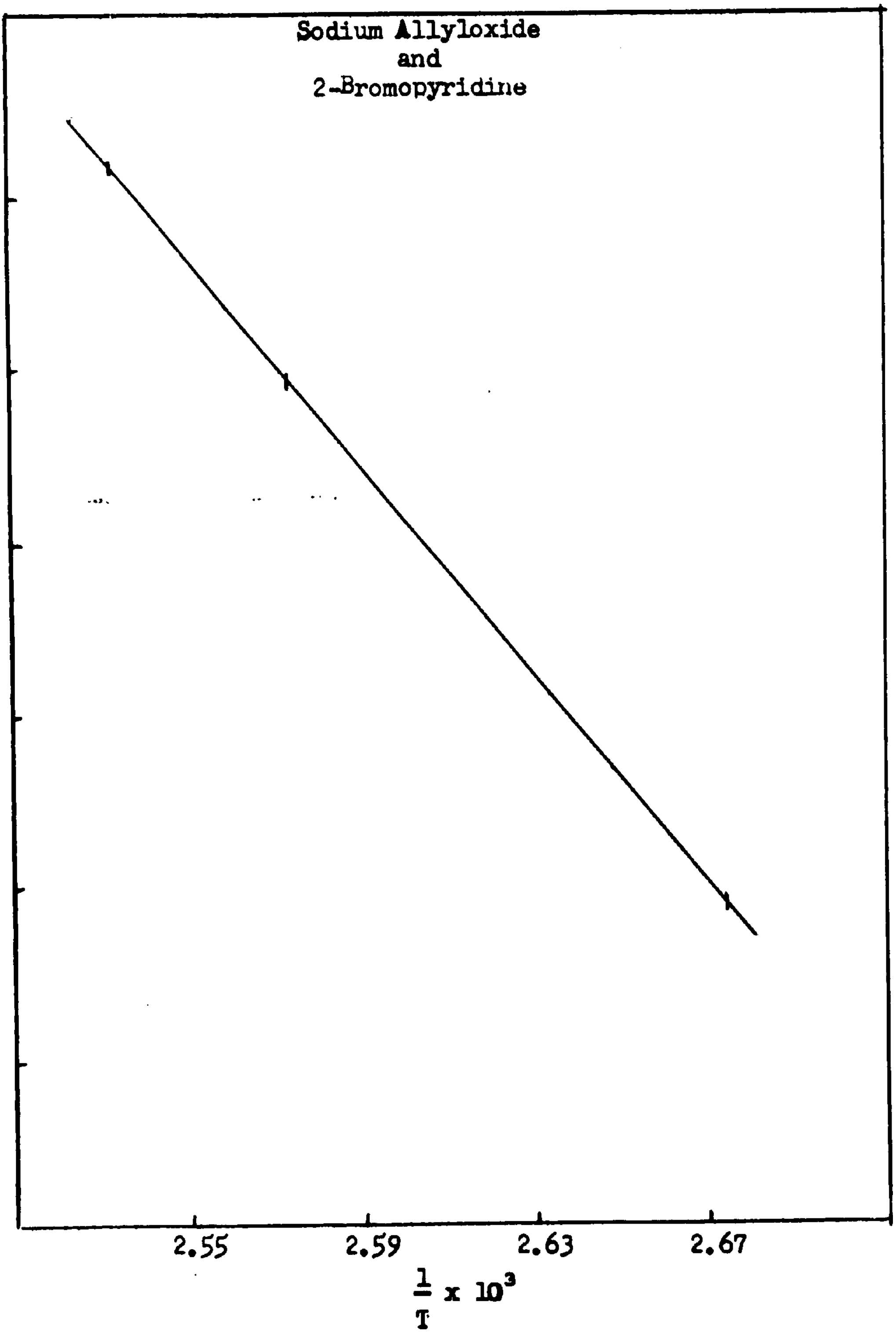

Sodium Allyloxide
and
2-Bromopyridine
-0.10
-0.30
-0.50
log k
-0.70
-0.90
-1.10
2.55
2.59
2.63
2.67
$\frac{1}{T} \times 10^3$

FIGURE 8

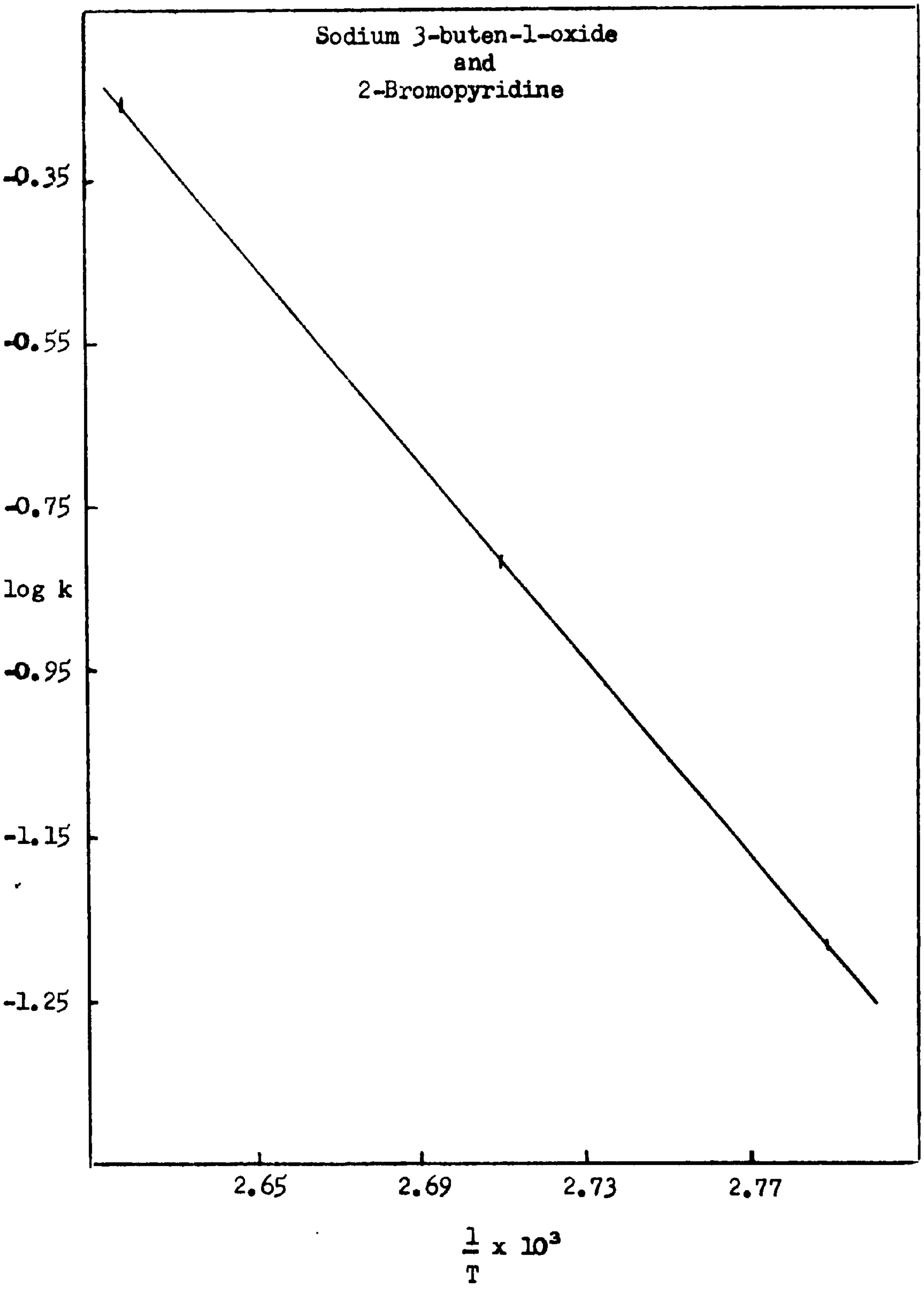

Sodium 3-buten-1-oxide
and
2-Bromopyridine
-0.35
-0.55
-0.75
log k
-0.95
-1.15
-1.25
2.65
2.69
2.73
2.77
$\frac{1}{T} \times 10^3$

FIGURE 9

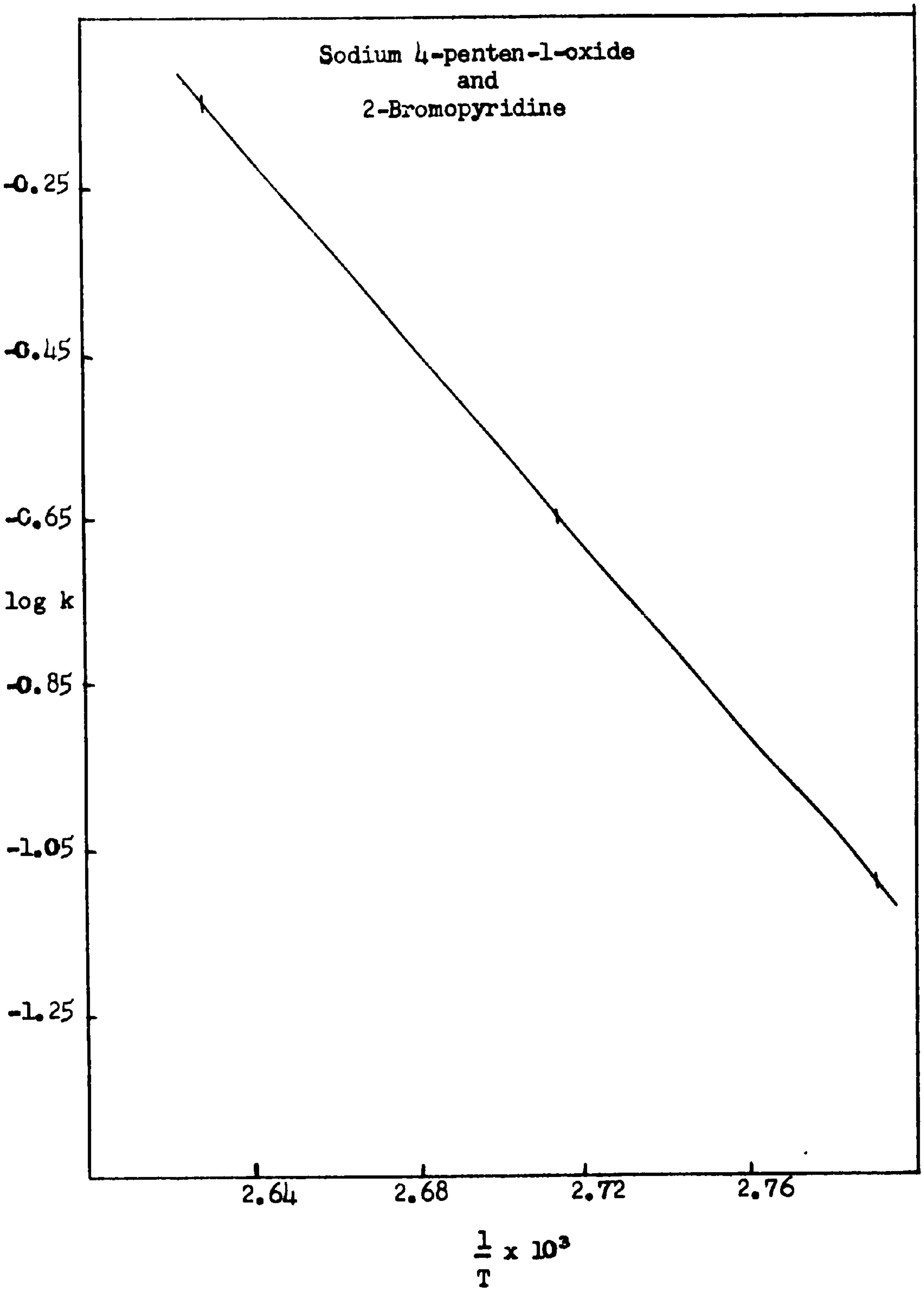

Sodium 4-penten-1-oxide
and
2-Bromopyridine
-0.25
-0.45
-0.65
log k
-0.85
-1.05
-1.25
2.64
2.68
2.72
2.76
$\frac{1}{T} \times 10^3$

FIGURE 10

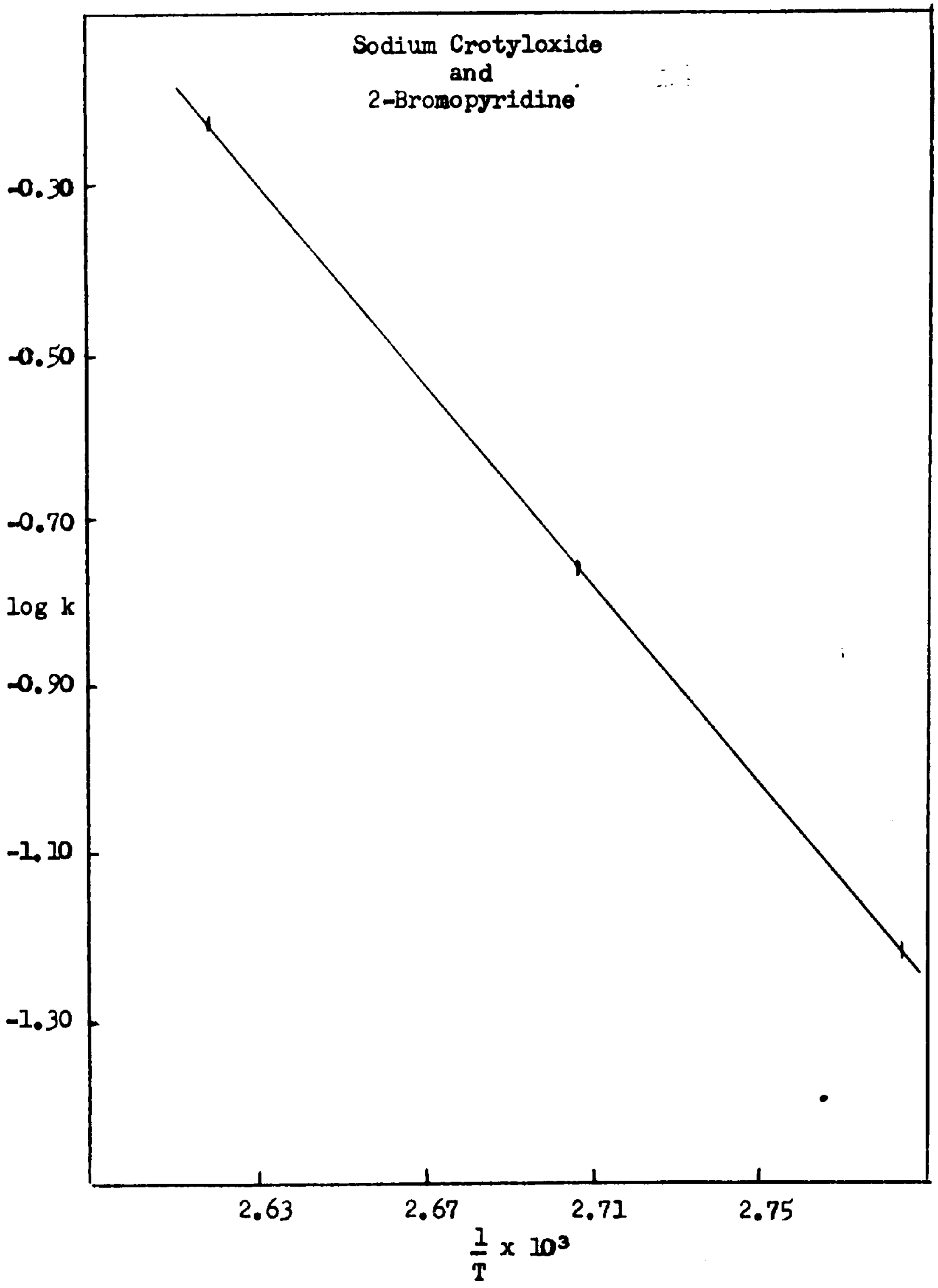

Sodium Crotyloxide
and
2-Bromopyridine
-0.30
-0.50
-0.70
log k
-0.90
-1.10
-1.30
2.63
2.67
2.71
2.75
$\frac{1}{T} \times 10^3$

FIGURE 11

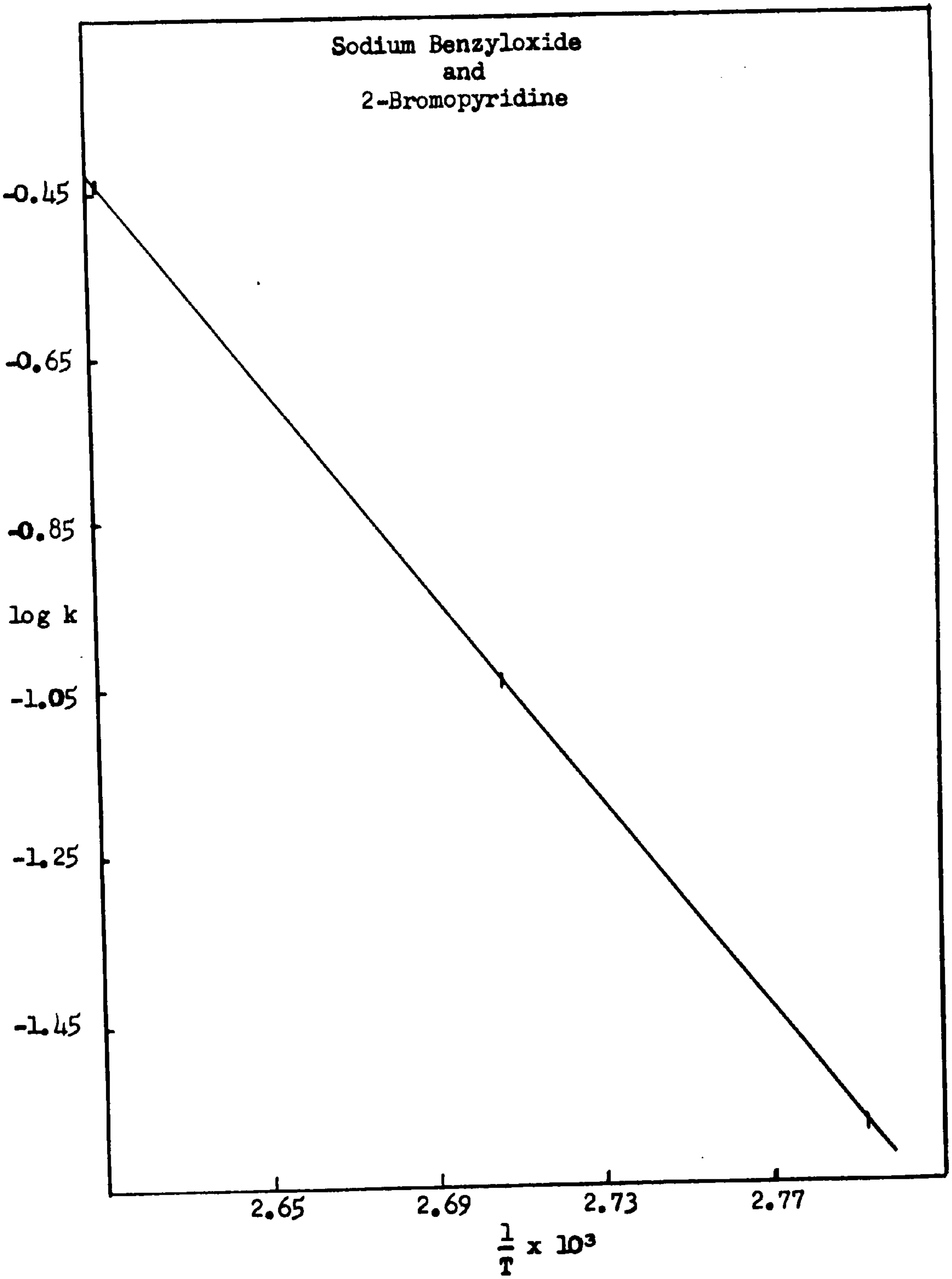
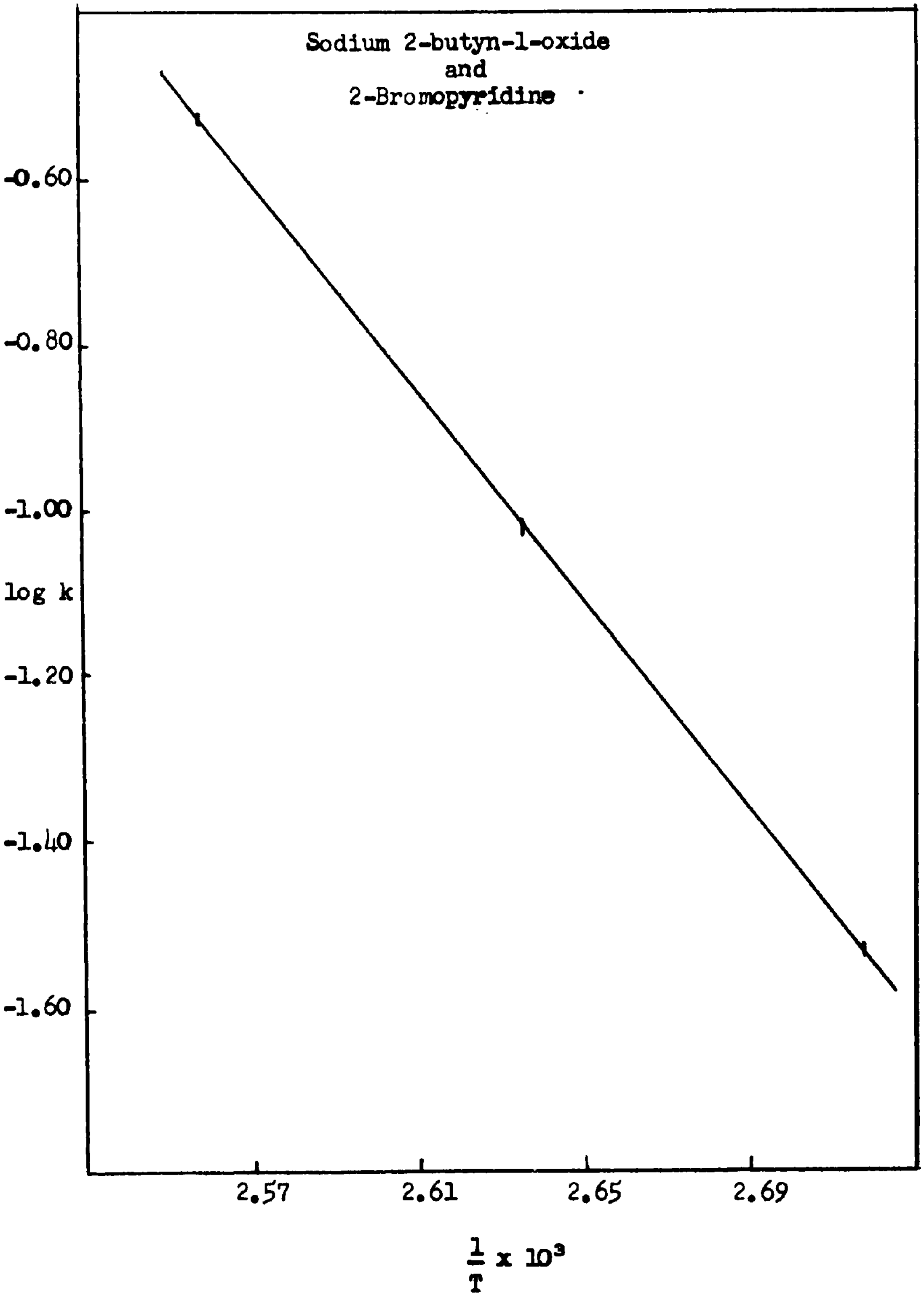

Sodium Benzyloxide
and
2-Bromopyridine
-0.45
-0.65
-0.85
log k
-1.05
-1.25
-1.45
2.65
2.69
2.73
2.77
$\frac{1}{T}$ x 10³

FIGURE 12


Sodium 2-butyn-1-oxide
and
2-Bromopyridine
-0.60
-0.80
-1.00
log k
-1.20
-1.40
-1.60
2.57
2.61
2.65
2.69
$\frac{1}{T} \times 10^3$

REFERENCES

(1). A. Williamson and H. Scrugham, J. Chem. Soc., 7, 237 (1855).

(2). T. E. Young, M. S. Thesis, Lehigh University, 1950.

(3). J. Way, M. S. Thesis, Lehigh University, 1951.

(4). R. Rubright, M. S. Thesis, Lehigh University, 1951.

(5). W. Samuels, M. S. Thesis, Lehigh University, 1952.

(6). G. Schrayer, M. S. Thesis, Lehigh University, 1952.

(7). K. R. Brower, Ph.D. Thesis, Lehigh University, 1953.

(8). D. G. Manly, Ph.D. Thesis, Lehigh University, 1956.

(9). R. J. Petfield, M.S. Thesis, Lehigh University, 1957.

(10). J. F. Bunnett and R. F. Zahler, Chem. Rev., 49, 273 (1951).

(11). J. Miller, Rev. Pure Appl. Chem., 1, 171 (1951).

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

(13). H. Mosher in R. Elderfield, "Heterocyclic Compounds," Vol. I, John Wiley and Sons, Inc., New York (1950) p. 401.

(14). B. A. Middleton and J. R. Partington, Nature, 141, 516 (1938).

(15). H. C. Lonquet-Higgins and C. A. Coulson, Trans. Faraday Soc., 43, 87 (1947).

(16). T. W. Taylor and W. Baker in N.V. Sidgwick, "Organic Chemistry of Nitrogen," Oxford Press, London, (1942) p. 523.

(17). A. Wohl, Ber., 32, 3486 (1899).

(18). A. E. Tschitschibabin, Ber., 56, 1879 (1923).

(19). F. W. Bergstrom and J. S. Buehler, J. Am. Chem. Soc., 64, 19 (1942).

(20). A. E. Tschitschibabin and O.A. Seide, J. Russ. Phys. Chem. Soc., 46, 1216 (1914).

(21). F. Blau, Monatsh., 7, 621 (1886).

(22). L. Balbiano, Gazz. Chim. ital., 11, 396 (1881).

(23). C. W. L. Bevan, J. Chem. Soc., 655 (1953).

(24). W. B. Whalley, J. Chem. Soc., 2241 (1950).

(25). F. Reizenstein and W. Breuning, J. prakt. Chem., 83, 97 (1911).

(26). R. Adams and V.V. Jones, J. Am. Chem. Soc., 69, 1803 (1947).

(27). W. T. Caldwell and E.C. Kornfeld, J. Am. Chem. Soc., 64, 1695 (1942).

(28). P. Friedlander and H. Ostermaier, Ber., 15, 332 (1882).

(29). G. Wenzel, Monatsh., 15, 453 (1894).

(30). J. Sice', J. Am. Chem. Soc., 75, 3697 (1953).

(31). J. C. Cain, Ber, 38, 2511 (1905).

(32). M. L. Crossley, R. H. Kienle, and C. H. Benbrook, J. Am. Chem. Soc., 62, 1400 (1940).

(33). C. K. Ingold, "Structure and Mechanisms in Organic Chemistry," Cornell University Press, Ithaca, New York, (1953) p. 306.

(34). J. Meisenheimer, Ann., 323, 205 (1902).

(35). D. G. Manly and E. D. Amstutz, J. Org. Chem., 21, 516 (1956).

(36). G. Gonis, M. S. Thesis, Lehigh University, 1959.

(37). F. H. Seubold Jr., J. Org. Chem., 21, 156 (1956).

(38). J. Hine, J. Am. Chem. Soc., 72, 2438 (1950).

(39). J. E. Stevens, C. L. McCabe, and J. C. Warner, J. Am. Chem. Soc., 70, 2449 (1948).

(40). G. Akerlof, J. Am. Chem. Soc., 50, 1272 (1928).

(41). J. Hine and M. Hine, J. Am. Chem. Soc., 74,5266 (1952).

(42). A. Unmack, Z. physik. Chem., 129, 349 (1927).

(43). H. L. Bradlow and C. A. Vanderwerf, J. Org. Chem., 16,1143 (1951).

(44). C. K. Banks, J. Am. Chem. Soc., 66, 1127 (1944).

(45). A. L. Wilds, "Organic Reactions," Vol. II, John Wiley and Sons, Inc., New York (1944) p. 203.

(46). A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," John Wiley and Sons, Inc., New York (1953) p. 23.

(47). S. Glasstone, K. Laidler, and H. Eyring, "The Theory of Rate Processes," McGraw-Hill Co. Inc., New York, (1941) p. 199.

(48). A. E. Waugh, "Elements of Statistical Methods," McGraw-Hill Book Co., New York (1943) p. 168.

(49). C. F. H. Allen and J. R. Thirtle, Org. Syn., Col. Vol. III, p. 136.

(50). M. G. Ettlinger and J. E. Hodgkins, J. Am. Chem. Soc., 77,1831 (1955).

(51). R. Shriner, R. Fuson and D. Curtin, "The Systematic Identifcation of Organic Compounds," John Wiley and Sons, Inc., New York (1958) p. 212.

(52). S. F. Birch and D. T. McAllan, J. Chem. Soc., 2556 (1951).

(53). L. A. Brooks and H. R. Snyder, Org. Syn., Col. Vol. III, p. 698.

(54). P. J. Ashworth, G. H. Mansfield, and M. C. Whiting, Org. Syn., 35, 20 (1955).

(55). W. W. Hartman and R. Phillips, Org. Syn., Col. Vol. II, p. 233.

VITA

Robert Joseph Petfield, son of William E. and Mary B. Petfield, was born September 26, 1930 in Bethlehem, Pennsylvania. He attended St. Ursula Parochial School and later was graduated from Allentown Central Catholic High School in June, 1948.

In September 1948, he entered Moravian College and received the degree of Bachelor of Science in Chemistry in 1952. In the fall of 1952, he commenced graduate study at Lehigh University, serving as a teaching assistant in general chemistry and the organic laboratory.

In July 1953, he was married to the former Valeria O. Szilagyi and at present is the father of two children, Dennis aged five and Diane aged two.

In the summer of 1953 he received the Quaker Oats Chemical Company Fellowship which led to the first reported 2-methoxyfuran and some of its precursors.

After spending two years in the U. S. Army as an administrative personnel specialist he worked for the General Aniline and Film Corporation thence he returned to Lehigh University. In June 1957, he was awarded the degree of Master of Science in chemistry. After several attempts to prepare ethyl 2-pyridyl pyruvate he turned to the present investigation sponsored in part by the Armstrong Cork Company and later by the Althouse Chemical Company.

He is a member of the American Chemical Society, the Society of the Sigma Xi, the Tau Kappa Epsilon Fraternity and the St. Ursula Holy Name Society.