

STUDIES ON THE MECHANISM OF AROMATIC ALKYLATIONS

- PART A: THE PREPARATION AND PROPERTIES OF
2,6-DI-TERTIARY-BUTYLPHENOL
- PART B: KINETIC STUDIES OF THE ALKYLATION OF
PHENOLS WITH TERTIARY HALIDES
- PART C: THE MECHANISM OF THE INHIBITION OF
PHENOL ALKYLATIONS BY OXYGENATED
COMPOUNDS

By

Frank A. Cassis, Jr.

AN ABSTRACT

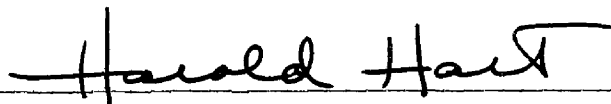
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DOCTOR OF PHILOSOPHY

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Approved

A handwritten signature in dark ink, appearing to read "Harold Hart", is written over a horizontal line.

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ABSTRACT

A kinetic study of the uncatalyzed alkylation of phenol was first reported in 1949 (1). The present investigation is concerned with further elucidation of the mechanism of this reaction, using the following experimental approaches: (a) a study of the effect of large ortho alkyl groups on the properties and para reactivity of the phenol molecule; (b) a detailed kinetic analysis of the alkylation of phenol with triphenylmethyl chloride in dilute solution and in an inert solvent; and (c) an investigation of the kinetics and mechanism of the reported inhibition of phenol alkylations by oxygenated compounds (1, 2).

2,6-Di-*t*-butylphenol was prepared by the alkylation of *p*-bromophenol with an excess of isobutylene, followed by reductive debromination with Raney Nickel-Aluminum alloy in alkaline solution. This phenol possessed a sterically hindered phenolic hydroxyl group, the presence of which was demonstrated by its complete insolubility in Claisen solution, and by the position of the infrared hydroxyl absorption band at 2.76μ . The rates of para bromination and diazonium coupling for this compound were found to be negligible when compared to those for 2,6-xyleneol. This is attributed to the greater steric inhibition of the customary para activating resonance of a

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hydroxyl group by the bulky tertiary butyl groups. Attempted nitrations of 2,6-di-*t*-butylphenol resulted in either cleavage of a tertiary butyl group to give 2,4-dinitro-6-*t*-butylphenol, or, under milder conditions, oxidative coupling to 3,3',5,5'-tetra-*t*-butyldiphenoquinone.

Relative rates of para tertiary butylation at 50° were determined for phenol, *o*-cresol, *m*-cresol, *p*-cresol, *o*-*t*-butylphenol, 2,6-xyleneol, and 2,6-di-*t*-butylphenol. The reaction was carried out using the phenol to be alkylated in large excess, and was followed by absorbing the evolved hydrogen chloride in sodium bicarbonate tubes followed by Volhard analysis for the chloride ion. The alkylation rate decreased markedly as the size and/or number of ortho substituents was increased. This indicates that the formation of the reaction transition state under the conditions employed is less favored when the phenolic hydroxyl group is sterically hindered.

A precise kinetic study of the alkylation of phenol and *o*-cresol with triphenylmethyl chloride was made in *o*-dichlorobenzene at 88°. The reaction was readily followed by measuring the increase in pressure of evolved hydrogen chloride at various time intervals in a constant-volume system.

It was found that the reaction was auto-catalyzed by the product, hydrogen chloride. When this material was introduced initially, overall third order kinetics were observed, the reaction being first order each in phenol, trityl chloride, and the hydrogen chloride. A mathematical analysis of the auto-catalyzed reactions demonstrated that the alkylation rate was satisfactorily expressed by the two-term equation:

$$\frac{dp}{dt} = k_0[\text{phenol}][\text{halide}] + k_1[\text{phenol}][\text{halide}][\text{hydrogen chloride}]$$

The values of k_0 and k_1 were determined graphically from the above expression. These constants were used to obtain calculated values of the reaction pressure at various times, which were in excellent agreement with the experimental values over the entire reaction. The k_0 value was observed to decrease markedly in going from phenol to o-cresol; however, the k_1 value for the latter approaches that obtained for the unsubstituted phenol. This indicates that the transition state requires maximum steric freedom of the hydroxyl group for the uncatalyzed portion of the alkylation.

A carbonium ion mechanism involving preliminary solvation of the halide by the phenolic hydroxyl group, or by the hydrogen chloride

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when present, was shown to be consistent with all the observed facts. The possibility of phenyl trityl ether as an intermediate, followed by acid catalyzed rearrangement to the alkylated phenol was shown to be untenable.

A precise kinetic study was also made of the inhibitory effect of varying amounts of dioxane and tetrahydropyran on the alkylation of phenol by t-butyl chloride at 50°. This inhibition is apparently due to the formation of oxonium type complexes between the ether added and the hydroxyl group of the phenol, which decreases the amount of phenol available for participation in the alkylation process.

A comparison of the observed reaction half times and those calculated for a 2:1 phenol-dioxane complex were in excellent agreement. Accordingly, the mono-functional tetrahydropyran was observed to give only half as much inhibition per mole as that obtained for dioxane.

References

1. H. Hart and J. H. Simons, J. Am. Chem. Soc., 71, 345 (1949).
2. J. J. Bordeaux, M.S. Thesis, Michigan State College (1949).

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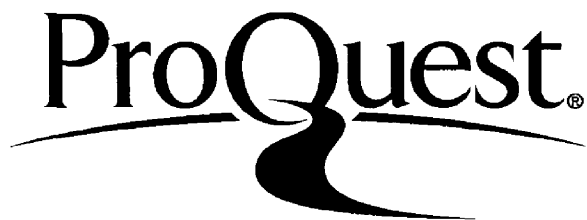
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TO MY MOTHER

INTRODUCTION

The alkylation of the aromatic nucleus has long been an important process to the organic chemist. Although several mechanisms of alkylation have been postulated over the past half-century, there have been only a relatively few kinetic studies of the reaction.

The uncatalyzed alkylation of phenol with tertiary halides, discovered in 1927 (1), conveniently provides an ideal system for a kinetic study of the mechanism of the alkylation process. Such an investigation was undertaken by Hart and Simons in 1949 (2). On the basis of their experimental evidence these investigators indicated the improbability of a high energy or simple ionic intermediate, and proposed instead what was termed as "the amphoteric medium effect." This effect depends in essence on the amphoteric properties of phenol for a one-step condensed phase reaction quite similar in theory to the termolecular mechanisms of Lowry (3), which have been more firmly established recently by Swain (4, 5).

The kinetic data obtained by Hart and Simons did not, however, entirely disqualify the possibility of a carbonium ion mechanism for the alkylation reaction. In view of the increasing evidence favoring

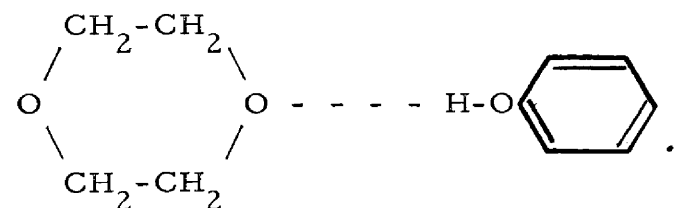
a carbonium ion intermediate in this and many other organic reactions, it was obvious that additional experimental evidence was necessary in order to establish a mechanism for the alkylation reaction that was consistent with all the known facts.

This study is therefore concerned with a further elucidation of the mechanism of this reaction by three experimental approaches.

First, it appeared desirable to synthesize phenols with large alkyl groups in the ortho positions, such as 2,6-di-*t*-butylphenol, and to study the effect of such groups on the rate of alkylation in the para position. If the mechanism were of the S_N1 type, then in an equivalent or identical solvent the rate of alkylation should not be greatly affected by the presence of large alkyl groups ortho to the hydroxyl. On the other hand, should the reaction involve a concerted mechanism, particularly one requiring coordination of the phenol with the halogen of the alkyl halide in the transition state (2), one would expect a decrease in the rate of para alkylation due to steric hindrance of the hydroxyl group by the bulky ortho substituents. Several recent investigations have demonstrated the large steric effect of such substituents on the reactivity and spectrum of the phenolic hydroxyl group (6, 7, 8). In all these cases, however, there was a substituent present in the para as well as the ortho position, thereby making a study of aromatic substitution reactions impossible.

Second, an examination of the kinetic data reported by Hart and Simons indicated the need for a kinetic analysis of this reaction in dilute solution, and in an inert solvent. This would permit the determination of the precise rate order with respect to phenol, and avoid various explanations that are necessary when the phenol is present in excess as the reaction solvent.

Third, in partial support of their concerted mechanism Hart and Simons demonstrated the inhibitory effect of dioxane on the alkylation of phenol. Bordeaux (9) later showed that this inhibition was probably due to the formation of a 1:1 oxonium complex between phenol and dioxane of the type



If the presence of an unhindered hydroxyl group is required in the transition state of the alkylation reaction, such a complex would indeed account for the large inhibition observed.

In view of the bi-functionallity of dioxane, however, it was of interest to investigate the stoichiometry and mechanism of this inhibition in more detail. A re-examination of the kinetic method used by Bordeaux created some doubt as to the accuracy of the

stoichiometric determination, and indicated that more precise kinetic data for the inhibition of phenol alkylations by dioxane were needed in order to firmly establish the nature of the postulated oxonium complex. In addition, it seemed advisable to verify the generality of the inhibition by extending this work to other oxygenated compounds.

The three approaches enumerated above have all been satisfactorily completed. For the sake of clarity in describing the studies carried out and the bearing that they have on the alkylation mechanism, this thesis has been developed in three experimental sections. However, it should be pointed out that each part is an outgrowth of the one preceding it, thus giving a series of stepping stones leading ultimately to an interpretation of the mechanism of the uncatalyzed alkylation of phenol.

HISTORICAL

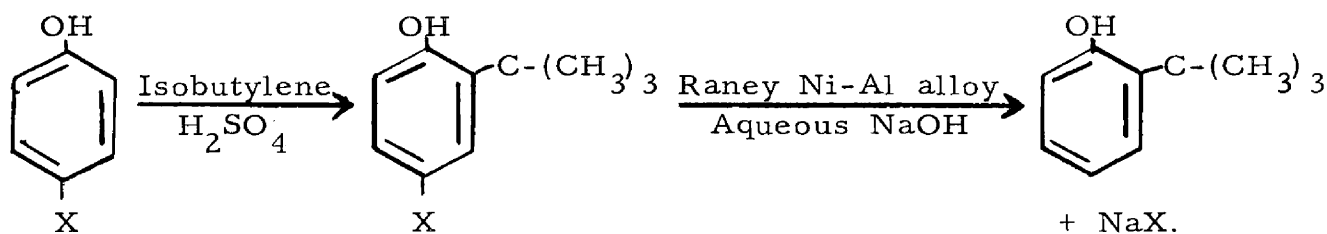
A. Preparation and Properties of Hindered Phenols

The preparation of alkylated phenols is quite commonly accomplished through the well-known Friedel and Crafts reaction using such catalysts as aluminum chloride, sulfuric acid, zinc chloride, and others. In most cases, however, the preponderance of product is the para substituted phenol. This orientation is even more striking when the alkylation is carried out with tertiary halides or alcohols. Indeed, Hart has recently described, for example, a preparation of p-t-butylphenol in 90-95% yields by this method (10), and several workers (1, 12) have reported previous to this that the direct alkylation of phenol was not satisfactory for the synthesis of o-t-butylphenol.

In 1934, however, Chichibabin (13) reported the synthesis of several ortho alkyl phenols in good yields from alcohols, phenols, and a phosphoric acid catalyst. Although the alkylation of phenol itself was not described by Chichibabin, predominant ortho substitution was reported for the benzylation and tertiary butylation of o-cresol. This unique orientation effect attributed to the use of phosphoric

acid was re-investigated by Hart and Haglund (14) in 1950 and the 6-t-butyl-o-cresol reported by Chichibabin was shown to be the 4-isomer.

Recently (15) the synthesis of o-t-butylphenol was reported in 70 percent yields using the scheme which is outlined below:



The raney Nickel-Aluminum alloy reduction of the halogenated intermediate, carried out in alkaline solution, prevented the rearrangement of the o-t-butylphenol to the para isomer.

2,6-Di-t-butylphenol has been reported by Pardee and Weinrich (16), and Stillson and Sawyer (17), the latter authors being the only ones to indicate its method of synthesis. The procedure used was quite similar to that described above for the o-t-butylphenol, except that the reduction step was carried out using potassium and liquid ammonia. No indication of yield was given.

It might be well to mention here some previous studies on the properties of hindered phenols. Following their synthesis of 2,4,6-tri-t-butylphenol in 1945, Stillson, Sawyer, and Hunt (8) investigated the properties of this compound. This phenol was found to be

insoluble in aqueous and alcoholic alkali and showed no customary phenol coloration with either aqueous or alcoholic ferric chloride. Treatment of the phenol, however, with a solution of phosphomolybdic acid and ammonium hydroxide yielded a deep blue color. This test, first developed by Platkovskaya and Vatkina (18) in 1937, will detect as little as one part hindered phenol in 8,500 parts of alcohol. All attempts to prepare a derivative utilizing the customary reactions of the hydroxyl group failed, except for the formation of a crystalline benzoate by refluxing a hexane solution of the sodium salt of the phenol (formed in liquid ammonia solution) with benzoyl chloride.

Shortly following the introduction of the class of compounds known as the hindered phenols, Coggeshall (6) conducted a study of these materials in order to determine the effect of ortho substituents on the intermolecular hydrogen bonding of phenols. This phenomenon is readily recognized in the infrared due to the formation of an absorption band at 3.0μ characteristic of hydroxyl groups in such complexes. In dilute solution in non-polar solvents, where there is little chance for hydrogen bonding to occur, only an absorption band at 2.75μ is obtained which is characteristic of the unperturbed hydroxyl group. Consequently, a wave shift of 0.25μ is obtained for phenol in going from dilute to concentrated solution. Coggeshall

postulated that large alkyl groups ortho to the hydroxyl would sterically minimize intermolecular hydrogen bonding and thereupon reduce this wave shift, with the magnitude of the reduction being a measure of the hydroxyl hindrance by the ortho substituents present. Various alkylated phenols were studied and divided into the following classes by virtue of the wave shift exhibited:

1. Unhindered phenols. Wave shift $> 0.15\mu$

Examples: p-cresol, 2,6-dimethyl-4-t-butylphenol

2. Partially hindered phenols. Wave shift $> 0.04\mu$ but $< 0.15\mu$

Examples: 2-methyl-4,6-di-t-butylphenol
2-t-butyl-4-methylphenol

3. Hindered phenols. Wave shift $< 0.04\mu$

Examples: 2,6-di-t-butyl-4-methylphenol
2,6-di-sec-butyl-4-methylphenol

The ultraviolet absorption spectrum of o-t-butylphenol reported by Hart (15) is very similar to that of phenol, with maxima of almost identical extinction coefficients at 271 and 278m μ . This was compared to the spectrum of p-t-butylphenol which is nearly identical to that of the ortho isomer, except that the entire spectrum is shifted by 6 m μ toward the red (peaks at 277 and 283 m μ). The spectrum of p-cresol as reported by Wolf and Herold (19) shows a similar shift toward the longer wavelengths, whereas o-cresol has its maxima at almost

identical wavelengths as phenol. This spectral shift due to a para alkyl substituent, regardless of its size, has been used as a criterion for structure assignment studies of alkylated phenols (14).

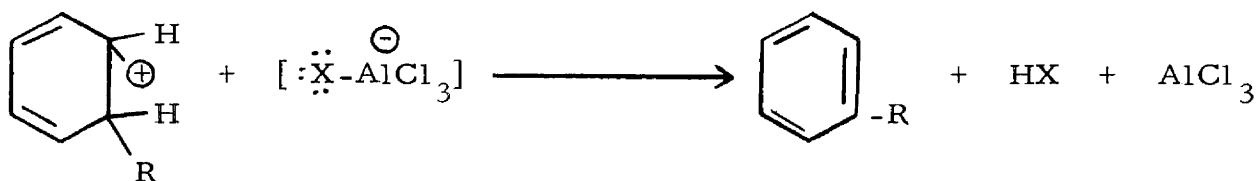
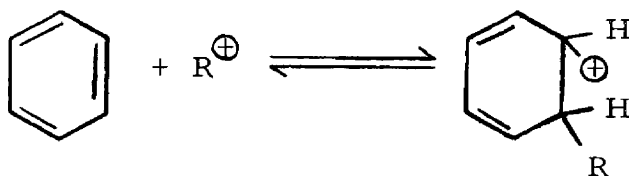
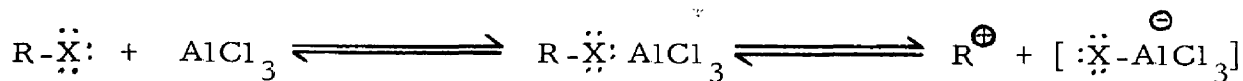
Before concluding, it should be pointed out that all the previous investigations have demonstrated the effect of ortho substituents on the reactivity of the hydroxyl group and do not show what effect, if any, these substituents have on the usual ring activation by the polar hydroxyl group. For this reason, a study of the spectra and para reactivity of a compound such as 2,6-di-t-butylphenol would be quite valuable and interesting.

B. The Mechanism of Aromatic Alkylation

Aromatic nuclear substitution has been divided into free radical and ionic mechanisms, with the latter subdivided into electrophilic and nucleophilic reactions. The ionic electrophilic substitutions have long been the center of attention, for in this class have been placed such important reactions as nitration, halogenation, acylation, sulfonation, and the reaction under consideration here, the Friedel-Crafts alkylation process.

Although few kinetic studies have been made of the mechanism of aromatic alkylation, ionic intermediates, such as those usually

associated with halogenation and nitration, have been favored by many investigators. The general mechanism for the aluminum chloride catalyzed alkylation consists of the formation of a carbonium ion, followed by electrophilic attack on the aromatic nucleus.



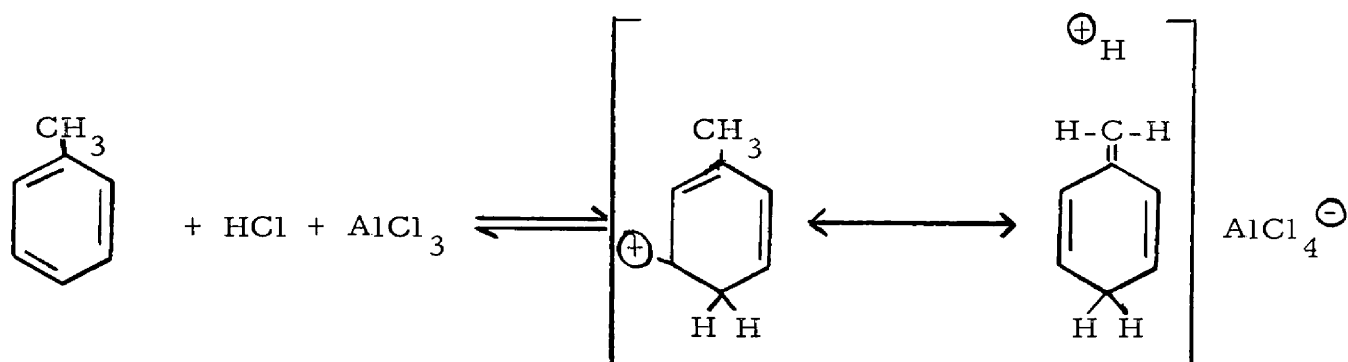
Considerable evidence has been obtained to explain the function of the catalyst in this reaction, as is shown in the first equation above. Although a solution of aluminum halide in benzene or of ethyl chloride in benzene shows negligible conductivity, it has been shown that a solution of all three conducts an electrical current with migration of aluminum to the anode compartment (20). More recent evidence in favor of preliminary carbonium ion formation was obtained through ready interchange of halogen in the presence of aluminum bromide. Thus, when benzyl chloride, and aluminum bromide were mixed in benzene solution, the offgas from the reaction

contained 25.67 percent HCl, and 74.33 percent HBr. On the basis of formation of the ion $[\text{:}\ddot{\text{C}}\text{l}^{\ominus}\text{-AlBr}_3]$, the values of 25 and 75 percent would be expected (21). Also, the fact that α -phenylethyl chloride racemizes rapidly in the presence of aluminum chloride and other Friedel-Crafts catalysts is best explained by the formation of the planar carbonium ion (22).

There has been a great deal of doubt concerning the subsequent steps of the alkylation reaction because of the reported formation of benzene-aluminum chloride complexes (23). By employing gallium trichloride as the alkylation catalyst, Ulich and Heyne (24) have obtained, however, the equilibrium constant for the formation of the catalyst-halide complex, and have shown that the rate of alkylation is directly proportional to the concentration of this complex and of the aromatic hydrocarbon. It was concluded, therefore, that a further activating function of the catalyst was negligible.

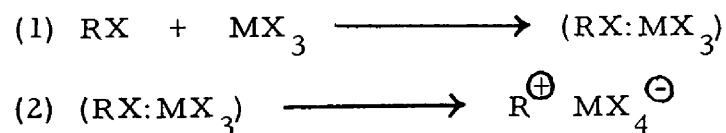
Since the function of the catalyst in this reaction consists in the generation of carbonium ions from the alkyl halide, it would be expected that other starting materials and reagents leading to carbonium ions should be capable of effecting alkylation. Indeed, Price (25) has summarized the use of olefins, alcohols, ethers, and esters for starting materials in the presence of such catalysts as boron trifluoride, hydrogen fluoride, and sulfuric acid.

Perhaps a brief mention should be made at this point of the school of thought concerning the ionic intermediate proposed for electrophilic aromatic substitution. Dewar (26) suggests that the electrophilic species reacts with the aromatic molecule through the formation of a π -complex. Several types of experimental data have shown the suitability of these π -electrons for such dative bond formation. Thus, Andrews and Keefer (27) have attributed the solubility of aromatic hydrocarbons in aqueous silver nitrate to the formation of complexes such as $\text{Ar-Ag}^{\oplus}$ and $\text{Ar-Ag}_2^{\oplus\oplus}$, while a similar explanation for the solubility of HCl-AlCl_3 mixtures in benzene was made by Brown and Brady (28). In a recent extensive study of such complexes, however, Brown and co-workers (29) have postulated the existence of aromatic carbonium salts of the type $\text{ArH}^{\oplus}\text{Al}_2\text{Br}_7^{\ominus}$ and $\text{ArH}^{\oplus}\text{AlBr}_4^{\ominus}$ (where Ar is C_6H_6), which can serve as a highly polar medium for the formation and reaction of ionic intermediates in the Friedel-Crafts reaction. These carbonium ion salts (σ -complexes) were found for benzene, toluene, m-xylene, and mesitylene and are illustrated by the following example:



In this connection it is of interest to note that a simple linear relationship was shown to exist between the stability of such σ -complexes and the rate of aromatic substitution (30). No such relationship is known to exist between substitution rates and the stability of the π -complexes originally proposed by Dewar (26).

At the same time, Brown and co-workers (29) extended their investigation of the AlCl₃-HCl catalyst to include its relationship with alkyl halides, which are generally used as substituting agents in the Friedel-Crafts reaction. Determination of the molecular weight of aluminum bromide in methyl bromide solution from various vapor pressure measurements indicated that these components existed as a 1:1 complex. It was therefore concluded that the initial phase in the customary aromatic alkylation reaction is the formation of a catalyst-alkyl halide complex, followed by ionization as a possible, but not essential, second stage.



It naturally follows that the ionization step would be expected to increase in importance when going from a primary to a tertiary alkyl halide.

With the cationic mechanism of aromatic substitution well established by the early forties, Simons and co-workers (31, 32) presented some challenging kinetic studies on the hydrogen fluoride catalyzed alkylation of toluene with t-butyl chloride. These papers show that although an ionic intermediate will explain the type of reaction rate curves obtained, the reaction proceeds at too rapid a rate to allow for the energy requirements of such an intermediate. On the basis of experimental observations, Simons (31) proposed a third-order mechanism which he termed the "amphoteric medium effect." This mechanism involved simultaneous bond-making and bond-breaking in the transition state, to avoid the necessity of a high energy ionic intermediate. It should be pointed out here that such experimental observations as the fact that the hydrogen fluoride catalyzed alkylation of benzene with d-sec-butyl alcohol yields sec-butyl benzene with 99.5 percent racemization, while in accord with the cationic mechanism, would be difficult to explain on the basis of the concerted mechanism suggested by Simons (36).

The rate of the reaction studied by Simons and co-workers was highly dependent on the pressure of the hydrogen fluoride catalyst. Since the kinetic activity of this catalyst in the reaction mixture was not known, nor its variance with temperature changes, it was not practical to study the rate over a temperature range in order to determine the activation energies. In addition to this, these reactions involved a material that was corrosive to glass, and therefore required a metal reaction system.

With the discovery by van Alphen in 1927 that phenols could be alkylated in the para position with tertiary alkyl halides in the absence of any added catalysts (1) followed by the work of Bennett and Reynolds (33) and Simons and Hart (34), a reaction was supplied which offered ideal conditions for kinetic study of the alkylation mechanism. The latter workers found that the alkylation with t-butyl chloride was a homogeneous, quantitative reaction that proceeds at a measurable rate at convenient temperatures. If the reaction were carried out in an evacuated glass system, it could readily be followed by means of the increase in pressure due to the evolution of hydrogen chloride gas.

Hart and Simons reported a kinetic analysis of the reaction in 1949 (2). The alkylations were carried out on phenol, p-cresol,

and anisole using t-butyl chloride as the halide. The important experimental observations from this work can be enumerated as follows:

1. The reaction exhibited a high order rate dependency upon phenol concentration.
2. Initial hydrogen chloride pressure had little or no effect on the reaction rate.
3. Calculated energies of activation were quite low, approximately 14-17 k. cal./mole.
4. Anisole failed to react under corresponding reaction conditions.
5. The reaction was almost completely inhibited by the addition of p-dioxane in diluent amounts.

The last two results indicated the importance of the hydroxyl group in the transition state of the reaction. The actual role of the dioxane in the inhibition was not determined by Hart and Simons.

Bordeaux (9) later carried out a kinetic study of the alkylation of phenol using varying amounts of dioxane as a diluent. On the basis of a series of calculations Bordeaux showed that the inhibition was probably due to the formation of a 1:1 oxonium complex between phenol and dioxane. There is no doubt of the merit of the suggestion

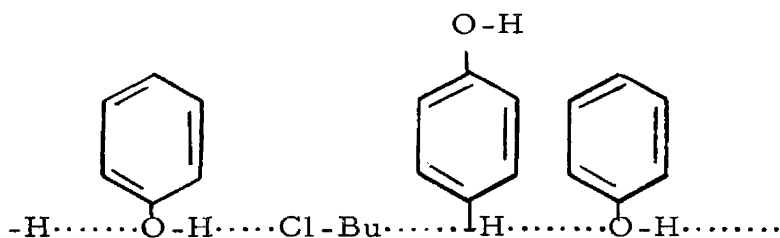
of such complexes for explaining the mechanism of the inhibition, as dioxane is basic and the formation of oxonium salts of this material has been demonstrated previously by Bartlett and Dauben (35). A close examination of the kinetic method used by Bordeaux, however, creates some doubt as to the accuracy of the stoichiometric determination, and indicates the need for more precise kinetic data in order to establish the role of oxygenated materials in the alkylation reaction.

On the basis of the experimental results enumerated above, Hart and Simons (2) considered three mechanisms, all of which could satisfactorily account for the rate data obtained.

The possibility of the formation of an unstable phenyl alkyl ether, followed by rearrangement of this ether in the presence of the generated hydrogen chloride, was discarded, since the reaction showed no catalysis or auto-catalysis by hydrogen chloride. A second possibility involved the preliminary formation of a free or solvated carbonium ion, followed by electrophilic attack at the para position of the phenol. Such a mechanism was not favored, since it was pointed out that calculations similar to those of Pearlson and Simons (31) gave a minimum energy requirements of 28 k.cal. per mole for the formation of a solvated t-butyl carbonium ion, in phenol at 45°. The

experimentally determined activation energies were 14-17 k.cal. per mole.

The third mechanism which was proposed by these investigators, and which has been mentioned before, was termed the "amphoteric medium effect." This mechanism, especially suited to the enumerated observations, involves a one-step condensed phase reaction which makes use of the amphoteric properties of phenol. Thus, it consists of polymolecular attack on the chlorine of the alkyl halide, and on the para hydrogen of phenol, as is shown schematically below.



The solid lines indicate the bonds prior to reaction, and the dotted lines indicate the bond shifts when reaction occurs. The chief point here is the concept of simultaneous breakage and formation of bonds with no requirement for a high energy intermediate capable of independent existence. This mechanism finds support in that it is similar to the suggestion of acid-base catalysis by Lowry (3), and the termolecular mechanisms proposed recently by Swain (4, 5).

Price (36) has criticized the inference of Simons and co-workers that free carbon cations, such as those postulated as intermediates in

the Friedel-Crafts reaction, cannot exist. He points to the indisputable evidence of Hughes and Ingold (37), of Hammett (38), and of Bartlett (39), for the transient existence of the triphenylmethyl cation in many nucleophilic displacement reactions. Swain (4), however, has shown quite conclusively that triphenylmethyl halides, and even methyl halides (5), can undergo displacement in benzene solution, requiring in the rate-determining step both pull on the leaving group and attack on carbon; i.e., by a "concerted" push-pull, or termolecular process. Even though benzene was the only solvent used, there is no apparent reason why such mechanisms should be less concerted in alcohol or even water solution (40).

Following a study of the formation of triphenylmethyl ethers with phenol and methyl alcohol, Swain pointed out that although kinetic order has been used more than any other evidence as a criterion for deciding which mechanism is operating in a particular case, it does not depend on mechanism alone, but rather on the degree of participation of the solvent (5). Thus, triphenylmethyl chloride in water gives first order kinetics (both attack on carbon and solvation of chlorine by the solvent); benzyl chloride with mercuric nitrate in water solution gives second order kinetics (attack on carbon by solvent and solvation of chlorine by phenol, and no participation by

solvent). Therefore, Swain prefers to say that all displacements involving triphenylmethyl, t-butyl, benzyl, and methyl halides in benzene solution occur by one mechanism, a termolecular one, regardless of the kinetic order observed.

It might be well to point out, before concluding this survey, that all through the history of the theory of aromatic substitution, reactions involving the phenol molecule have offered some unexplainable results on the basis of conventional electrophilic substitution. For example, when iodine monochloride is used as a chlorinating agent, iodine rather than chlorine is introduced into the benzene ring as a result of the unequal charge distribution between the dissimilar halogen atoms:



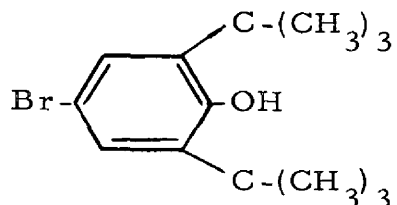
Although some chlorination occasionally occurs even with iodine monochloride, Militzer has shown (41), and it is not clear why, that iodine monobromide acts exclusively as a brominating agent for phenol. Similarly, although the kinetics of halogenation of benzene is consistent with the carbonium ion mechanism, Painter and Soper (42), and recently Berliner (43) have indicated from iodination kinetics that the halogenation of phenols is a different, more complex process.

In addition, although the reactions of formaldehyde and aromatics supposedly proceed by attack of a protonated formaldehyde cation, $\oplus \text{CH}_2\text{-OH}$ (36), the well-known condensation of formaldehyde and phenols presumably involves a different mechanism, deriving its driving force from something other than the electrophilic nature of the formaldehyde-proton complex (36).

PART A

THE PREPARATION AND PROPERTIES OF
2,6-DI-TERTIARY-BUTYLPHENOL

Experimental

4-Bromo-2,6-di-t-butylphenol

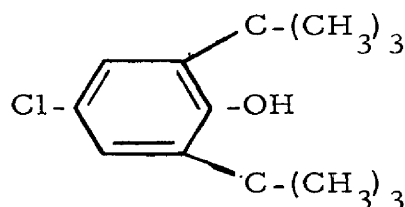
A mixture of p-bromophenol (86.5 g., 0.5 mole), 200 ml. of benzene, and 4 ml. of 98 percent sulfuric acid was treated at $65 \pm 5^\circ$ for ten hours with two moles of isobutylene in an alkylation vessel similar to that used by Stillson, Sawyer, and Hunt (8). After extraction with 20 percent alkali to remove the unreacted p-bromophenol or any monoalkylated product, the benzene solution was washed with water until neutral to litmus, dried over anhydrous sodium sulfate, and the solvent removed at reduced pressure. Any t-butylbenzene formed by alkylation of the solvent was also removed at this point. The residue was fractionally distilled in a nitrogen atmosphere through a Vigreux column. The distillate, b.p. $126-128^\circ$ at 4 mm., yielded white crystals on cooling, which, recrystallized from aqueous ethanol, melted at $83-83.5^\circ$. The yield was 51 g. (35.6%).

Anal. Calcd. for $\text{C}_{14}\text{H}_{21}\text{OBr}$: Br, 28.03 percent. Found: Br, 27.95 and 27.75 percent.

When p-xylene was used as the solvent, alkylation of the solvent was minimized, and the di-alkylated product was obtained in a yield of 47 percent. At 70° in the absence of a solvent, and with the isobutylene under 200 p.s.i. in a steel bomb, 23 percent of the desired product was obtained.

In each case, neutralization of the initial alkali extract, and fractional distillation of the organic layer yielded 20 to 25 percent of 4-bromo-2-*t*-butylphenol, b.p. 129-131° at 6 mm.

4-Chloro-2,6-di-*t*-butylphenol



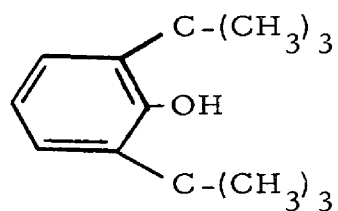
A mixture of p-chlorophenol (64 g., 0.5 mole) and 100 g. of 85 percent sulfuric acid was treated at 70±5° for three hours with 1.5 moles of *t*-butyl alcohol in a three-necked, one-liter flask equipped with a stirrer and thermometer. Fifty grams of 98 percent sulfuric acid was added rapidly at the end of each of the first two hours, in order to maintain the acid concentration. After stirring for an additional hour, the syrupy red solution was poured onto cracked ice and the product extracted with benzene. The benzene solution was

then washed with bicarbonate and extracted with Claisen solution. The benzene layer was dried over anhydrous potassium carbonate and the solvent removed at reduced pressure. The residue was fractionally distilled through a Vigreux column. The distillate, b.p. 111-115^o at 5 mm., yielded white crystals on cooling, which, re-crystallized from ligroin, melted at 75-76^o. The yield was 29 g. (24%).

Anal. Calcd. for C₁₄H₂₁OCl: Cl, 14.76 percent. Found: Cl, 14.61 and 14.70 percent.

The Claisen solution extract yielded about 5 percent of 4-chloro-2-t-butylphenol after neutralization. When the above procedure was followed with p-bromophenol, 5 percent of 4-bromo-2-t-butylphenol was recovered from the alkali extract, but the benzene solution yielded no 4-bromo-2,6-di-t-butylphenol; only polymeric residues were obtained.

2,6-Di-t-butylphenol



A mixture of 4-bromo-2,6-di-t-butylphenol (10 g., 0.035 mole), 50 ml. of 95 percent ethanol and 30 g. of Raney nickel-aluminum

alloy in a one-liter flask equipped with a reflux condenser was treated, over a period of thirty minutes with 300 ml. of 10 percent aqueous sodium hydroxide. The mixture was refluxed for an additional hour, filtered, and the nickel washed with 10 percent alkali followed by benzene. The aqueous layer was then cooled and poured into 250 ml. of concentrated hydrochloric acid. After extraction with benzene, combination of the washings and drying over anhydrous sodium, sulfate, the solvent was stripped using a Vigreux column. The residue yielded 6.7 g. (93%) of 2,6-di-*t*-butylphenol, b.p. 94-98° at 5-6 mm.

The product of the alkali reduction was a colorless liquid, while the same product reported by Stillson and Sawyer (17) was claimed to be a yellow solid, m.p. 38-39°. The product was therefore subjected to infrared analysis as a test of purity and structure. The spectrum showed the presence of the hindered hydroxyl at about 2.76 μ but also indicated the presence of a small amount of an aliphatic carbonyl compound. This impurity was suspected of being 2,6-di-*t*-butylcyclohexanone, which has been isolated as the major product from the reduction of 4-bromo-2,6-di-*t*-butylphenol by hydrogen in the presence of palladium chloride on charcoal (44).

The liquid reaction product was, therefore, further fractionated in an attempt to eliminate the carbonyl impurity. When the

fractionated product was solidified in dry ice and filtered immediately, a white solid was obtained, which gave white prisms from 95 percent ethanol; m.p. 37-37.5°. A sample of the 2,6-di-t-butylcyclohexanone (supplied to us by R. H. Rosenwald, Universal Oil Products Company) gave a melting point of 38-38.5°; when mixed with a small amount of the crystalline phenol, immediate liquefaction occurred at room temperature.

Anal. Calcd. for $C_{14}H_{22}O$: C, 81.5 percent; H, 10.68 percent.

Found: C, 81.6 and 81.45 percent; H, 10.80 and 10.75 percent.

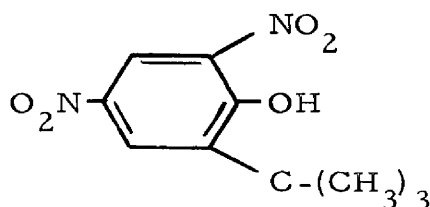
Potassium in Liquid Ammonia Reduction

In a one-liter, two-necked flask, 400 g. of liquid ammonia was condensed on 10 g. (0.035 mole) of 4-bromo-2,6-di-t-butylphenol. Potassium metal was introduced (mixture continuously stirred) until the solution took on a permanent blue color. Ammonium chloride was added to destroy the unreacted potassium and the ammonia was allowed to evaporate overnight. The residue was dissolved in petroleum ether, washed with water until neutral to litmus and dried over anhydrous sodium sulfate. The solvent was removed at reduced pressure and the residue fractionated through a Vigreux column. The product, b.p. 94-98° at 5-6 mm., weighed 3.5 g. (48.6%).

Tests for the Hindered Phenol

The 2,6-di-*t*-butylphenol obtained from both methods of reduction yielded a deep blue color when treated with phosphomolybdic acid and ammonium hydroxide (18). The product was insoluble in 20 percent sodium hydroxide, and showed no color change when treated with alcoholic ferric chloride solution.

Nitration: 4,6-Dinitro-2-*t*-butylphenol



To 1 g. of 2,6-di-*t*-butylphenol was cautiously added 5 ml. of a 1:1 mixture of concentrated nitric and glacial acetic acids. The solution was warmed for one minute, then poured onto cracked ice. After filtration and recrystallization from dilute methanol, yellow plates were obtained, m.p. 124-125°. (The literature value [46] for 4,6-dinitro-2-*t*-butylphenol is 124°.) A mixed melting point with picric acid, 85-100°, proved that only one alkyl group underwent cleavage during the nitration.

Anal. Calcd. for $C_{10}H_{13}O_5N_2$: N, 11.66 percent. Found: N, 11.82 and 11.73 percent.

Attempted Nitration Without Cleavage

To 1.03 g. (0.005 mole) of 2,6-di-*t*-butylphenol was added a solution of 0.315 g. (0.005 mole) of concentrated nitric acid in 2 ml. of glacial acetic acid, and the temperature was held below 0°. After several minutes, the mixture was poured onto cracked ice. The reddish-brown oil was washed by decantation with water and sodium bicarbonate, then dissolved in 95 percent ethanol. On dilution with water, crystals separated which on recrystallization from aqueous ethanol gave dark red needles, m.p. 245-247°.

Anal. Calcd. for $C_{28}H_{40}O_2$: C, 83.2 percent; H, 9.85 percent. Found: C, 82.5 and 82.7 percent; H, 9.69 and 9.65 percent.

This product was identified as 3,3',5,5'-tetra-*t*-butyldiphenone on the basis of the above analysis, coupled with a subsequent study in this laboratory by W. J. Detroit on the properties and spectra of several substituted diphenonequinones (45).

Acid Rearrangement

The warm solution of five drops of 98 percent sulfuric acid in one ml. of 2,6-di-*t*-butylphenol was further heated for several minutes, then poured into cold water. The organic product was taken up in petroleum ether, and the latter washed with 10 percent aqueous

alkali to extract any rearranged product. Acidification, followed by extraction with ligroin and evaporation of the solvent yielded crystals which, recrystallized from ligroin, melted at $55-55.5^{\circ}$; mixed with an authentic sample of 2,4-di-t-butylphenol, $55-56^{\circ}$.

Relative Rates of Bromination and Coupling

Treatment of 2,6-di-t-butylphenol with bromine in carbon tetrachloride solution showed no loss in bromine color over a period of thirty minutes. Similar treatment using 2,6-xylenol as the phenol gave decoloration of the bromine solution in less than one minute.

To a cold solution of 1 g. of 2,6-xylenol in 20 ml. of 5 percent sodium hydroxide, was added an excess of diazotized aniline. After a few minutes the solution was filtered free of small amounts of resinous material, and the filtrate was neutralized with acetic acid. After filtration and recrystallization from ligroin, yellow plates were obtained, m.p. $94.5-95.5^{\circ}$. The melting point reported for 4-phenylazo-2,6-xylenol is $95-96^{\circ}$.

Attempted coupling with 2,6-di-t-butylphenol in alcoholic sodium hydroxide under the same conditions resulted in quantitative recovery of the starting material.

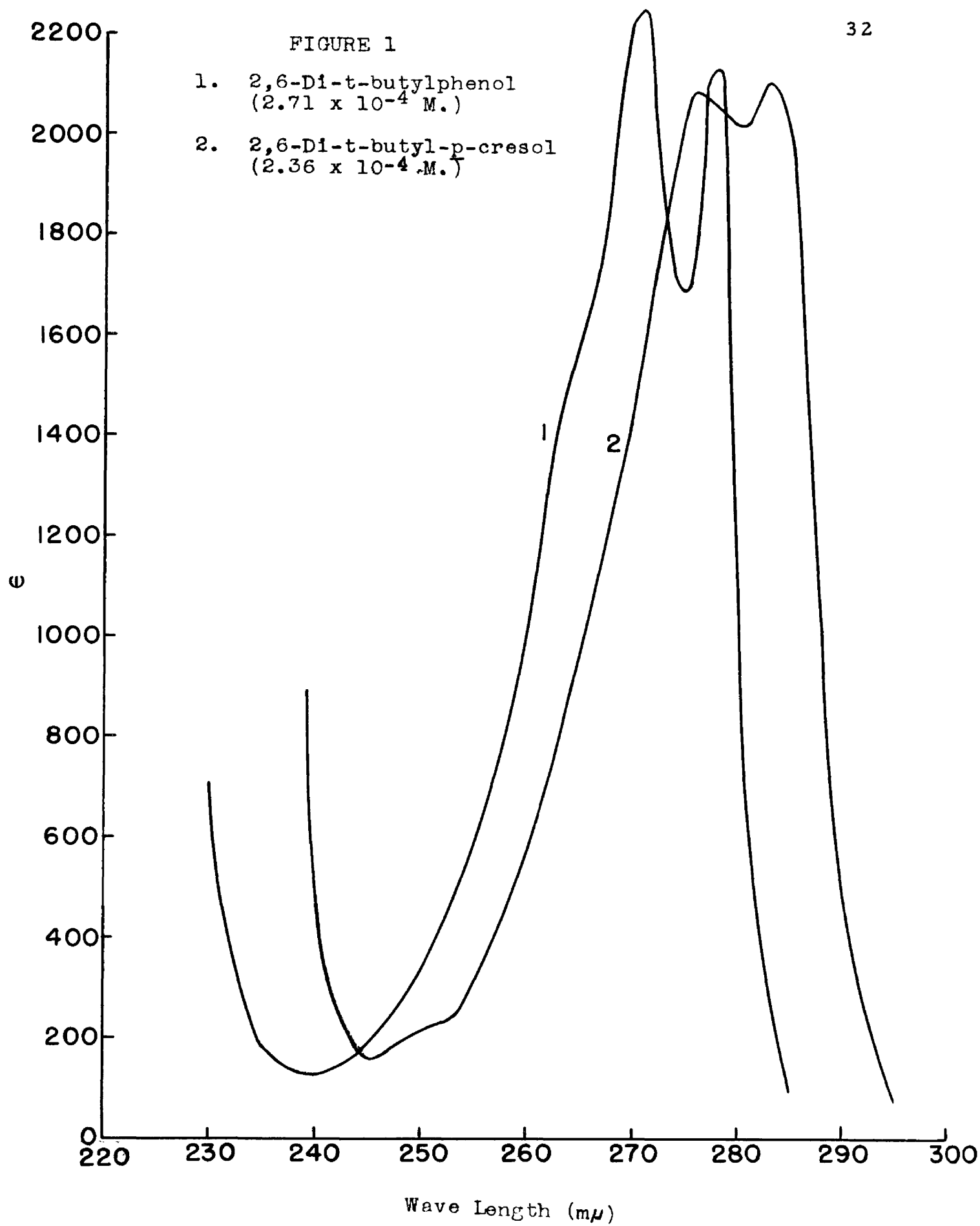
Absorption Spectra

The ultraviolet absorption spectra shown in Figures 1 and 2 were determined with a Beckman spectrophotometer (Model DU), using 1-cm. quartz cells. The cyclohexane solvent (for the phenols) was freed of benzene by passage through activated silica gel, followed by fractionation. Absolute alcohol was used as solvent for the quinone. The 2,6-di-*t*-butyl-4-methylphenol was obtained from the Koppers Company, Pittsburgh, Pennsylvania, and was purified by distillation (146° at 20 mm.) and recrystallization from ligroin, m.p. 69-70°.

The infrared absorption spectra (Figures 3 and 4) were obtained through the generosity of Dr. G. B. B. M. Sutherland and Dr. W. R. Vaughan, University of Michigan, Ann Arbor.

FIGURE 1

1. 2,6-Di-t-butylphenol
(2.71×10^{-4} M.)
2. 2,6-Di-t-butyl-p-cresol
(2.36×10^{-4} M.)



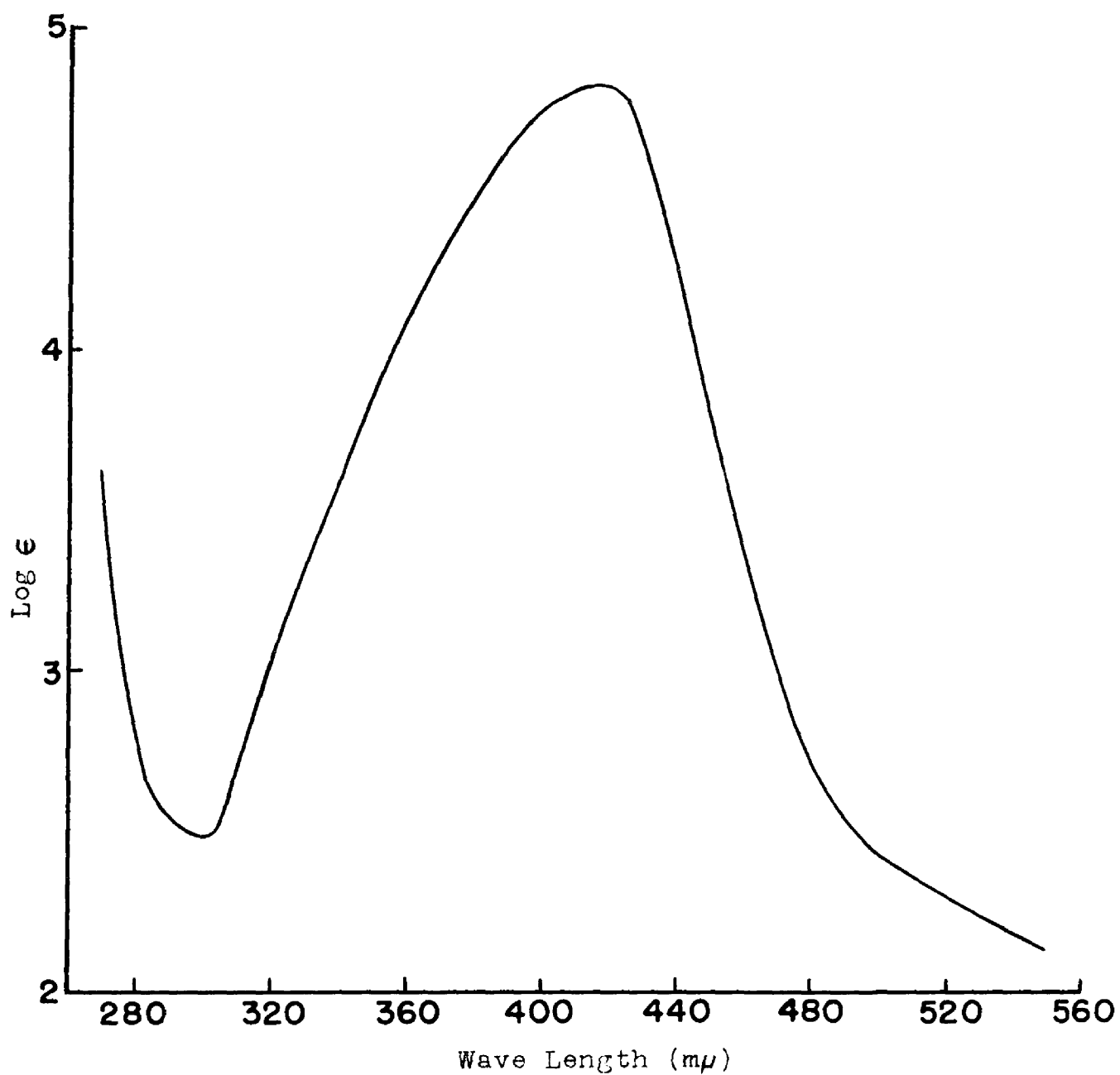


FIGURE 2. The Ultraviolet Absorption Spectrum of 3,3',5,5'-tetra-*t*-butyl-*p*-diphenoquinone.

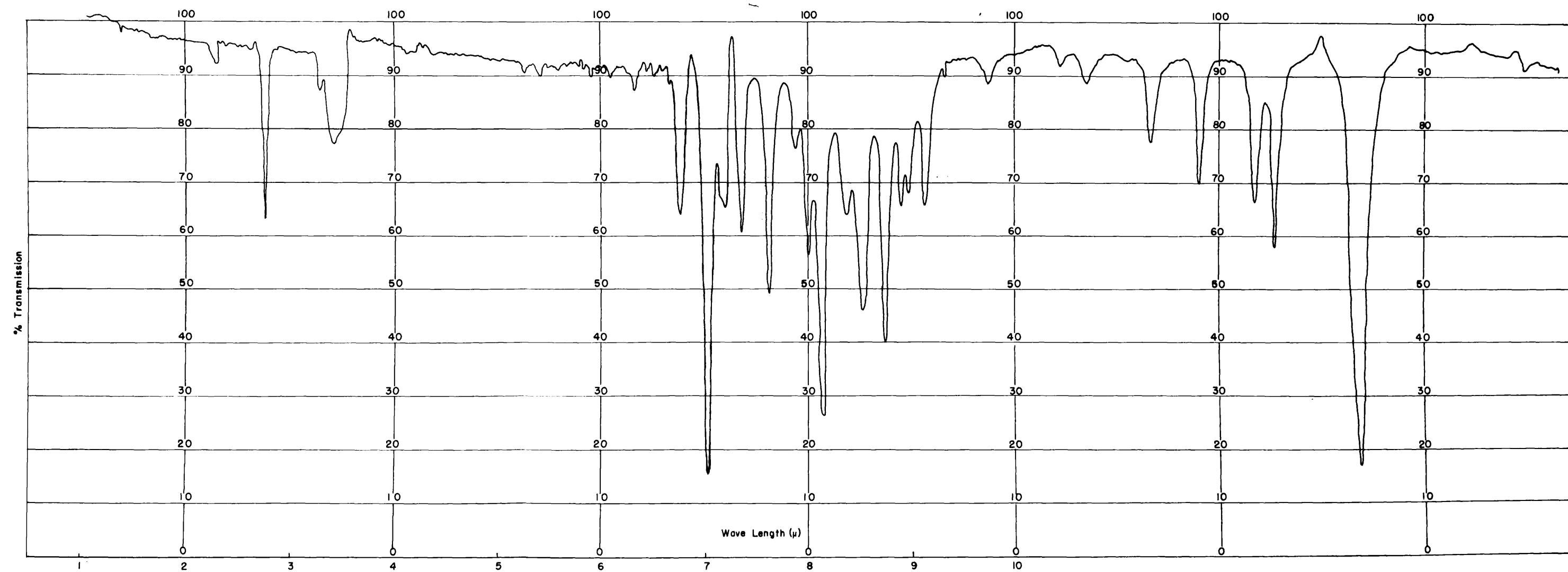


FIGURE 3. Infrared Absorption Spectrum of 2,6-Di-1-butylphenol

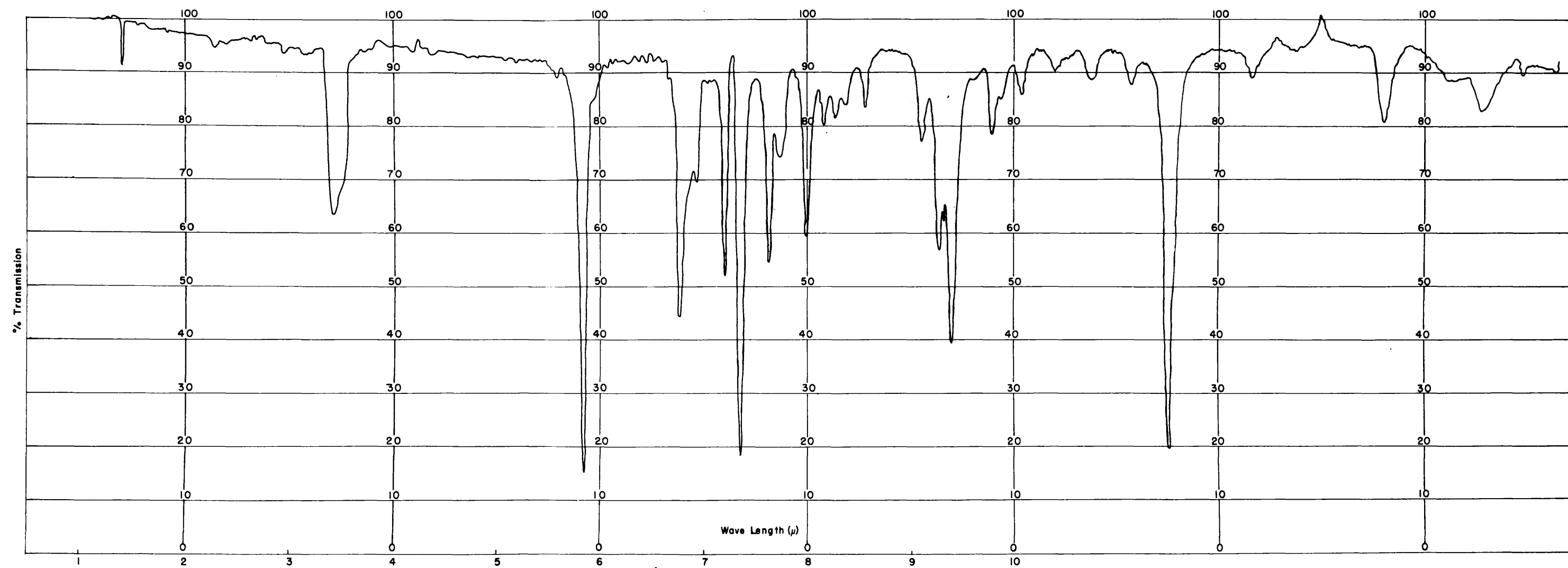
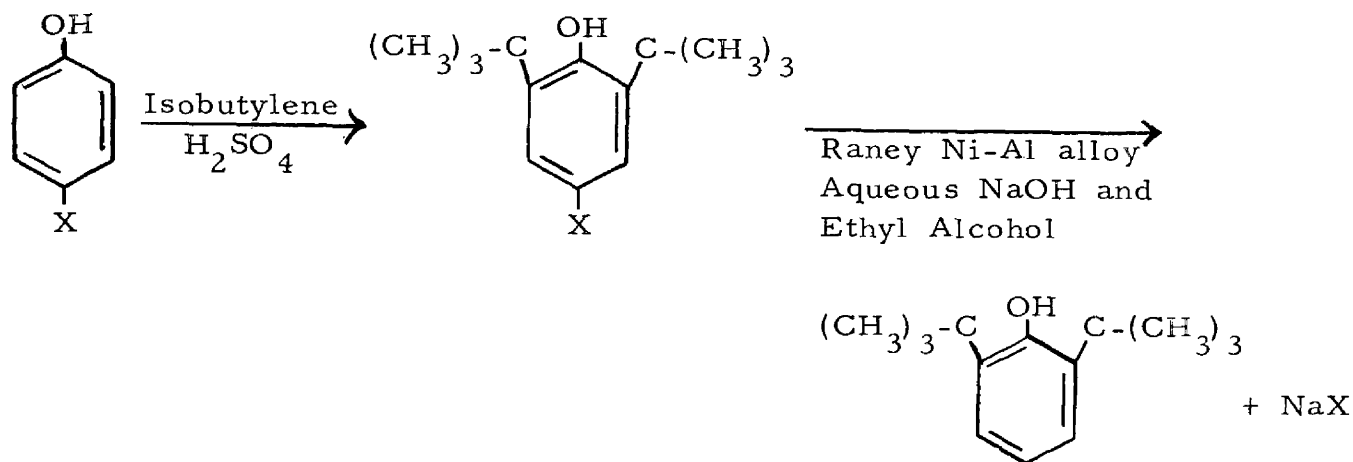


FIGURE 1 Infrared Absorption Spectrum of 2,6-Di-t-butylcyclohexanone

Discussion

The following scheme represents the series of reactions by means of which 2,6-di-*t*-butylphenol was synthesized in this work:



This procedure is essentially the same as that outlined by Hart (15) for the preparation of *o*-*t*-butylphenol.

Considerable difficulty in the alkylation step was encountered in attempting to introduce the second *t*-butyl group. This difficulty undoubtedly arises because of the high steric requirements of the two *t*-butyl groups. A study of the alkylation step was therefore made, and the results are summarized in Table 1.

Experiment 2 (Table 1) produced the highest yield of the desired product. Considerable quantities of *t*-butylbenzene were obtained in Experiment 1 due to preferential alkylation of the solvent after introduction of the first *t*-butyl group. The formation of such

TABLE 1

EFFECT OF ALKYLATION METHOD ON YIELD OF
2,6-DI-T-BUTYL-4-HALOPHENOL

Expt.	Reagents			Cat- alyst	Temp. (° C.)	Time (hrs.)	Mono-	Di-
	Phenol	Alkyl- ating Agent	Solvent				Alkyl- ated Prod- uct (%)	Alkyl- ated Prod- uct (%)
1	p-bro- mo- phenol	isobu- tylene	ben- zene	98% H ₂ SO ₄	65± 5	10	29	35.6
2	p-bro- mo- phenol	isobu- tylene	p-xy- lene	98% H ₂ SO ₄	65± 5	10	18	47
3	p-bro- mo- phenol	isobu- tylene*	none	98% H ₂ SO ₄	70		25	23
4	p- chloro- phenol	t-butyl alcohol	85% H ₂ SO ₄		75		5	24
5	p-bro- mo- phenol	t-butyl alcohol	85% H ₂ SO ₄		75			none

* Under 200 p.s.i. in steel bomb.

a by-product was minimized by using p-xylene as the solvent. Attempts to increase the yield of di-alkylated product in Experiment 3, by carrying out the reaction under pressure in a steel bomb and in the absence of a solvent, failed because of increased formation of polymeric residues. The other alkylation method (Experiments 4 and 5), although producing a fair amount of desired product with p-chlorophenol yielded only polymeric materials when the bromoisomer was used.

The reduction of the halogen intermediate was carried out using Raney Nickel-Aluminum alloy and aqueous alkali according to the procedure of Papa, Schwenk, and co-workers (47), and the phenol was solubilized by the addition of ethyl alcohol to the reaction mixture. This reduction method afforded a superior yield (93%) to the procedure of Stillson and Sawyer (17), who used potassium and liquid ammonia. Although the product reported by these workers was a solid, m.p. 38-39^o, both methods of reduction afforded us colorless liquids. At that time, we were informed by Dr. R. H. Rosenwald of the Universal Oil Products Company, that his group had succeeded in preparing what was thought to be crystalline 2,6-di-*t*-butylphenol, m.p. 38-38.5^o, by the reduction of 2,6-di-*t*-butyl-p-bromophenol with hydrogen in the presence of palladium on charcoal. When our phenol

failed to crystallize after the addition of a sample of Dr. Rosenwald's product, both materials were subjected to ultraviolet analysis. While our material gave the characteristic phenol spectrum (see Figure 1), the solid product furnished us by Dr. Rosenwald gave no absorption in this region. This product was subsequently shown to be 2,6-di-*t*-butylcyclohexanone (44). It is known that phenols can be converted to the corresponding cyclohexanones by partial hydrogenation. However, the mild conditions (room temperature and 50 atm.) used by Rosenwald, which effected such a conversion are quite surprising and certainly bear further investigation. For example, Whitaker (48) has reported the preparation of several alkyl cyclohexanones by hydrogenation with Adams platinum catalyst. 2,6-Di-*t*-butyl-4-methylphenol required a temperature of 200° at 150 atm. pressure for conversion to the corresponding cyclohexanone. It might also be pointed out that further hydrogenation to the cyclohexanol was impossible with such a molecule due to the steric protection of the carbonyl by the *t*-alkyl groups.

In view of these observations, the infrared absorption spectrum of our product was obtained, and a slight concentration of the aliphatic carbonyl group was detected by virtue of the characteristic absorption band at 5.8 μ (for example, see Figure 4 for the infrared

spectrum of the pure carbonyl compound). Chemical separation of such an impurity being almost impossible due to the large steric hindrance of the t-butyl groups, the phenol was carefully fractionated and, after freezing in dry ice and immediate vacuum filtration, afforded a solid which gave white prisms from ethanol, m.p. 37-38^o. The infrared spectrum of this product (Figure 3, experimental section) showed no absorption band at 5.8 μ .

A study was also made of the reactions and properties of 2,6-di-t-butylphenol and several points of this study are worthy of discussion here.

When the phenol was nitrated with concentrated nitric acid in glacial acetic acid (1:1) at room temperature, a yellow solid, identified as 4,6-dinitro-2-t-butylphenol was isolated. This product is identical with that obtained by Ipatieff, Pines and Friedman (46) from the nitration of 2,4-di-t-butylphenol. In the latter case, the 4-t-butyl group was cleaved from the ring, whereas in the present instance one of the 2-t-butyl groups was cleaved. This result is also in accord with the report by Stevens (49) of the dealkylation of ortho alkyl phenols during distillation in acidic media, and the rearrangement of o-t-butylphenol to the para isomer in the presence of sulfuric acid, reported by Hart (15). Our product also underwent

rearrangement, to 2,4-di-*t*-butylphenol, under the conditions described by the latter investigator.

An attempt at nitration without cleavage, using a 1:6 nitric to acetic acid mixture at 0° yielded small quantities of dark red needles, m.p. 245-247°, which contained no nitrogen. The analysis of this compound agreed with that calculated for 3,3',5,5'-tetra-*t*-butyl-p-diphenoquinone. Similar oxidation products have been isolated in a number of nitrations of substituted phenols as well as from other phenol oxidations. As further proof of structure, the absorption spectrum of this compound is shown in Figure 2. The major peak in the spectrum, at 418 mμ, is similar to that reported by Valyashko and Shcherbak (50) for diphenoquinone, but shifted slightly toward a longer wave length. Detroit and Hart (51) have recently reported the preparation and spectra of diphenoquinone and several alkylated derivatives.

Several preliminary experiments were carried out to compare the relative para reactivity of this highly hindered phenol with 2,6-dimethylphenol, which by the standards set up by Coggeshall (6) based on the infrared spectrum, would be classed as an unhindered phenol. The large difference in the steric effect of the methyl and tertiary butyl groups is also exemplified by the solubility behavior of the

two compounds. Whereas 2,6-dimethylphenol is soluble in 20 percent sodium hydroxide, the di-*t*-butyl derivative is completely insoluble even in alcoholic potassium hydroxide (Claisen's solution). In the first experiment it was found that the dimethylphenol rapidly decolorized a solution of bromine in carbon tetrachloride while the di-*t*-butylphenol showed no bromination after a much longer period of reaction. More conclusive evidence of decreased reactivity at the para position in the more hindered phenol was obtained by the diazonium coupling reaction. The 4-phenylazo-2,6-dimethylphenol was obtained from the dimethylphenol and diazotized aniline quite easily, while several attempts with the 2,6-di-*t*-butylphenol gave practically quantitative recovery of the starting material.

An explanation of the above results using known electrical effects of alkyl groups appears untenable. The introduction of ortho alkyl groups can affect ring activity by virtue of their inductive and hyperconjugative effects. Berliner (52) carried out a study of the relative electronic effects of the methyl and tertiary butyl groups by measuring the rates of bromination of toluene and *t*-butylbenzene in 85 percent acetic acid. The results of this work show that toluene is brominated five times faster than the *t*-butyl derivative. This difference was attributed to the large degree of hyperconjugation that

is possible in the methyl group, which supposedly overcomes the greater inductive effect of the t-butyl group. In a recent book on hyperconjugation, however, Baker (53) has disclosed the recent kinetic studies of Conn, Hughes, and Jones for the nitration of a series of alkyl benzenes. Although these studies verify the over-all results obtained by Berliner for comparative activity of toluene and t-butylbenzene, these workers are careful to point out that the proportion of isomerides formed in the reaction shed a different light on the explanation of the rate increase in going from t-butylbenzene to toluene. Thus, the following relative rates of reaction were obtained:

Ring Substituent	Me	Et	i-Pr	t-Bu	H
Relative Rate	100	97	87	73	6.8

However, the proportion of isomerides determined gave partial rate factors of the following magnitude:

<u>Ring Substituent</u>	<u>% Ortho</u>	<u>% Meta</u>	<u>% Para</u>
Me	54.6	3.2	42.2
t-Bu	12.3	8.7	79.0

Consequently, even though the over-all rate of nitration of toluene was faster than t-butylbenzene, the apparent activation of the positions meta and para to the alkyl groups is much greater in the latter compound, and must be attributed to the greater inductive effect of the t-butyl group, since there are no α -hydrogens available in this group

for hyperconjugation. Baker, therefore, points out that the determining factor in the over-all rates is the ortho substitution, which is much slower in *t*-butylbenzene because of the larger steric effect of the *t*-butyl group.

On the basis of these studies one would expect a greater para activation in 2,6-di-*t*-butylphenol than in the dimethyl derivative because of the larger inductive effect of the *t*-butyl group. The fact that this is not the case, indicates that an alternative mechanism must be sought. Steric hindrance of the hydroxyl group in the phenol molecule, by the large *t*-butyl groups, could prevent coplanarity between this group and the benzene ring, thereby reducing the electron density at the para position by virtue of a steric inhibition of the usual hydroxyl resonance. This would account for the lack of bromination and diazo coupling which was observed for the hindered 2,6-di-*t*-butylphenol.

Both the ultraviolet and infrared absorption spectra of the 2,6-di-*t*-butylphenol were determined. The former is given in Figure 1 with that of 2,6-di-*t*-butyl-4-methylphenol for comparison. The major peaks at 271 and 278 μ are identical with those of phenol and other ortho alkylated phenols, and indicate the absence of any alkyl group in the para position.

The infrared absorption spectrum is shown in Figure 3. The hydroxyl absorption band occurring at $2.76\ \mu$ is indicative of a highly hindered hydroxyl group, since Coggeshall (6) has shown that an unhindered hydroxyl, in concentrated solution, will exhibit characteristic absorption at $3.0\ \mu$ wavelength due to probable association or intermolecular hydrogen bonding. In 2,6-di-*t*-butylphenol, all intermolecular hydrogen bonding is apparently prevented.

PART B

KINETIC STUDIES OF THE ALKYLATION OF PHENOLS
WITH TERTIARY HALIDES

Experimental

I. Materials

The phenol was J. T. Baker Chemical Company material, and was purified by distillation at atmospheric pressure with a small amount of benzene to remove the water. The fraction boiling 175 to 183° at atmospheric pressure was further fractionated in a Vigreux column, the material boiling from 180 to 182° being retained. The phenol was then degassed and further purified for kinetic samples in an apparatus similar to the one described by Hart and Simons (2). The degassing was accomplished by alternate freezing, evacuation, and thawing. The apparatus design then enabled distillation at 20 mm. in a nitrogen atmosphere, such that a 50 ml. fore-cut could be discarded before collection of the phenol used in the kinetic measurements. The phenol was stored in a desiccator under a nitrogen atmosphere until ready for use.

The t-butyl chloride was Eastman Kodak white label material. This was dried over potassium carbonate (anhydrous), and fractionated in a nitrogen stream, retaining the sample which boiled constantly at 52° at atmospheric pressure and had a refractive index of n_D^{20} 1.3851. The halide was then placed in a small distilling system,

degassed according to standard techniques, and distilled and collected in a nitrogen atmosphere.

The triphenylmethyl chloride (hereafter referred to as trityl chloride) was Mathieson Chemical Company practical grade. This material was treated twice in benzene solution with decolorizing charcoal, followed by recrystallization from benzene-pentane solution. The faintly yellow tinted crystals were filtered rapidly, dried, and stored in a vacuum desiccator over mineral oil. The dried crystals were as coarse as granulated sugar and had a melting point of 110-111^o. All operations in this purification were designed to exclude atmospheric moisture.

The p-dichlorobenzene was fractionated through a Vigreux column with a small amount of benzene to remove traces of water. The fraction boiling 180-181^o at atmospheric pressure was retained and stored in a nitrogen atmosphere.

The other phenols used in the relative rate studies were all carefully fractionated and stored under nitrogen until used. In addition to fractionation, the 2,6-xyleneol (Edcan Laboratories) was recrystallized from petroleum ether, m.p. 49^o. The purification of the 2,6-di-*t*-butylphenol was described in Part I of this thesis.

II. Apparatus

A. Relative Rates of Alkylation

The apparatus used is shown in Figure 1. It consisted of a 125 ml. reaction flask, A, with a nitrogen bubbler extending to the bottom of the flask. The flask was sealed to a condenser at B, which was fitted at the top with a 14/35 male ground glass joint, C. The condenser was attached to a tube, D, with a three-way stopcock, E, whose outlets were fitted with 14/35 male ground glass joints, F, to which sodium bicarbonate tubes were connected. The sodium bicarbonate tubes were connected to a dry ice trap by means of a rubber joint, G. The reaction flask was shaken manually at intervals, and a continuous stream of dry nitrogen gas was bubbled through the reaction mixture during the course of the reaction. The reaction flask was submerged in a constant temperature bath maintained at $50.0 \pm 0.1^{\circ}$ during the experiments.

B. Quantitative Kinetic Measurements

A schematic diagram of the rate apparatus is shown in Figure 2 with photographs of various parts of the system appearing on following pages.

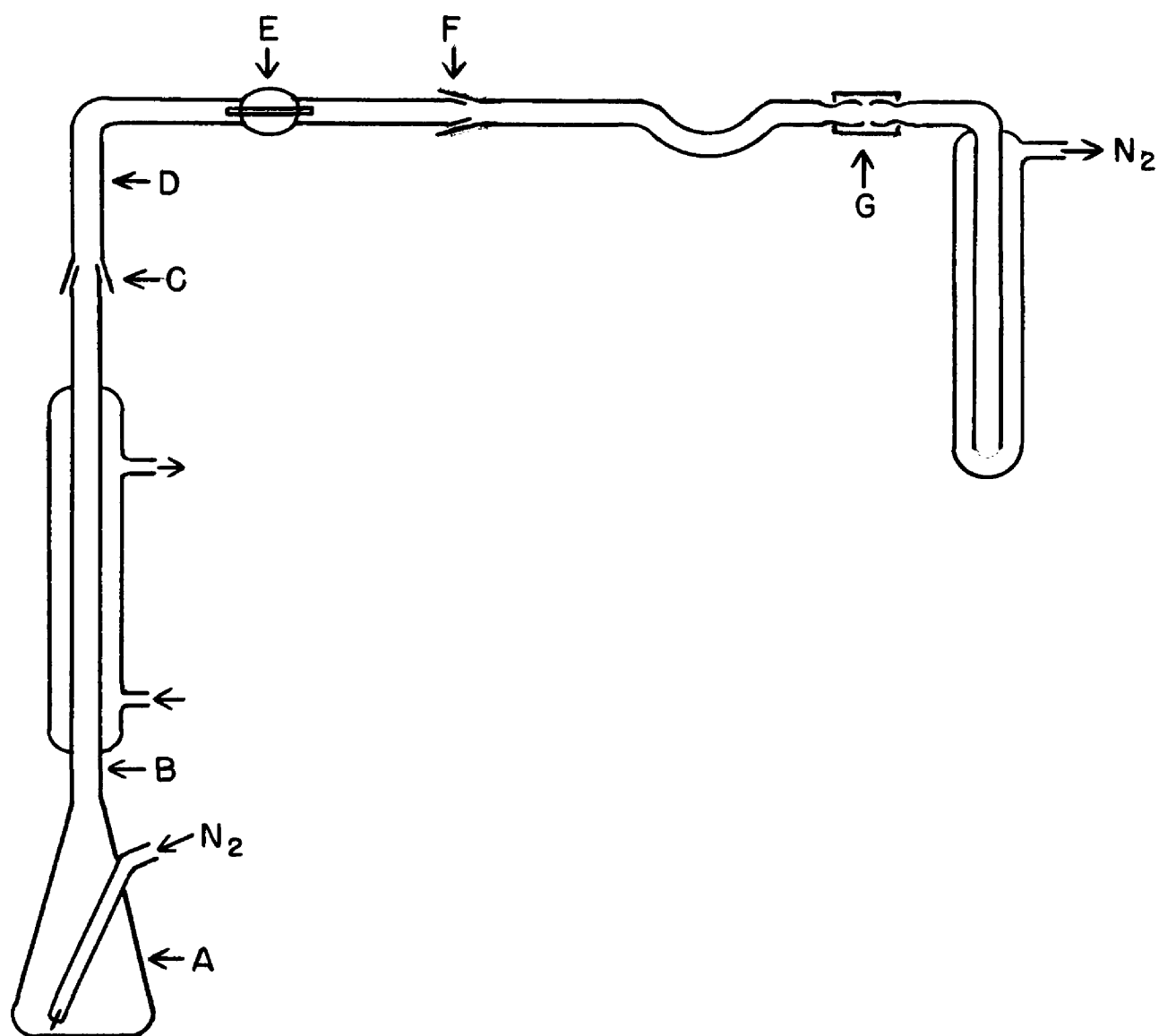


FIGURE 1. Apparatus for the Measurement of Relative Rates of Reaction.

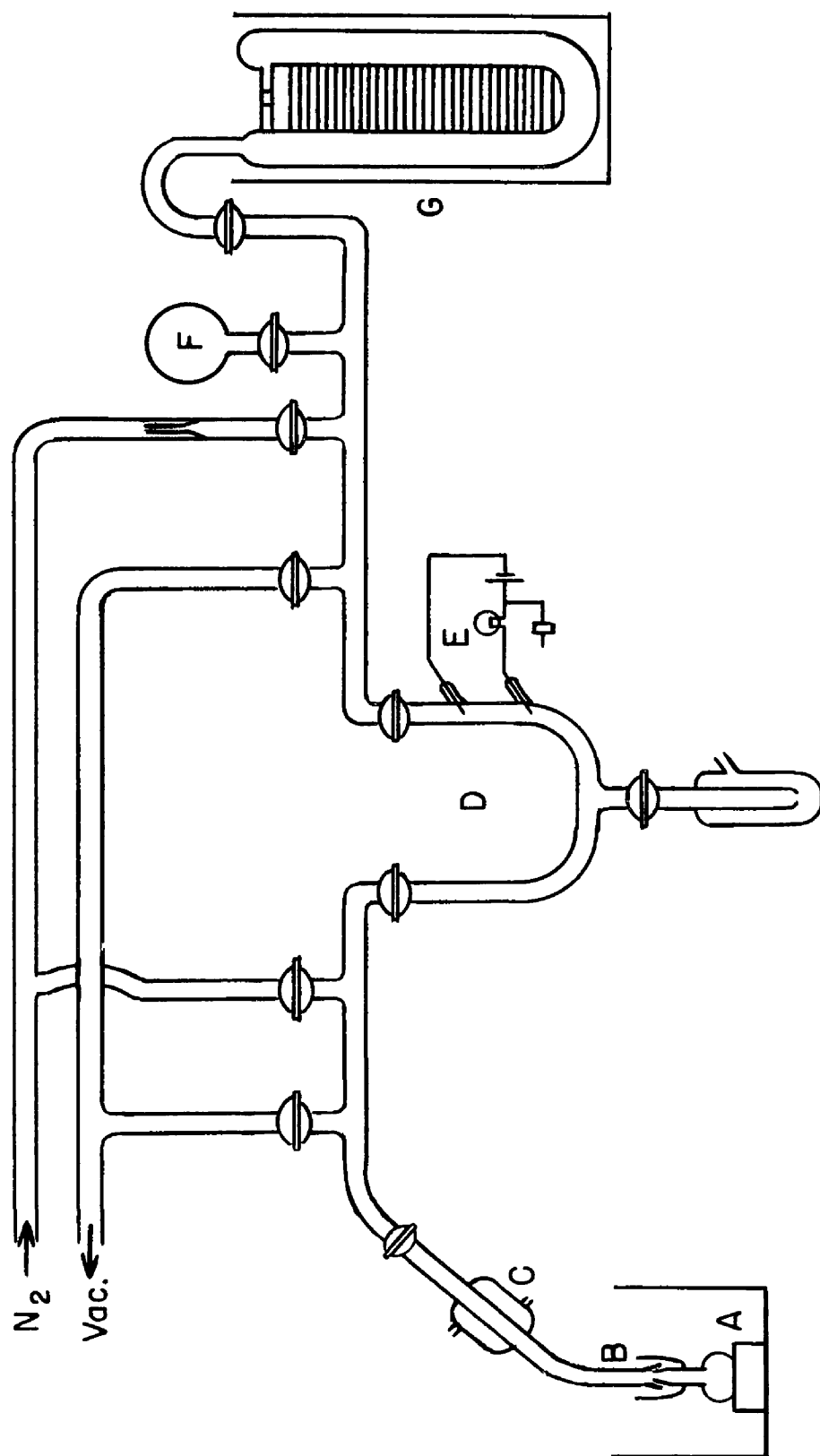
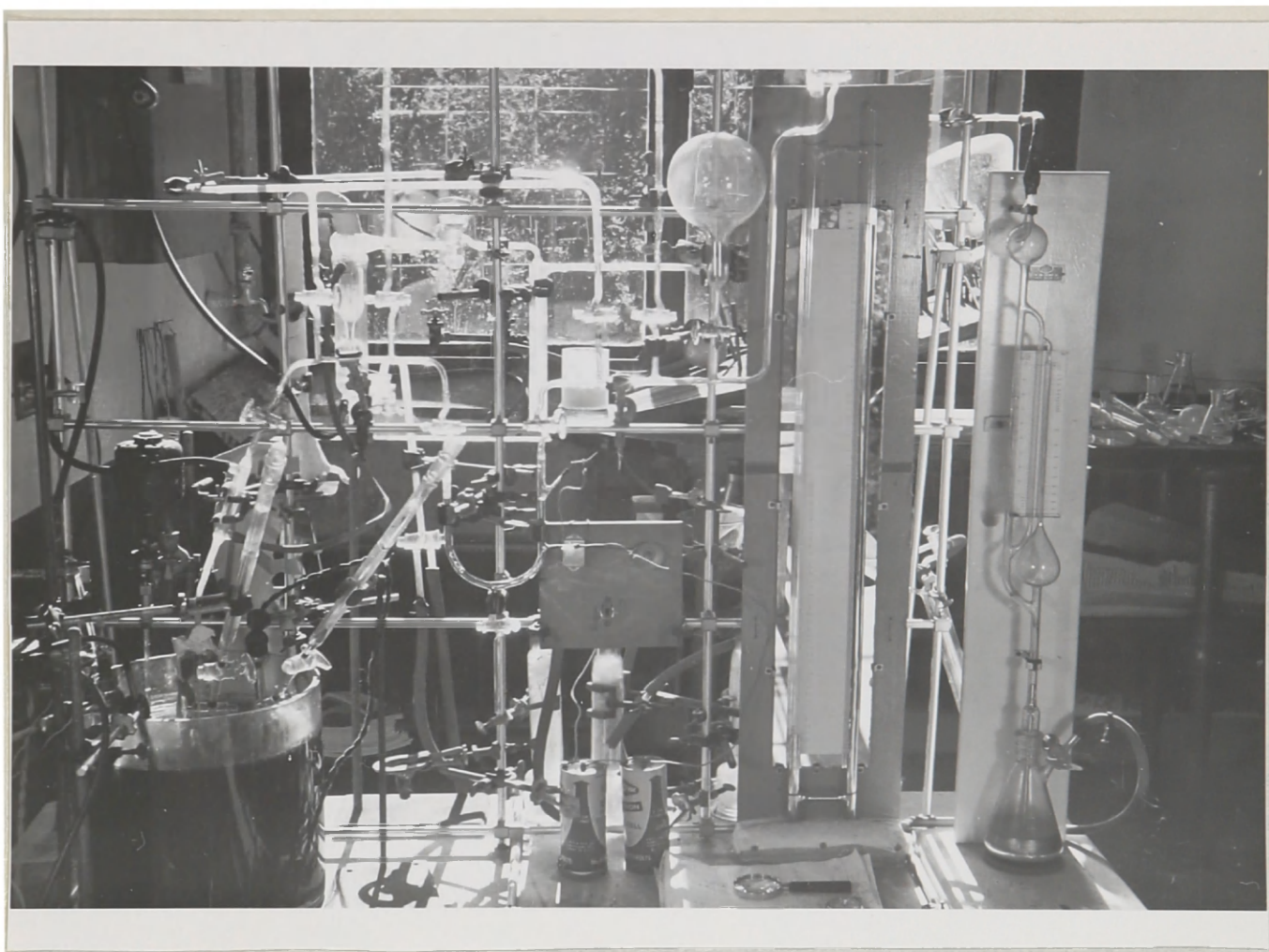
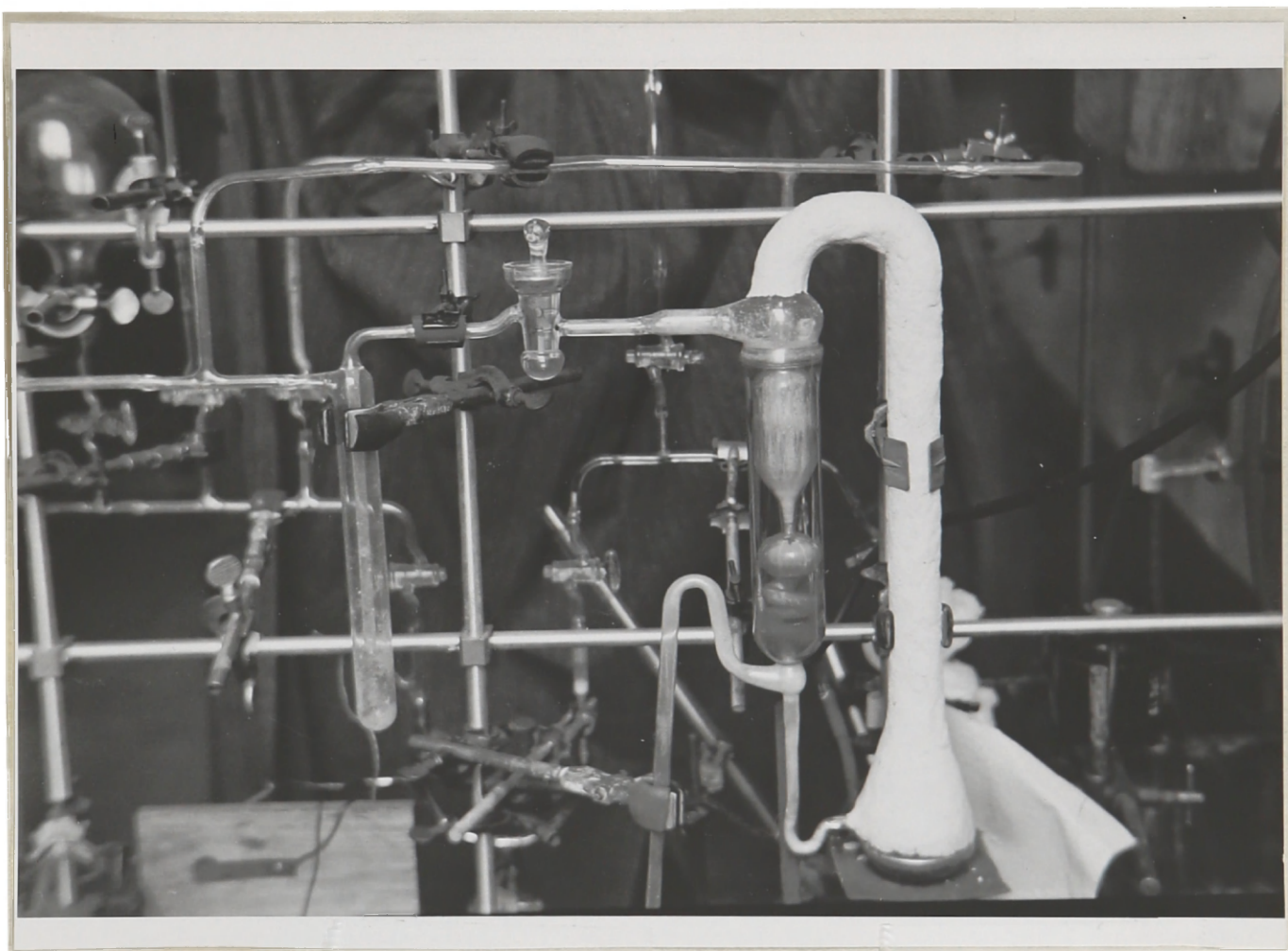


FIGURE 2. The Rate Determining Apparatus.







A well-detailed picture of the reaction flask is shown in the first photograph. It consisted of a 125 ml. Florence flask, sealed at the neck to a mercury seal 14/35 male ground glass joint. The reaction vessel contained two exit tubes joined to the flasks just below the base of the neck. Each of these tubes was connected via two 4-ml. stopcocks to a 15-inch, 15 mm. (O.D.) piece of glass tubing, sealed at the end with a 24/40 female ground glass joint. These tubes thereby furnished the ampoule chambers from which the phenol and halide solutions were admitted to the reaction flask. The reagent ampoules were varying lengths of 12 mm. glass tubing that were sealed off with 1-1/2 inch capillary tip, which would slide into the bore of the top stopcock when the ampoules were placed in the addition chambers. The top of the chambers could be closed off with 24/40 male plugs, so that the reaction system could be completely evacuated.

The reaction flask was connected to the rest of the system through the 24/40 mercury seal joint (B). Since some of the reactions were studied at elevated temperatures, a condenser (C) was used to prevent the distillation of the reactants to cooler parts of the system. The remainder of the reaction side of the differential manometer (D) consisted of 1 mm. capillary tubing with lines to a vacuum and dry nitrogen source.

The outside of the differential manometer contained an electric rest point signalling device (E) which consisted of both a light and buzzer for indicating completion of the circuit. The rest of the system contained a one-liter buffer volume (F), a calibrated manometer (G), and lines to the vacuum and dry nitrogen sources. The nitrogen inlet contained a fine inverted capillary to permit the increase in pressure on the outside of the differential manometer by very small increments.

The nitrogen source was a commercial cylinder. The nitrogen was dried by passing it through a tube of phosphorus pentoxide and the pressure was regulated by means of a mercury blowout valve set at approximately 100 mm. above atmospheric pressure. A Cenco Hy-Vac pump in series with a mercury vapor pump provided the source of vacuum.

The reaction flask was submerged in a constant temperature bath of ethylene glycol, such that 90 percent of the reaction system was thermostatted at $88 \pm 0.01^{\circ}$. Excellent stirring was obtained in the reaction mixture by a glass covered magnetic stirring bar sealed in the reaction flask. Considerable care had to be taken, however, in order to protect the magnetic stirring motor which was placed in the hot glycol bath. A method that finally proved effective

was to encase the rubber electrical lead to the motor in a copper tube that was fastened to the motor case through an airtight brass fitting. The bottom of the case was metal sealed, and the entire outfit coated with glyptal resin and covered with hard-surfaced black friction tape. The reaction flask, when clamped in the bath, rested less than one-half inch above the stirring motor.

III. Method of Measuring Rate and Operation Procedure

A. Relative Rates of Alkylation

The percentage of alkylation during a definite time interval was determined by collecting the evolved hydrogen chloride in a sodium carbonate tube and determining the chloride content by the Volhard method.

The mixture of the t-butyl chloride and substituted phenol was allowed to react, with a slow stream of dry nitrogen bubbling through the mixture. A consistent rate of agitation and nitrogen flow was maintained throughout the measurements. At the end of the defined time interval, the sodium carbonate tube was removed, its contents dissolved in water, and an aliquot was acidified with nitric acid and analyzed for chloride by the Volhard method.

When nitrobenzene was used as the solvent, a blank experiment (in which the phenol was omitted) showed no dehydrohalogenation of the t-butyl chloride under the conditions of the experiment. A qualitative test made in each of the experiments also showed that little if any isobutylene was collected in the dry ice trap, during the course of reaction.

B. The Alkylation of Phenol with Trityl Chloride

(1) Preparation of Samples. Since small traces of water would lead to incorrect data due to the generation of hydrogen chloride by hydrolysis of the halide, extreme care was exercised in the handling of all reagents in order to exclude moisture.

The ampoule, described in the section on apparatus, was drawn out slightly to form a constriction near the top, and then weighed with a stopper. The purified phenol was then pipetted in, the tube filled with dry nitrogen and re-weighed. The previously degassed solvent was then added, the mixture frozen, and the ampoule sealed under vacuum. The weight of o-dichlorobenzene was then obtained by difference when the two halves of the ampoule were weighed.

The trityl chloride was made up by weight in o-dichlorobenzene solution. A specified amount was added to a weighed ampoule, the

mixture frozen, and the ampoule sealed under vacuum. The two halves of the ampoule were then weighed, giving the weight of the solution sample by difference.

When hydrogen chloride was added to test for acid catalysis, the phenol ampoule was attached to a hydrogen chloride generator and the dried gas bubbled through the mixture for several minutes, before the ampoule was sealed.

(2) Measurement Procedure. The method of following the rate of the reaction was to add a known weight of alkyl halide to a known weight of phenol in a thermostatted vessel, and then measure the increase in pressure due to the evolution of hydrogen chloride gas in a constant volume system.

When making measurements, the phenol solution was added to the reaction vessel and temperature and pressure equilibrium were rapidly established. The tertiary halide was then admitted and time versus pressure readings were made. The reaction was followed in most cases until 85 to 100 percent complete.

Thus, the ampoules were placed in the chambers of the reaction flask so that the capillary tip extended into the bore of the top stopcock, and the chambers were closed off to the atmosphere. The entire system was then evacuated, sparked, and checked for leaks.

Mercury was then admitted to the differential manometer until contact with the upper tungsten lead was made. Both sides of the system were then filled with dry nitrogen and twice re-evacuated in order to insure the presence of very little oxygen in the system, and therefore, very little oxidation of the phenol during the course of the reaction. With the system evacuated the phenol solution was admitted to the reaction vessel by turning the stopcock gently in order to break the capillary tip. The tube was then gently flamed and the lower stopcock closed so that the chamber area would not be included in the reaction system volume. (Early work showed that two stopcocks were necessary for this procedure, as small pieces of glass often prevented the closing of the stopcock used to crack the capillary tip.)

After approximately thirty minutes the halide solution was admitted in the same manner as described above. The stopwatch was started as soon as the stopcock was opened admitting the halide, and in all experiments this stopcock was opened for a period of only thirty seconds.

Readings were begun in every case as quickly as possible. The nitrogen was bled in to the outside of the differential manometer in small increments and readings were taken on the "make" of contact with the upper tungsten lead. Readings were taken as frequently

as possible (every few minutes) at the beginning of the reaction and less frequently as the reaction proceeded.

After the completion of a run, the halide addition tube was rinsed with hot aqueous ethanol. The water caused hydrolysis of any trityl chloride that remained behind in the addition tube. These rinsings were therefore analyzed for chloride by the Volhard procedure, and these determinations showed that less than 0.1 percent of the halide remained behind.

The reaction vessel was then thoroughly cleaned, dried and re-joined to the system for the subsequent run.

IV. The Nature of the Alkylations

The reaction between *t*-butyl chloride and phenol, used in the relative rate studies was demonstrated to be essentially quantitative, yielding p-*t*-butylphenol with no dehydrohalogenation.

When nitrobenzene was used as a solvent, Experiments 8 to 10, Table 1, a blank experiment in which phenol was omitted, showed no dehydrohalogenation under reaction conditions.

Trityl chloride was found to react with phenol in the same manner, giving p-tritylphenol. After completion of Experiment 4, Table 2, the reaction mixture was cooled and a white solid separated

rapidly. The precipitate was filtered, and recrystallized from hot benzene; m.p. 280-281⁰. Literature value for p-tritylphenol is 282⁰ (4). Following the completion of Experiment 5, Table 2, the same procedure was used to separate the product of the o-cresoltrityl chloride reaction. Recrystallization from hot benzene gave a white solid, m.p. 185-186⁰.

Anal. Calcd. for C₂₆H₂₂O: C, 89.12 percent; H, 6.33 percent. Found: C, 89.32 percent; H, 6.48 percent.

The melting point of this product is the same as that reported by Iddles and co-workers (54) for the alkylation of o-cresol with trityl carbinol in the presence of a sulfuric-glacial acetic acid catalyst. At the same time and in two subsequent publications (55, 56), Iddles verified the assigned structure (p-trityl-o-cresol) by a series of independent syntheses which eliminated the possibility of ortho orientation for the incoming trityl group, or side chain alkylation of the methyl group.

A blank experiment involving the heating of trityl chloride in o-dichlorobenzene solvent at 90⁰, showed no hydrogen chloride evolution over a period of 24 hours. This indicated that no solvent alkylation had occurred, and that the solvent would not interfere with the rate determinations.

Results and Calculations

I. Relative Rates of Alkylation

The experiments which were carried out are summarized in Table 1. The data obtained from the Volhard analyses were in the form of moles of hydrogen chloride evolved in a given time interval, t . Since this was equivalent to the moles of alkyl halide which had reacted, the percentage of alkylation for time t (last column, Table 1) could be calculated as follows:

$$\% \text{ alkylation} = \frac{\text{moles evolved HCl}}{\text{initial moles of t-butyl chloride}} \times 100$$

Two and sometimes even three check runs were made on each experiment, and as can be seen from the tabulations the results were quite reproducible in spite of the crude rate-determining method used.

II. Alkylations with Triphenylmethyl Chloride

A. Data

Due to the rate-determining method described in the experimental section, a hundred or more time versus pressure readings were obtained in each experiment. Numerous kinetic measurements were carried out; consequently, a complete tabulation of the data

TABLE 1

RELATIVE RATES OF ALKYLATION OF SUBSTITUTED PHENOLS
WITH t-BUTYL CHLORIDE

Expt.	Moles of t-Bu Cl	Substi- tuent on Phenol	Moles of Phenol	Solvent	Moles of Solvent	Total Reac- tion Time (hrs.)	Temp. (° C.)	Alkyl- ation (%)
1	0.01	none	0.1			2	50	41±2 ^a
2	0.005	2-t- butyl	0.05			~	50	2.3
3	0.01	2- methyl	0.1				50	2.7± 0.2
4	0.01	2,6-di- methyl	0.1				50	1.4± 0.2
5	0.005	2,6-di- t-butyl	0.05				50	0.0
6	0.01	4- methyl	0.1				50	2.2± 0.1
7	0.01	3- methyl	0.1				50	22±2 ^b
8	0.1	none	0.1	Nitro- benzene	0.25	24 48	75	9±1 ^b 14±1 ^b
9	0.1	2,6-di- t-butyl	0.1	Nitro- benzene	0.25	24 48	75	0.8 1.3
10	0.1	2,6-di- t-butyl with 0.1 mole phenol	0.1	Nitro- benzene	0.25	48	75	13.7

^a Average of three runs.^b Average of two runs.

from each individual experiment would be prohibitive. A summary of the essential results obtained from nine of the experiments is given in Table 2.

Time versus pressure plots were made for each run, and several of these are illustrated in Figure 3. These curves show the consistency of the measurements in any one experiment, and for the sake of clarity in the drawings only one experimental point out of every ten is included.

Experiments 8 and 9, Table 2, represent two runs carried out with phenol and t-butyl chloride, under the same conditions used by Hart and Simons (2). Since the results obtained in these runs were in agreement with those previously reported, it was assumed that the rate-determining apparatus was functioning properly.

B. Treatment of Data

The experimental plots of pressure versus time (Figure 3) gave "S" shaped curves in all runs except number 7. In this run, the phenol ampoule was saturated with anhydrous hydrogen chloride before being admitted to the reaction vessel. Since the "induction period" was eliminated in this reaction (see Figure 3, curve number 7), it was reasonable to assume that an increase in reaction rate

TABLE 2

KINETIC STUDIES OF THE ALKYLATION OF PHENOLS
WITH TRIPHENYLMETHYL CHLORIDE IN
o-DICHLOROBENZENE AT 88°

Expt.	Molarity Phenol (M/L)	Molarity Halide (M/L)	P _o (mm.)	P _f (mm.)	k _o (1 mole-1 min-1)	k ₁ (1 mole-2 min-1)
1	0.315(P)	0.631	88.2	542.2	0.2037	0.001744
2*	0.610(P)	0.629	71.5	525.5	0.4296	0.005381
	0.610(P)	0.629	73.8	529.0	0.4389	0.0054305
					Appr.k _o = 0.2786	Appr.k ₁ = 0.005812
3	0.9132(P)	0.6105	87.4	657.0	0.78623	0.0081475
4	1.184(P)	0.5935	126.2	670.5	1.0869	0.013125
					Appr.k _o = 0.6814	Appr.k ₁ = 0.012950
5	1.184(C)	0.5921	101.5	757.5	0.3327	0.010353
6	1.368(C)	0.3571	162.0	435.0	0.3552	0.010114
7**	1.368(C)	0.3571	279.1	553.4		0.009779
8	10.55(P)	0.01112(B)	107.8	506.2	0.01241	(t _{1/2} = 55.2 min.)
9	10.61(P)	0.009881(B)	104.5	499.7	0.01357	(t _{1/2} = 53.1 min.)

* Check runs made at this concentration.

**Hydrogen chloride added initially.

P = phenol.

C = o-cresol.

B represents the number of moles of t-butyl chloride added to the phenol (in place of trityl chloride).

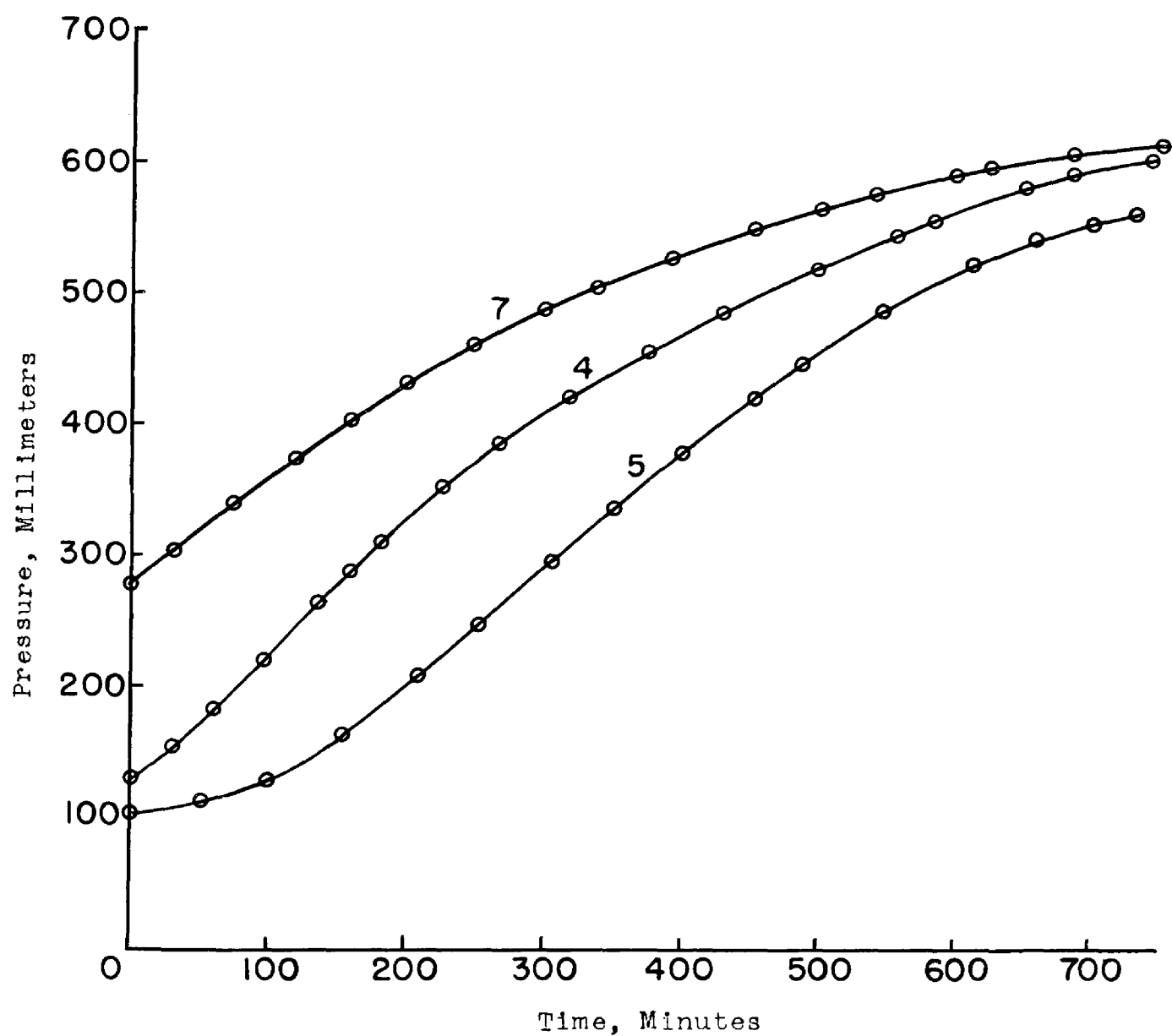
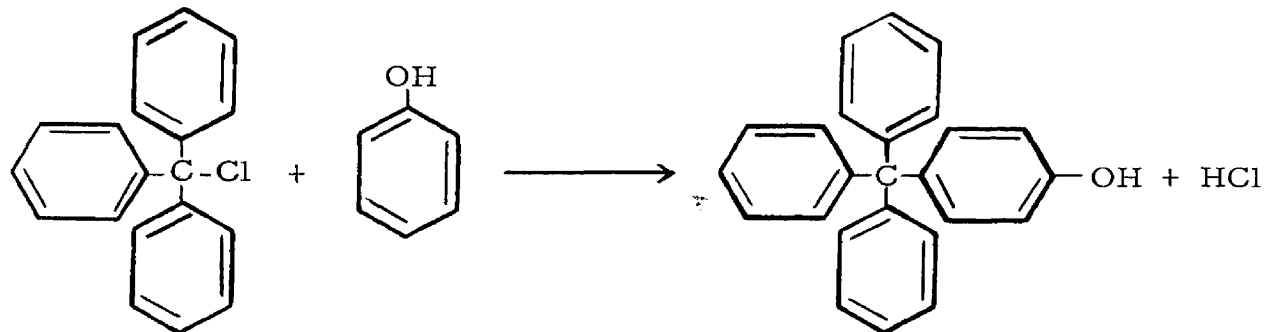


FIGURE 3. Pressure vs. Time Curves for Experiments 4, 5, and 7, Table 2.

was brought about in all the other experiments following the formation of a sufficient concentration of hydrogen chloride in the reaction.



Working with this hypothesis the following equation was applied in an attempt to describe the reaction rate:

$$dp/dt = k_1 [\text{phenol}] [\text{halide}] [\text{HCl}] \quad (1)$$

Using "a" as the initial phenol concentration, and "b" as the initial halide concentration, the above terms would be represented from the experimental data at any time during the reaction as:

$$[\text{phenol}] = a - [(p - p_o)/(p_f - p_o)]a$$

$$[\text{halide}] = b - [(p - p_o)/(p_f - p_o)]b$$

$$[\text{HCl}] = p - p_o$$

where p represents the instantaneous pressure, p_o the initial reaction pressure (a total of the vapor pressures of the solvent, phenol, and halide), and p_f the final equilibrium pressure.

Substituting the above in equation (1) we get

$$dp/dt = k_1 [a - (p - p_o)/(p_f - p_o) a] [b - (p - p_o)/(p_f - p_o) b] [p - p_o]$$

which can be simplified by expanding and collecting terms to:

$$dp/dt = k_1 ab[(p_f - p)/(p_f - p_o)]^2 [p - p_o] \quad (2)$$

or

$$[dp/(p_f - p)^2 (p - p_o)] = [k_1 ab/(p_f - p_o)^2] dt$$

Integration of the latter gives

$$[1/(p_f - p_o)] \left[[1/(p_f - p)] + [1/(p_f - p_o)] \ln[(p - p_o)/(p_f - p_o)] \right] = [k_1 ab/(p_f - p_o)^2] t + C[p_f - p_o] \quad (3)$$

Evaluation of the constant of integration is impossible here, however, because on setting $t = 0$ and $p = p_o$, the equation becomes

$$[1/(p_f - p_o)] \left[[1/(p_f - p_o)] + [1/(p_f - p_o)] \ln[(p_o - p_o)/(p_f - p_o)] \right] = C,$$

which is indeterminate due to the nature of the log term.

By multiplying equation (3) through by $(p_f - p_o)$, however, it can be revised to the form of an equation representing a straight line:

$$\left[[1/(p_f - p)] + [2.303/(p_f - p_o)] \log[(p - p_o)/(p_f - p)] \right] =$$

$$[k_1 ab/(p_f - p_o)] t + C[p_f - p_o]^2$$

Therefore, using Y to represent the left side of the equation, a plot of Y versus t should yield a straight line when the experimental data are applied to the equation. A plot of this type for Experiment 4 is shown in Figure 4. It is readily seen that the equation holds exceptionally well for the latter part of the reaction, but gives no straight-line relationship during the first 150 minutes of reaction.

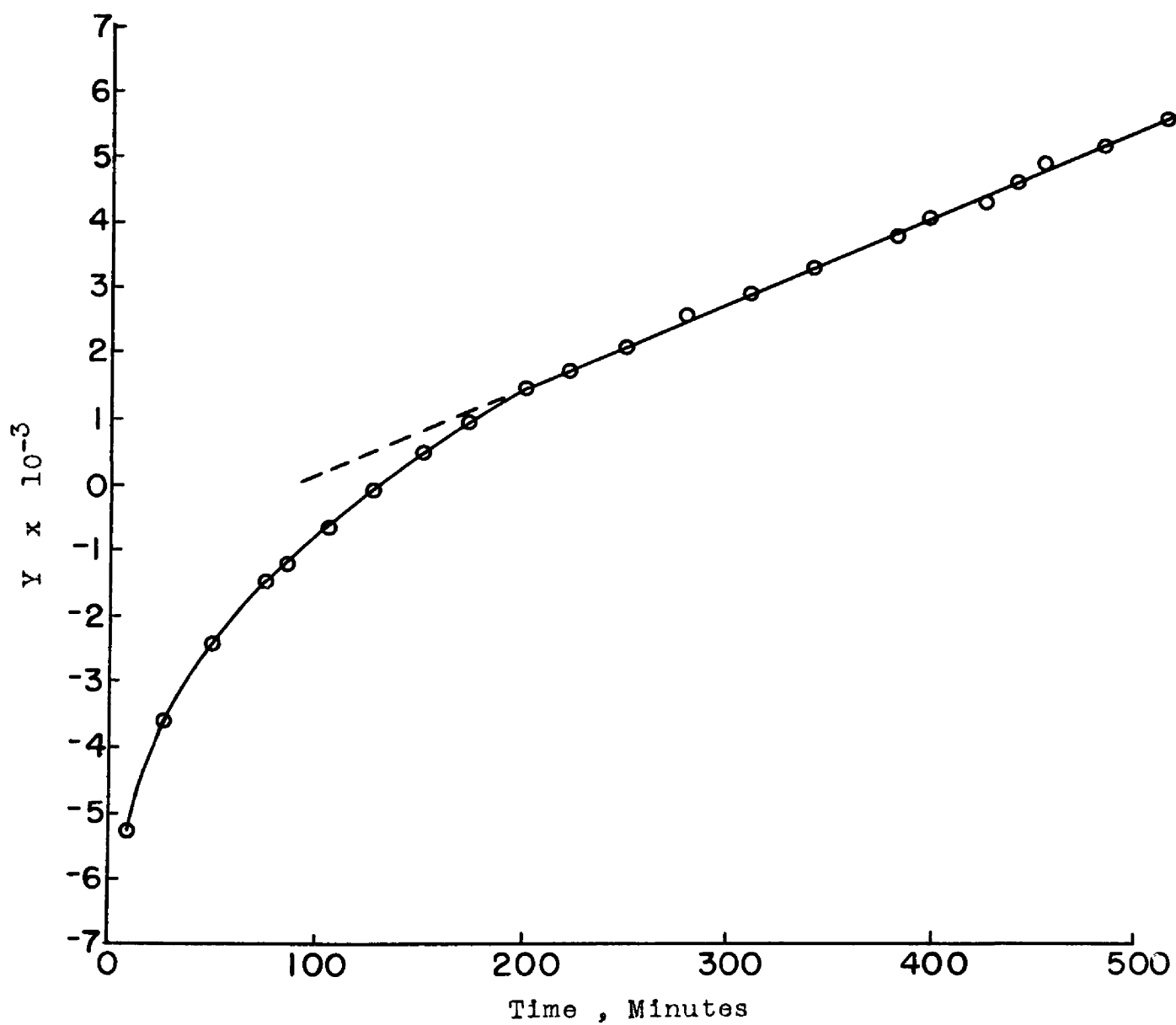


FIGURE 4. Application of Data to Third Order Rate Equation, Experiment 4.

Since the latter part of the reaction was represented so well by equation (1), it became apparent that the initial rate might be described by the same equation minus the HCl term, which of course would be of insignificant magnitude near the beginning of the reaction. Thus,

$$dp/dt = k_o [\text{phenol}][\text{halide}] \quad (4)$$

Transcribing this to the experimental units, expanding, and collecting terms as was done in the previous case, we get

$$dp/dt = k_o ab[(p_f - p)/(p_f - p_o)]^2$$

or,

$$[dp/(p_f - p)^2] = [k_o ab/(p_f - p_o)^2]dt$$

Upon integration one then obtains

$$[1/(p_f - p)] = [k_o ab/(p_f - p_o)^2]t + C \quad (5)$$

Thus, when $t = 0$, $p = p_o$, the integration constant, C , becomes equal to $[1/(p_f - p_o)]$. Substituting this value for C in equation (5), we obtain the expression

$$[1/(p_f - p)] = [k_o ab/(p_f - p_o)^2]t + [1/(p_f - p_o)] \quad (6)$$

which once again is the form equation for a straight line. Consequently, a plot of $[1/(p_f - p)]$ versus $[t]$ should give a straight-line relationship when applied to the experimental data, if the initial rate is satisfactorily represented by equation (4). Such a plot is shown

for Experiment 4 in Figure 5. Once again the marked deviation from a straight line is seen; it is readily apparent, however, that the deviation does not begin till after the first 125 minutes of reaction. From the foregoing results, therefore, it is reasonable to assume that a combination of equations (1) and (4) might well describe the entire reaction rate. Thus,

$$dp/dt = k_o[\text{phenol}][\text{halide}] + k_1[\text{phenol}][\text{halide}][\text{HCl}] \quad (7)$$

The evaluation of the rate constants in the above equation was attempted by considering the two parts of equation (7) separately, and using the two graphical methods which have just been described. Each rate constant was derived from the slope of the straight-line portion of the derivative curves, exemplified by Figures 4 and 5. This was done for several runs, and the values obtained appear in Table 2, designated as the approximated values of k_o and k_1 . In order to test the accuracy of the constants evaluated in this manner, a calculated curve for Experiment 2 was prepared from equation (9) resulting from the integration of equation (7), which follows. The solid curve in Figure 6 represents this calculated curve, while the dotted line shows a similar plot of the experimental data for comparison. Since the experimental points show considerable deviation from the calculated curve, it is obvious that the determined values of the

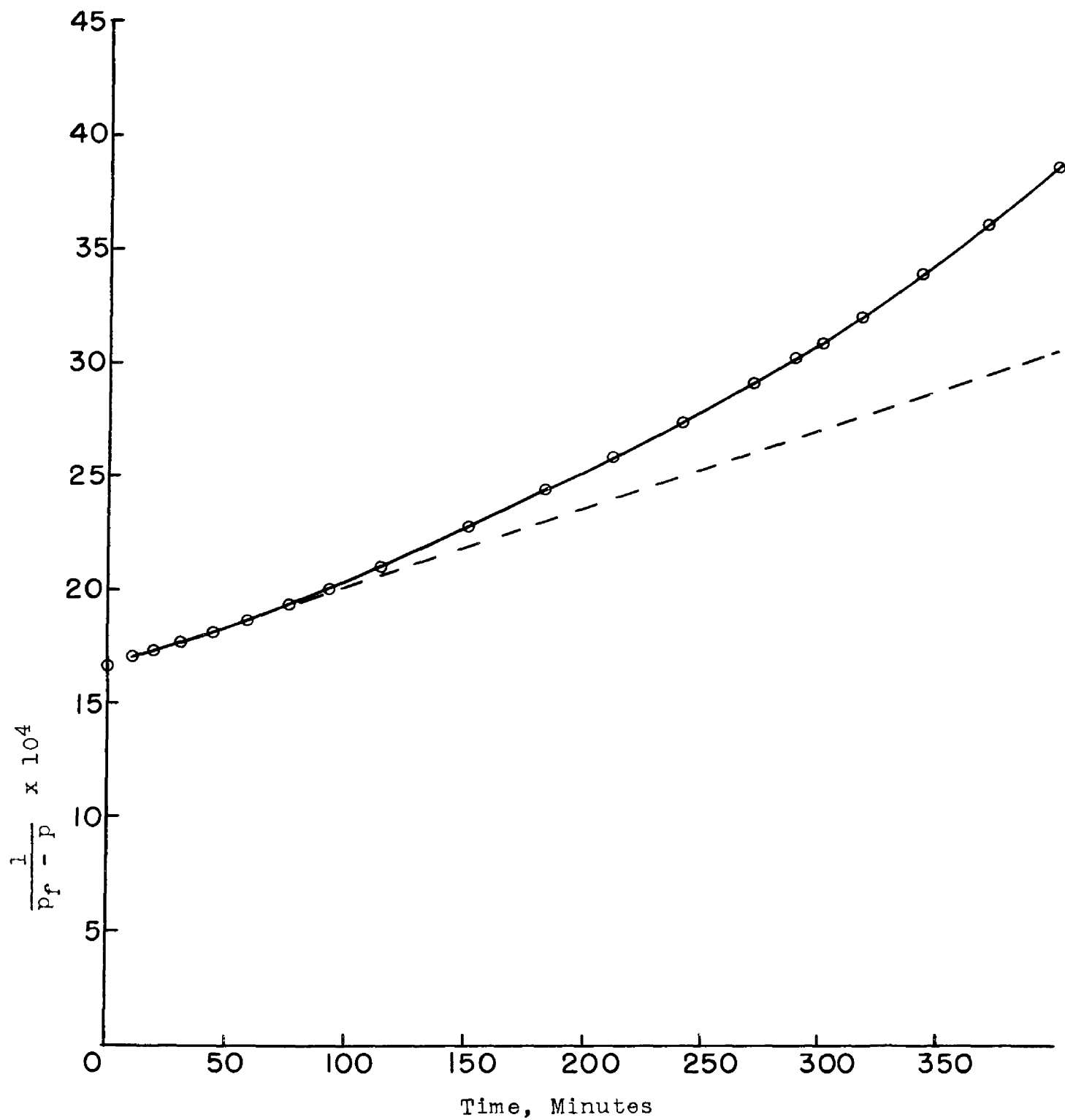


FIGURE 5. Application of Data to Second Order Rate Law, Experiment 4.

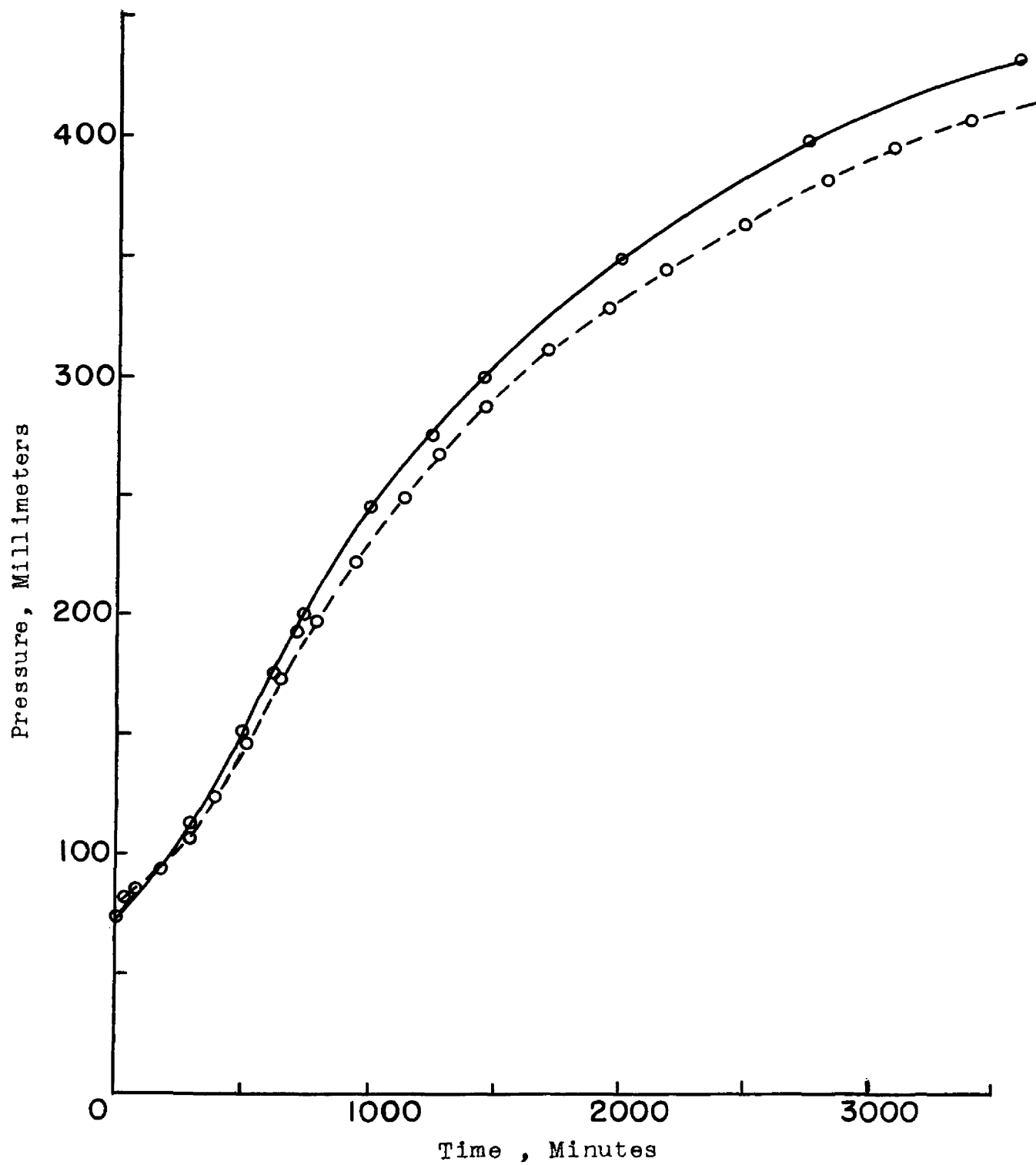


FIGURE 6. Comparison of Calculated Curve from Approximated Rate Constants and Observed Curve from Experiment 2.

rate constants are in error. Consequently, the application of these constants, obtained by treating the beginning and end of the reaction separately as provided by equations (1) and (4), gives a theoretical rate curve of the same shape as that observed, but does not reproduce the observed curve as accurately as one might like. In particular, the values of k_o seem to be quite a bit off, as seen from Table 2.

Equation (7) was therefore evaluated in the following manner: Transcribing to the experimental terms as described previously, we get

$$\begin{aligned} dp/dt = k_o \left[a - [(p - p_o)/(p_f - p_o)]a \right] \left[b - [(p - p_o)/(p_f - p_o)]b \right] + \\ k_1 \left[a - [(p - p_o)/(p_f - p_o)]a \right] \left[b - [(p - p_o)/(p_f - p_o)]b \right] \left[p - p_o \right] \end{aligned}$$

Expanding and collecting terms,

$$\begin{aligned} dp/dt &= k_o ab[(p_f - p)/(p_f - p_o)]^2 + k_1 ab[(p_f - p)/(p_f - p_o)]^2 [p - p_o] \\ dp/dt &= ab[(p_f - p)/(p_f - p_o)]^2 [k_o + k_1(p - p_o)] \\ dp/dt &= [ab/(p_f - p_o)^2] [p_f - p]^2 [k_o + k_1(p - p_o)] \end{aligned} \quad (8)$$

Equation (8) can now be transformed to an integrable form,

$$[dp/(p_f - p)]^2 [k_o - k_1 p_o + k_1 p] = [ab/(p_f - p_o)^2] dt$$

Upon integration of the above we then get

$$\left[\frac{(p_f - p_o)^2}{k_1(p_f - p_o) + k_o} \right] \left[\frac{1}{p_f - p} - \frac{1}{p_f - p_o} + \frac{k_1 \cdot 2.303}{k_1(p_f - p_o) + k_o} \log \frac{[k_1(p - p_o) + k_o][p_f - p_o]}{(p_f - p)k_o} \right] = abt \quad (9)$$

It was quite obvious at this point that the integrated form was too complex for a reasonable evaluation of the reaction constants. Attention was therefore turned to the unintegrated form (equation 8). If this equation is rearranged as follows,

$$[(dp/dt)/(p_f - p)^2] = [(k_1 ab)/(p_f - p_o)^2][p - p_o] + [(abk_o)/(p_f - p_o)^2] \quad (10)$$

we once again have the mathematical expression for a straight line.

Thus, if $[(dp/dt)(p_f - p)^2]$ were plotted against $[p - p_o]$, the result should be a straight line for all the experimental data if equation (10) satisfactorily represents the reaction. In such a case, the term $[(k_1 ab)/(p_f - p_o)^2]$ would represent the slope of this line, and $[(abk_o)/(p_f - p_o)^2]$ would be equal to the value of the intercept, from which then k_o and k_1 could be evaluated.

The determination of (dp/dt) for the "Y" term of equation (10) was carried out according to the method described by Hart and Simons (2). A plot of the experimental data was first made on large graph paper, and a spline was used to draw a smooth curve through these points. Normals to the rate curves were then drawn with a

plane first-surface mirror held in a small frame at right angles to the plane of the curve. The normal was established when the curve and its image appeared to give no perceptible break. The slope of the rate curve, $[dp/dt]$, was then determined as the negative reciprocal of the slope of the normal. About fifteen to twenty slopes were determined for each curve, at regular time intervals throughout the reaction.

The value of p_0 was determined by extrapolation of the reaction curve to zero time. Since the reaction curve was quite flat near the beginning of the reaction, this determination could be made with considerable accuracy. The value of p_f was found experimentally in all the runs, with the exception of the very slow phenol alkylations. In these runs it was found that the data near the end of the reaction gave a linear plot of $[dp/dt]$ versus p . Therefore, p_f was found by extrapolation of this line to $[dp/dt] = 0$. This linearity was justified by the substitution of some actual data, obtained near the end of the reactions, in equation (10). When this was done at several pressures, it was found that the reaction rate, $[dp/dt]$, divided by the instantaneous pressure gave values that changed proportionally with the change in pressure. The best plot was determined by the method of least squares (57). The accuracy of the values of p_f by this method was

checked in several reactions by comparison with the experimentally determined p_f values. The difference was of the order of one percent.

The values of "a" and "b" representing the initial concentration of the phenol and halide, were determined by using both experimentally measured densities, and available data from the literature for the densities of the phenols used in each experiment. The density of the halide-solvent combination was determined at the reaction temperature in the usual manner and the volume of solution was calculated. The volume of the phenol at the reaction temperature was calculated from the literature densities, its solution in the halide-solvent mixture being assumed to be perfect. Since the solutions were dilute, this assumption probably did not introduce an appreciable error. Once the total reaction volume was calculated the molarities of the phenol and halide could be determined in the usual way.

Having determined the necessary values for testing the applicability of equation (10), plots of $[(dp/dt)/(p_f - p)^2]$ versus $[p - p_o]$ were made and are illustrated in Figure 7. Straight lines were obtained over the entire alkylation reaction. The best straight line was determined in each case by the method of least squares, which

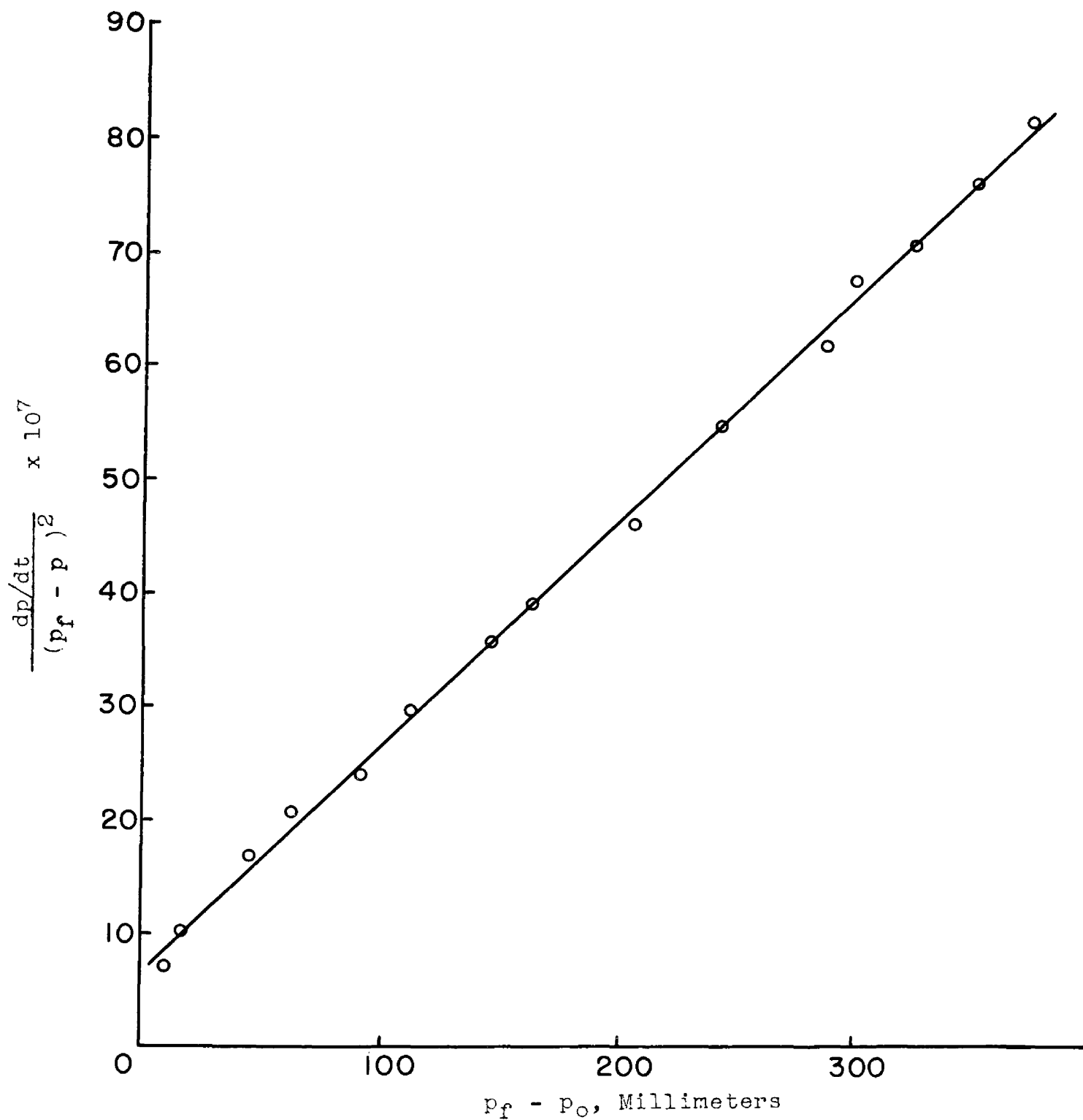


FIGURE 7. Adherence of Auto-Catalyzed Reaction to Equation 10.

automatically yields the values for the slope and intercept. The values of k_1 and k_o , columns 6 and 7, Table 2, could then be calculated. The accuracy of the constants determined in this way is illustrated in Figure 8, which shows the closeness of the fit of the calculated curve (prepared from equation 9) and the experimental points. The results for Experiments 1 through 6 were therefore determined by this procedure, and are tabulated in Table 2.

The mathematical approach to Experiment 7 was varied slightly since anhydrous hydrogen chloride was added before the reactants were mixed in the reaction vessel. Since the rate curve for this reaction shows no induction period (see Figure 3), the first term of equation (7) can be discarded and the reaction described by

$$dp/dt = k_1 \left[a - [(p - p_o)/(p_f - p_o)]a \right] \left[b - [(p - p_o)/(p_f - p_o)]b \right] [p - p_o'] \quad (11)$$

This equation differs from equation (2) only by virtue of the p_o' term, which represents the zero pressure observed in Experiment 6. Since the latter run is exactly the same as Experiment 7, save for the added hydrogen chloride in Experiment 7, the $[p - p_o']$ term represents the acid concentration as a sum of the hydrogen chloride added $[p - p_o']$ plus that which is formed during the alkylation $[p - p_o]$.

Rearranging (11), we get

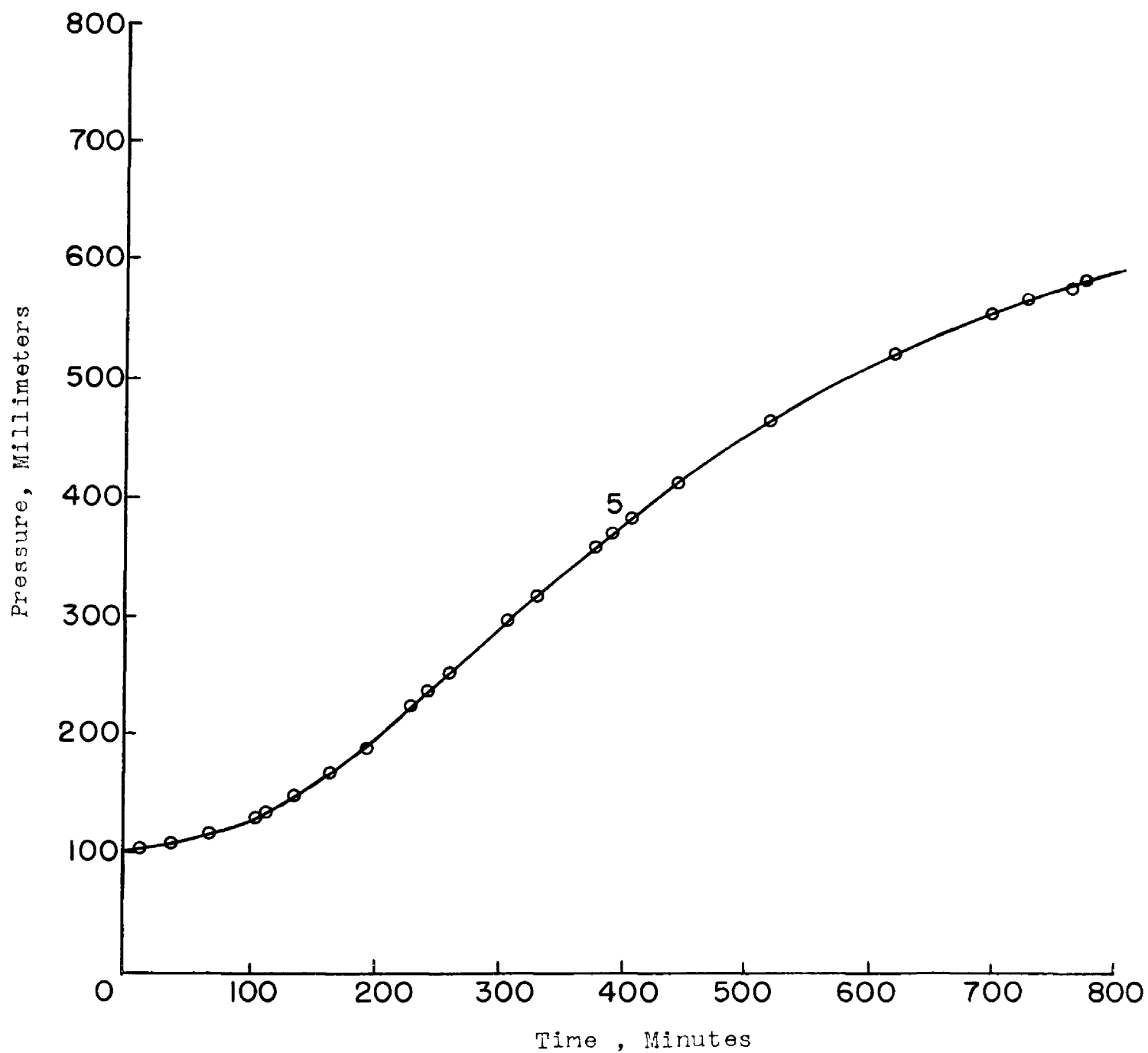


FIGURE 8. Comparison of Calculated Curve from Equation 3 and Experimental Data from Experiment 5.

$$[(dp/dt)/(p_f - p)^2] = [(k_1 ab)/(p_f - p_o)^2][p - p_o] \quad (12)$$

which is the equation of a straight line having a zero "y" intercept.

This plot is shown in Figure 9, and the linearity shows the applicability of equation (11) to the alkylation when hydrogen chloride is present in sufficient concentration at the beginning of the reaction.

The slope of this line was thus equal to $[(k_1 ab)/(p_f - p_o)^2]$ from which the k_1 value, shown in Table 2, is obtained.

Since several alkylations were made at varying phenol concentrations, the results can be used in an attempt to determine the kinetic order of the reaction with respect to phenol. As can be seen in Table 2, the k_o and k_1 rate constant values show a marked change with change in phenol concentration. This would be expressed mathematically thus,

$$k = [\text{phenol}]^n$$

where n represents the exponential rate dependence on the phenol concentration. Converting from exponential form to log form,

$$\log k = n \log[\text{phenol}]$$

we arrive at an expression for a straight line, having a slope of n .

If the reaction showed a first-order dependence on phenol concentration, theoretically, the rate constant would show no change with varying phenol concentration, and thus the slope of the above

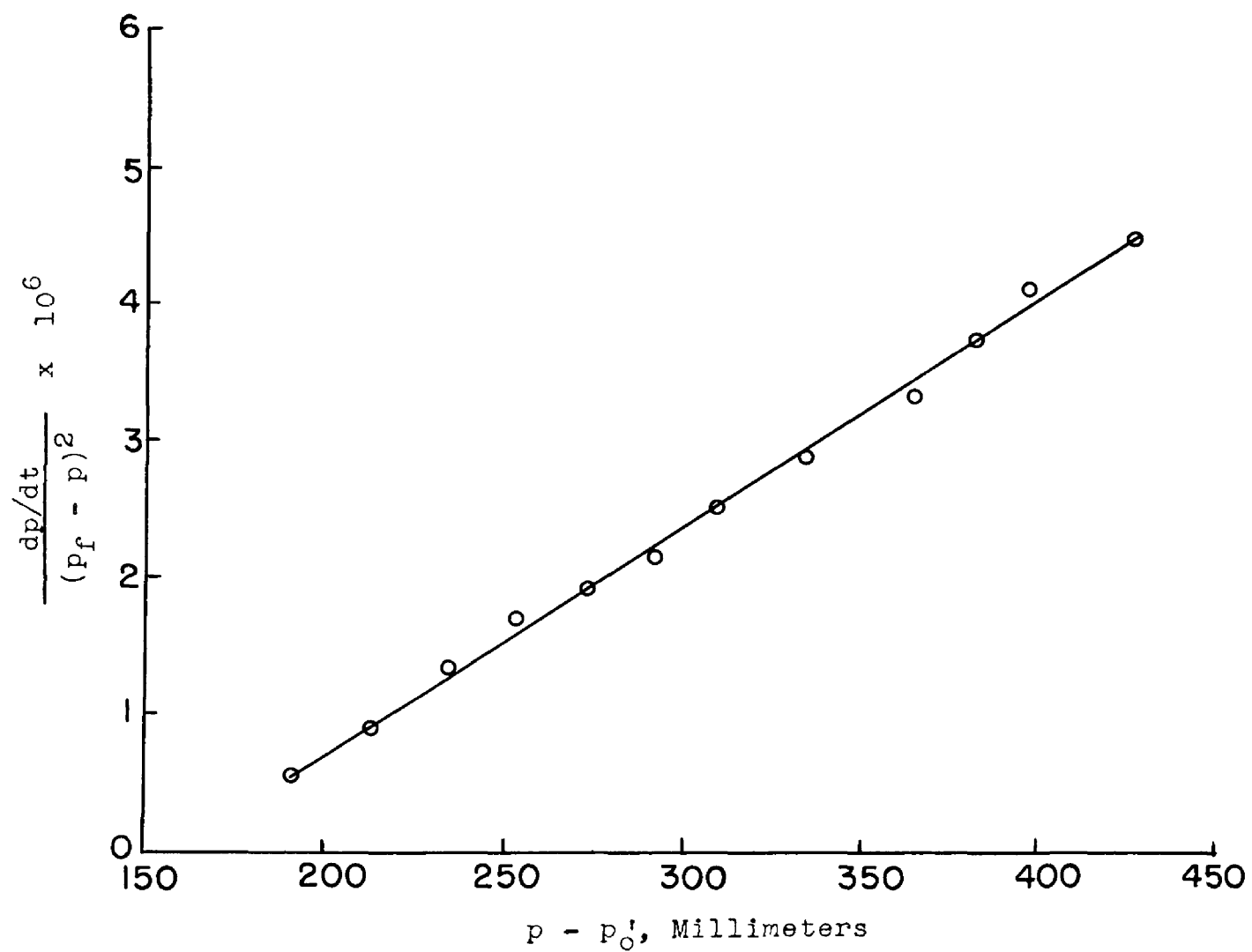


FIGURE 9. Adherence of Catalyzed Alkylation to Third Order Rate Law.

plot would be zero. Therefore, the kinetic order with respect to phenol must be determined from such a plot as the slope plus one, or $[n + 1]$. Graphs of $\log k_0$ and $\log k_1$ versus log of the phenol concentration are shown in Figure 10, and their significance will be discussed in the section to follow.

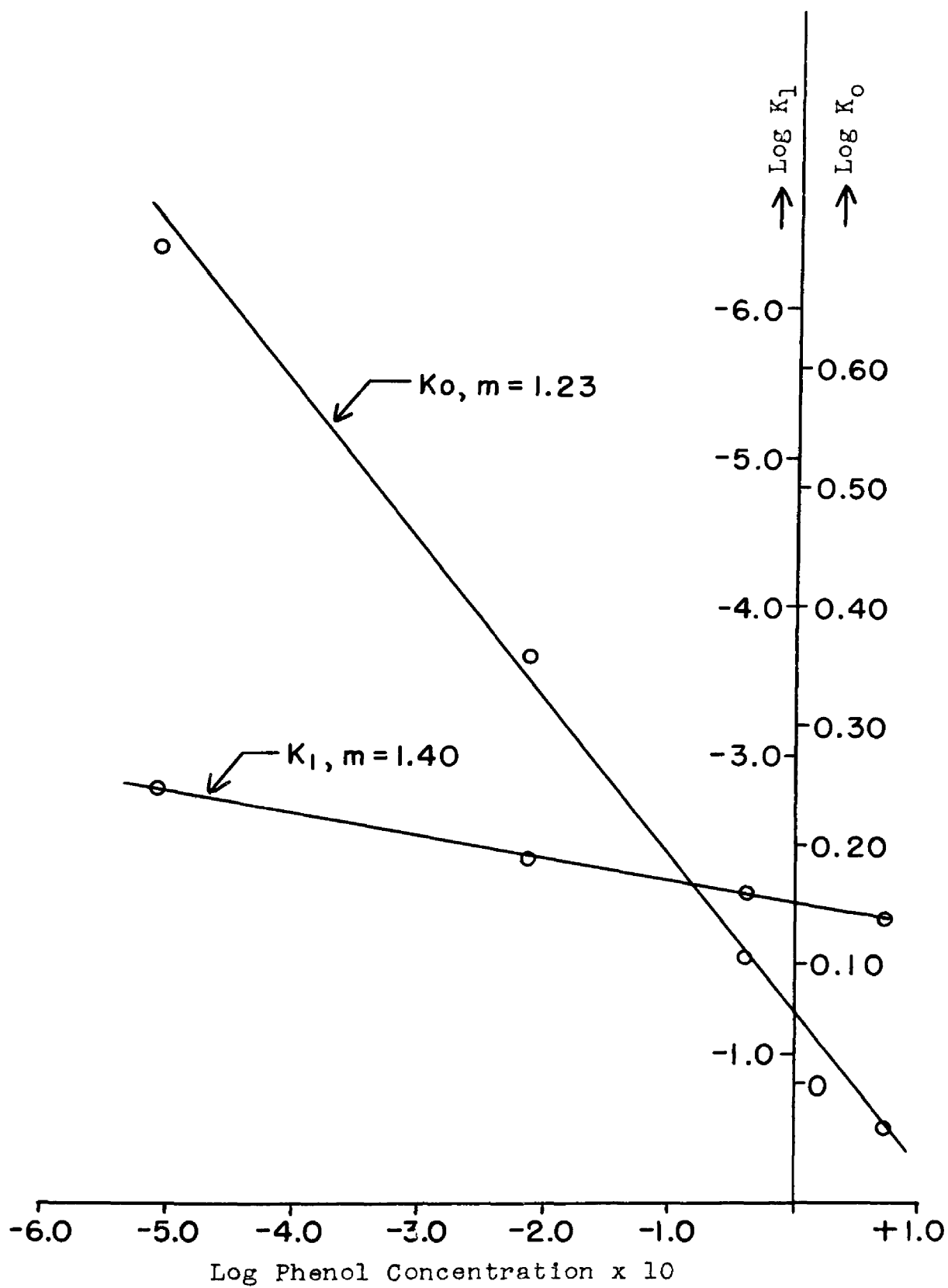
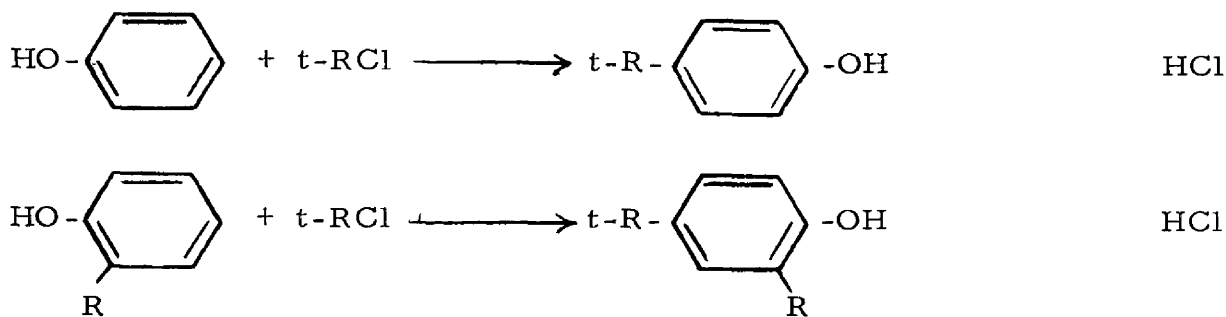


FIGURE 10. Variation of Rate Constants With Log of Phenol Concentration.

Discussion

The alkylation of phenol and various alkylated phenols was carried out using both *t*-butyl chloride and trityl chloride as the alkylating agents. In each case the over-all reactions can be described by the following equations:



The results are summarized in Table 1 in the previous section. Experiments 1 through 7 were carried out with the phenol to be alkylated present in large excess; consequently, the reaction medium could hardly be considered as equivalent from one experiment to another. The large rate decrease observed in going from unsubstituted phenol to the highly hindered 2,6-di-*t*-butylphenol may therefore be the result of several factors. Substitution in the ortho positions should decrease the efficiency of phenols for solvating carbonium ions and/or in coordinating the halogen of the *t*-butyl chloride. That the effect is predominantly steric is indicated by the greater reactivity of 2,6-dimethylphenol as compared with the di-*t*-butyl derivative. The

opposite result would have been predicted on the basis of the relative activation of the para position due to the inductive effect of the alkyl groups.

Meta and para cresol (Experiments 6 and 7) both alkylate ortho to the hydroxyl and consequently represent comparable reactions. The solvent properties of these two molecules are very similar (58); thus, the large enhancement of alkylation rate for m-cresol over the para isomer is ascribed here to the increased electron density at the 6-position caused by the inductive and/or hyperconjugative effect of the methyl group.

It became obvious at this point in our study, that in order to avoid a multiplicity of explanations caused by high phenol concentrations in the reaction medium, the kinetics must be studied in dilute solution and in an inert solvent. The alkylation decreases in rate quite rapidly when solvents such as p-xylene, et cetera, are used. In relative rate Experiments 8 to 10, an attempt was made to use nitrobenzene, but here again the rate was exceedingly slow, even at 75° C. These experiments do, however, represent determinations in more dilute solution, and once again the marked decrease in rate for the 2,6-di-*t*-butylphenol is observed.

In order to overcome the rate decrease when an inert solvent is employed, we turned our attention to higher-boiling halides, so that the reaction rate could be increased by elevating the temperature. Trityl chloride made possible a determination of more precise alkylation kinetics in dilute solution (see Table 2 of the previous section), and in addition eliminated the possibility of dehydrohalogenation of the tertiary chloride. Ortho dichlorobenzene was selected for the reaction solvent, as it offered an inert medium of a moderately polar nature ($\epsilon = 7.8$).

The alkylations of phenol were carried out at several phenol concentrations in order to determine the order of the reaction with respect to phenol. At the lower concentrations, when the instantaneous pressure was plotted against the reaction time, "S" shaped curves were obtained. The apparent induction period was not readily noticeable at the higher concentrations of phenol, but was even more evident in the alkylation of o-cresol.

Since the measurements were made in an all-glass reaction system and at an elevated temperature, the possibility of apparatus leakage was first investigated as an explanation for the type of curves obtained. Reaction 6 was therefore carried out at a reduced halide concentration so that the final system pressure would be well

below atmospheric pressure, unless leakage occurred. The reaction curve leveled off and held at 435 mm. pressure.

The only other logical explanation for the induction period was that the reaction was auto-catalyzed by the hydrogen chloride formed during the alkylation. Reaction 7 was therefore carried out using the same concentrations and conditions of Reaction 6, except that anhydrous hydrogen chloride was added to the cresol ampoule before it was broken in the reaction system. As can be seen from the experimental curve (Figure 3), the induction period was completely eliminated under these conditions, indicating that it was, indeed, the hydrogen chloride which was responsible for the auto-catalysis.

The experimental data obtained in Experiment 7 are represented satisfactorily by the third-order equation,

$$dp/dt = k_1[\text{cresol}][\text{trityl chloride}][\text{HCl}]$$

Once the role of the hydrogen chloride was understood in the reaction, it was readily seen that the other experimental curves should be fitted by a two-term equation, arranged so that one term would increase and another term decrease in importance as the reaction proceeded. Thus, the "S" shaped curves, for all the other alkylation experiments, were defined by the expression,

$$dp/dt = k_o [\text{phenol}][\text{halide}] + k_1 [\text{phenol}][\text{halide}][\text{HCl}]$$

where k_o is a second-order rate constant and k_1 the third-order rate constant discussed above.

Examination of these rate constants, Table 2, reveals, however, that they vary consistently with change in phenol concentration (i.e., from one run to another, although they are constant for any given run). A log-log plot of phenol concentration versus the rate constants k_o and k_1 gives a slope in both cases of slightly greater than 1.00 (Figure 10), which would lead to a reaction order of approximately 2 with respect to phenol. This would appear to be inconsistent with the rate-determining equations. One must consider, however, that the concentration of phenol (0.315 M to 1.184 M) is still too great for really ideal kinetic measurements. It therefore appears reasonable to assume that the change in phenol concentration is great enough to cause a change in solvent character, which in turn would account for the variation in the reaction rate constants.

It is interesting to note the large decrease in k_o when o-cresol is used in the experiments in place of phenol. If Experiments 4 and 5 are compared, where the aromatic concentrations are equivalent, we see that the initial reaction rate for the o-cresol alkylation is just about 1/3 that of phenol. The k_1 value for the cresol, however,

is nearly as great as that for the phenol alkylation, which would lead one to believe that the hydrogen chloride, following its formation in the reaction, assumes a role in the alkylation mechanism which was performed initially by the o-cresol, and somewhat less efficiently than by the unsubstituted phenol.

Mechanism

Before formulating a mechanism for the reaction under consideration, it will be well at this point to correlate the facts presented in past investigations with those resulting from our kinetic studies concerning the effect of hydrogen chloride on the alkylation reaction.

In 1927 van Alphen (1) showed that phenyl trityl and *o*-cresyl trityl ethers could be transformed by hydrogen chloride to para alkylated phenols. Based on this evidence, this worker concluded that the alkylation of phenol with tertiary halides proceeded by way of an ether intermediate, which, being unstable in the presence of hydrogen chloride, underwent rearrangement to the alkylated phenol.

The kinetic studies of Hart and Simons (2), however, indicated that when alkylation was carried out in an excess of phenol as the solvent, it was neither auto-catalyzed by the product, hydrogen chloride, nor catalyzed by added hydrogen chloride.

We have found that when the reaction is carried out in dilute solution, the reaction rate is slow enough to observe auto-catalysis by the hydrogen chloride formed during the reaction. This apparent induction period is eliminated when hydrogen chloride is added initially to the reaction mixture, and the reaction is found to be

first-order with respect to hydrogen chloride. It therefore appears that when the alkylation is carried out in excess phenol, as was done by Hart and Simons, the reaction is too rapid to give evidence of the auto-catalysis. Furthermore, the stirring technique used in the present work was superior to that employed by Hart and Simons, and permitted precise rate measurements within one or two minutes after the beginning of the reaction. This is important in detecting auto-catalysis.

In connection with this discovery one should also consider the kinetic studies of Swain (4, 5) on the reaction of trityl chloride with phenol in benzene solution. The reaction product in this case was found to be phenyl trityl ether, but the rate-determining method employed in this work required that the hydrogen chloride produced in the reaction be consumed by pyridine present in the reaction medium. Although this study appears to add support to van Alphen's postulation that the ether is first formed in the alkylation of phenol, followed by hydrogen chloride rearrangement, it is entirely possible that the nature of the reaction is completely changed by the presence of pyridine in the reaction medium.

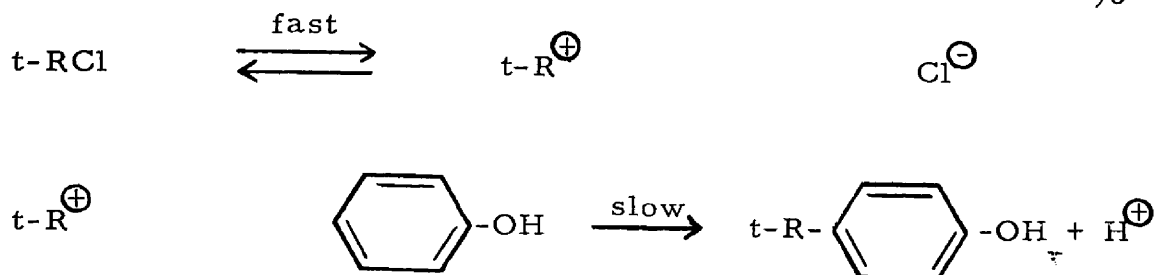
On the basis of these considerations and the facts presented in the discussion section, there appear to be two general, and

essentially different mechanisms that might well explain the facts observed, and thus describe the alkylation of phenol by tertiary halides in dilute solution.

The first of these would involve the preliminary formation of the phenyl trityl ether as an unstable intermediate, followed by the rearrangement of this ether in the presence of the generated hydrogen chloride to form the *p*-trityl phenol. On the basis of some recent experiments with the trityl ether of *o*-cresol (59), this mechanism does not appear tenable for the alkylation reaction. Thus, when a 0.5 molar solution of trityl *o*-cresyl ether in benzene was treated with dry hydrogen chloride for ten minutes at 60°, a 90 per cent yield of *o*-cresol was isolated from a 10 per cent alkali extract of the reaction mixture. From the alkali-insoluble material a 70 per cent recovery of trityl carbinol, which is the expected hydrolysis product of trityl chloride, was made. The reaction between the ether and hydrogen chloride, therefore, is a very rapid cleavage, and not a rearrangement. Since the starting materials used in the alkylation are the primary products of the ether cleavage, it follows that the alkylated phenol is formed directly and not by way of the ether.

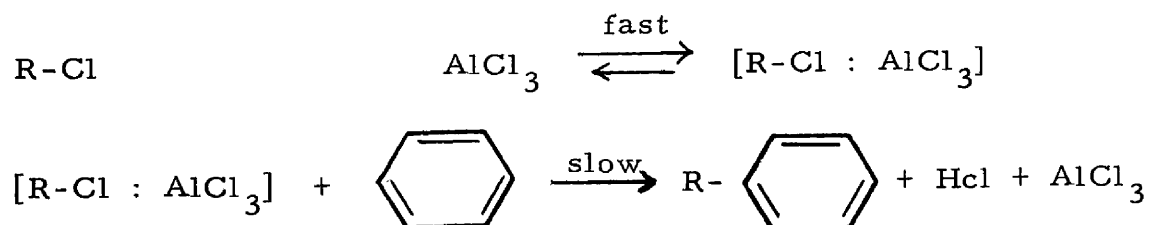
In the light of these facts it is of interest to note the actual data reported by Swain (4) for the kinetics of formation of the phenyl trityl ether. With a phenol molarity of 0.056 in benzene solution at 25°, Swain determined a third-order rate constant of $0.004 \pm 0.002 \text{ l}^2 \cdot \text{mole}^{-1} \cdot \text{min.}^{-1}$. By comparison, at our lowest reaction concentration (phenol molarity = 0.315) in o-dichlorobenzene at 88°, the reaction rate as exemplified by the third-order rate constant is only 0.001744 $\text{l}^2 \cdot \text{mole}^{-1} \cdot \text{min.}^{-1}$. The formation of the ether under the conditions used by Swain, therefore, appears to be a much faster conversion than the alkylation reaction, which once again indicates that the reaction under study is completely changed in nature by the presence of pyridine in the reaction mixture.

A second and preferred mechanism, which is consistent with all the data obtained in this study, involves the primary ionization of the tertiary halide to form a free or solvated carbonium ion, which then attacks the para position of the phenol to form p-trityl-phenol. Such a mechanism is described by the following sequence, where R is the triphenylmethyl group:



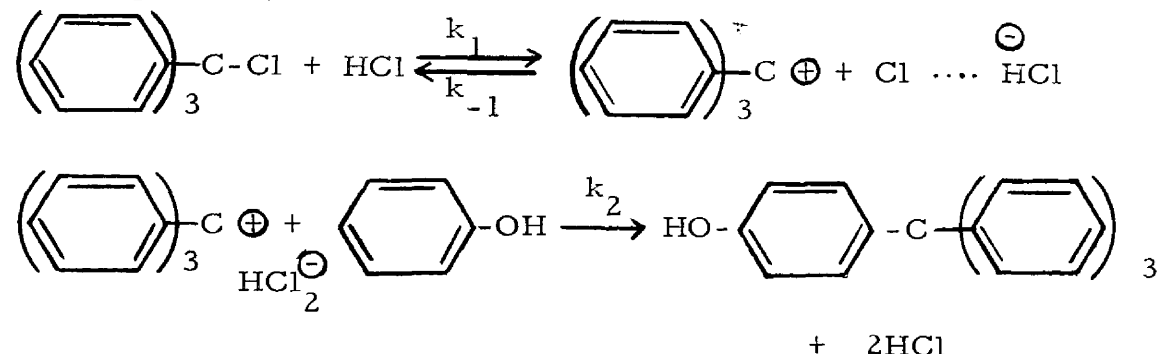
with the electrophilic attack at the para position constituting the rate-determining step. It is reasonable that this be the slow step because the tertiary carbonium ion is the most easily formed of carbonium ions, and is in turn the most unreactive following its formation, due to the stabilizing effect of resonance.

As to the contribution by hydrogen chloride in the alkylation, it is quite likely that it would facilitate the rapid formation of the carbonium ion for its attack on the phenol molecule. Grayson and Brown (60) have recently shown that the alkylation of benzene with a primary halide proceeds by a third-order mechanism involving the alkyl halide, AlCl_3 , and the aromatic component. The rate-determining step in this reaction is described as a nucleophilic attack by benzene on a halide- AlCl_3 complex.



The couple $[R-Cl : AlCl_3]$ is least ionic when R is primary, and most ionic when R is tertiary.

For the third-order mechanism we can therefore write the mechanistic equations,



from which the following rate law can be derived:

$$V = [(k_1)(k_2)(\text{HCl})(\text{C}_6\text{H}_5\text{C}_3\text{H}_7\text{Cl})(\text{phenol})]/[(k_{-1} + k_2)(\text{phenol})]$$

When k_{-1} is large as compared to k_2 , which must be the case here (the equilibrium concentration of the carbonium ion has to be very small), then the expression reduces to the third-order rate law,

$$\begin{aligned}
 V &= [(k_1)(k_2)(\text{HCl})(\text{C}_6\text{H}_5\text{C}_3\text{H}_7\text{Cl})(\text{phenol})]/[k_{-1}] \\
 &= [k_3(\text{HCl})(\text{C}_6\text{H}_5\text{C}_3\text{H}_7\text{Cl})(\text{phenol})]
 \end{aligned}$$

When the hydrogen chloride is not present initially in the reaction mixture, the solvolysis of the tertiary halide is undoubtedly undertaken by the phenol present, which is known to have a high affinity for halogen. This effect is realized in the k_o values (Table 2) for

comparative runs of phenol and o-cresol. The latter is less effective at solvating carbonium ions, and therefore gives a slower rate of reaction. However, as soon as the hydrogen chloride is formed, the k_1 values for o-cresol alkylation approach that of phenol as the o-cresol is replaced by hydrogen chloride in the solvolysis step.

Before concluding, some mention should be made as to the relationship of this proposed mechanism to the "amphoteric medium effect" of Hart and Simons (2), and the termolecular mechanisms of Swain (4). Indeed, Swain has pointed out (5) that there is no significant difference between a termolecular reaction and one involving preliminary, reversible formation of a polar complex or solvated ion of two reactants, followed by a slow reaction with the third. Since such an interpretation is statistically less probable in dilute solution, it appears more useful at present to subscribe to the general concept of the displacement reaction accepted by most investigators. In the case of the work of Hart and Simons (2), however, such a termolecular mechanism is highly probable since the reaction was carried out in phenol as a solvent. We have shown the importance of the phenol molecule for solvation of the halide when no other catalyst is present, and in view of the accepted amphoteric properties of phenol, there is no doubt that a concerted mechanism, of the type

proposed by Hart and Simons (2), provides an attractive alternative when the reaction conditions favor a mechanism of relatively low energy requirements.

PART C

THE MECHANISM OF THE INHIBITION OF PHENOL ALKYLATIONS
BY OXYGENATED COMPOUNDS

Experimental

I. Materials

The phenol and t-butyl chloride used in this investigation were purified by the same method as that described in Part B.

The dioxane, an Eastman Kodak product, was purified by the method described by Fieser (61). One liter of dioxane was refluxed with 14 ml. of concentrated hydrochloric acid for twelve hours. The mixture was then cooled and saturated with potassium hydroxide pellets. The layers were separated, and the dioxane was treated with fresh potassium hydroxide, decanted, and refluxed with sodium for twenty-four hours. Fresh sodium was added at definite intervals until the metallic surface remained bright. The dioxane was then distilled from the sodium, stored over sodium and in a nitrogen atmosphere until ready for use.

The tetrahydropyran was prepared from duPont dihydropyran by catalytic hydrogenation. To 8 g. of Raney nickel catalyst in a rubber-stoppered hydrogenation bottle was added 50.5 g. (0.6 mole) of dihydropyran. The bottle was shaken under forty pounds hydrogen pressure for thirty minutes, the catalyst allowed to settle, and the

product decanted off for distillation. The fractionated tetrahydropyran, b.p. 85-86^o, was stored under nitrogen until ready for use.

II. Preparation of Samples

Since the apparatus used was the same as that described in Part B, the samples were prepared in much the same manner. After the phenol was added to the ampoule, stoppered and weighed, the oxygenated compound was added, the mixture frozen in dry ice and the ampoule sealed under vacuum. The weight of the oxygenated compound was then obtained from the total weight by difference.

The tertiary halide samples were prepared in the same manner, using standard techniques for degassing and sealing off the samples. Care was taken to keep oxygen and traces of moisture from the samples.

III. Measurement Procedure

The rate of reaction was followed in the same manner as described in Part B for the quantitative kinetics measurements.

Following each run the halide addition tube was rinsed with 95 per cent ethanol, and the rinsings analyzed for chloride by the Volhard procedure, allowing fifteen minutes for reaction of silver

nitrate with the organic halide. The weight of alkyl halide in the ampoule was then corrected for the amount which remained behind. This correction was usually less than one percent.

Results and Calculations

I. Data

As was pointed out previously, the experimental technique and rate-determining method used here is essentially the same as that described in Part B of this thesis. Anywhere from 100 to as many as 200 time-versus-pressure readings were obtained for each run, and space prevents their tabulation. However, several plots of these data are shown in Figure 1, and these curves will point out the consistency of the measurements in any one experiment. Only one out of every ten points is shown on these curves for the sake of clarity in the plots.

II. Treatment of Data

A summary of the essential data and results is shown in Table 1. The experimentally determined first-order rate constants (k) and the reaction half times ($t_{1/2}$) are given in columns 8 and 9, respectively, and were determined by the following procedure.

The uncatalyzed alkylation of phenol in the presence of excess phenol was determined to be first-order with respect to the tertiary halide. Thus, the reaction is represented mathematically by the equation,

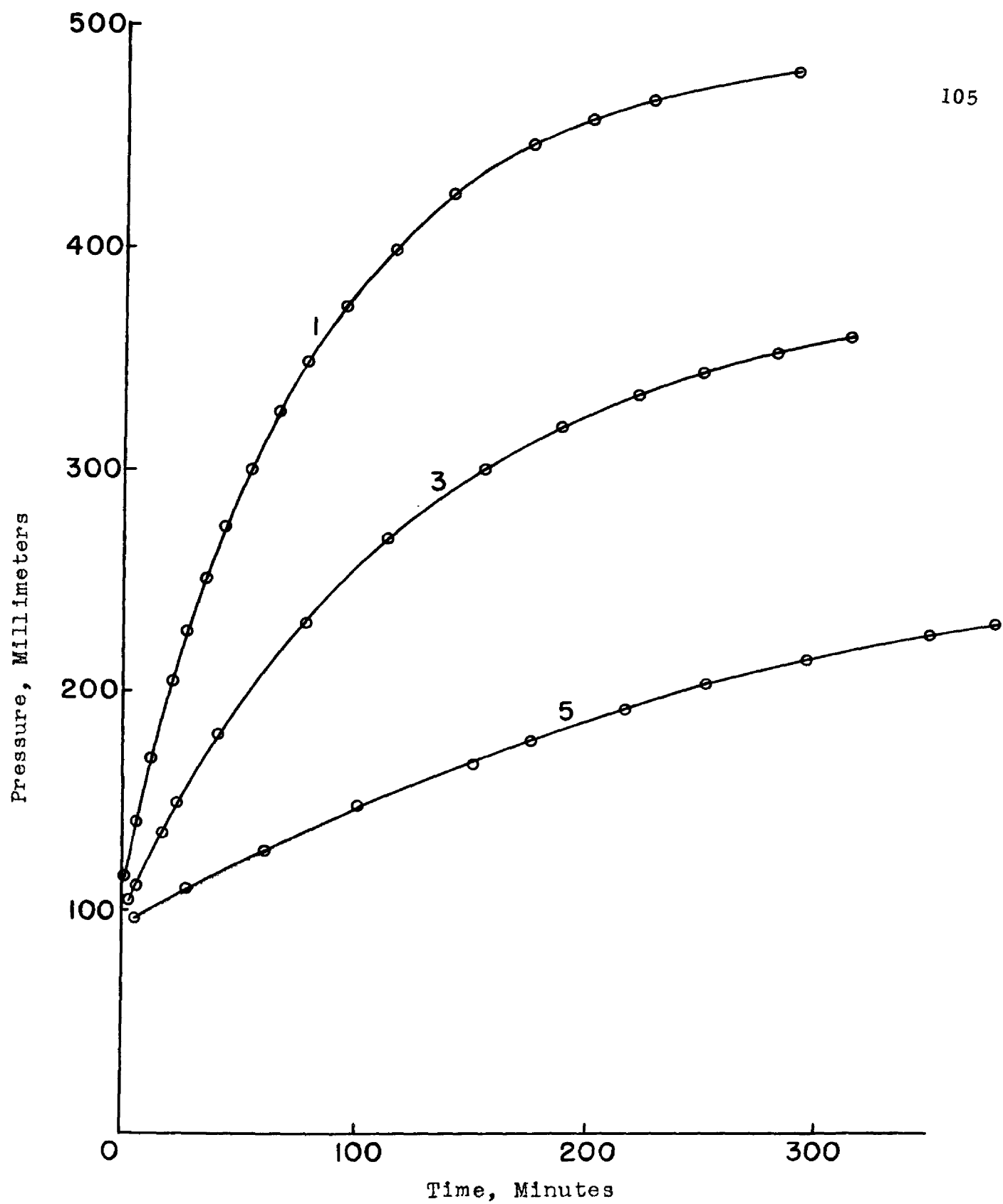


FIGURE 1. Pressure vs. Time Curves for Experiments 1, 3, and 5, Table 1.

TABLE 1

KINETIC DATA FOR THE ALKYLATION OF PHENOL IN THE
PRESENCE OF OXYGENATED COMPOUNDS

Expt.	t-Bu Cl Moles	Phenol Moles	Oxygenate Moles
(1)	(2)	(3)	(4)
-	0.01112	0.2156	
	0.009881	0.2165	
	0.009150	0.2120	0.006082 D
	0.01071	0.2166	0.01347 D
	0.01050	0.2123	0.02405 D
	0.01167	0.2223	0.03722 D
	0.01129	0.2164	0.01221 P
	0.01129	0.2091	0.02422 P
	0.01140	0.2142	0.03472 P
10	0.011575	0.2133	0.03248 X

* These values were calculated on the basis that the added oxygenate acts only as a diluent.

Meaning of symbols used:

D = 1,4-dioxane.

P = tetrahydropyran.

X = p-xylene.

TABLE 1 (Continued)

Molarity* Phenol	P _f	P _o	k	t _{1/2}
(5)	(6)	(7)	(8)	(9)
10.55	506.2	107.8	0.01241	55.2
10.61	499.7	104.5	0.01357	53.1
10.28	401.2	98.1	0.007158	96.7
9.90	419.4	100.8	0.003884	178.6
9.46	413.2	95.0	0.001515	457.8
9.08	501.4	100.2	0.0004637	1497.3
9.86	434.3	106.1	0.005828	119.0
9.38	432.0	103.6	0.002580	268.8
9.06	390.0	132.0	0.001561	423.7
9.00	375.1	97.8	0.004742	146.1

$$dc/dt = kc$$

where c is the halide concentration.

Integrating,

$$\ln c = kt + \text{constant}$$

therefore,

$$\log c = (k/2.303)t + \text{constant}$$

Since the halide concentration in our measurements is represented by the term $(p_f - p)$, the equation is revised to read:

$$\log (p_f - p) = (k/2.303)t + \text{constant}$$

where p represents the instantaneous total pressure, p_f the final equilibrium pressure, t the time, and k the first-order velocity constant. Thus, when $\log(p_f - p)$ is plotted against time, a straight line should be obtained, the slope of which is equal to $(k/2.303)$.

This plot for some of the experiments is shown in Figure 2. It is readily seen how well the straight-line relationship held throughout the experiments.

The rate constants (k) were then obtained from these graphs as the product of the slope and 2.303. The values of p_f in most cases were determined experimentally by allowing the reaction to go to completion. In the case of the very slow reactions, however, the p_f value was determined by extrapolation of the straight line

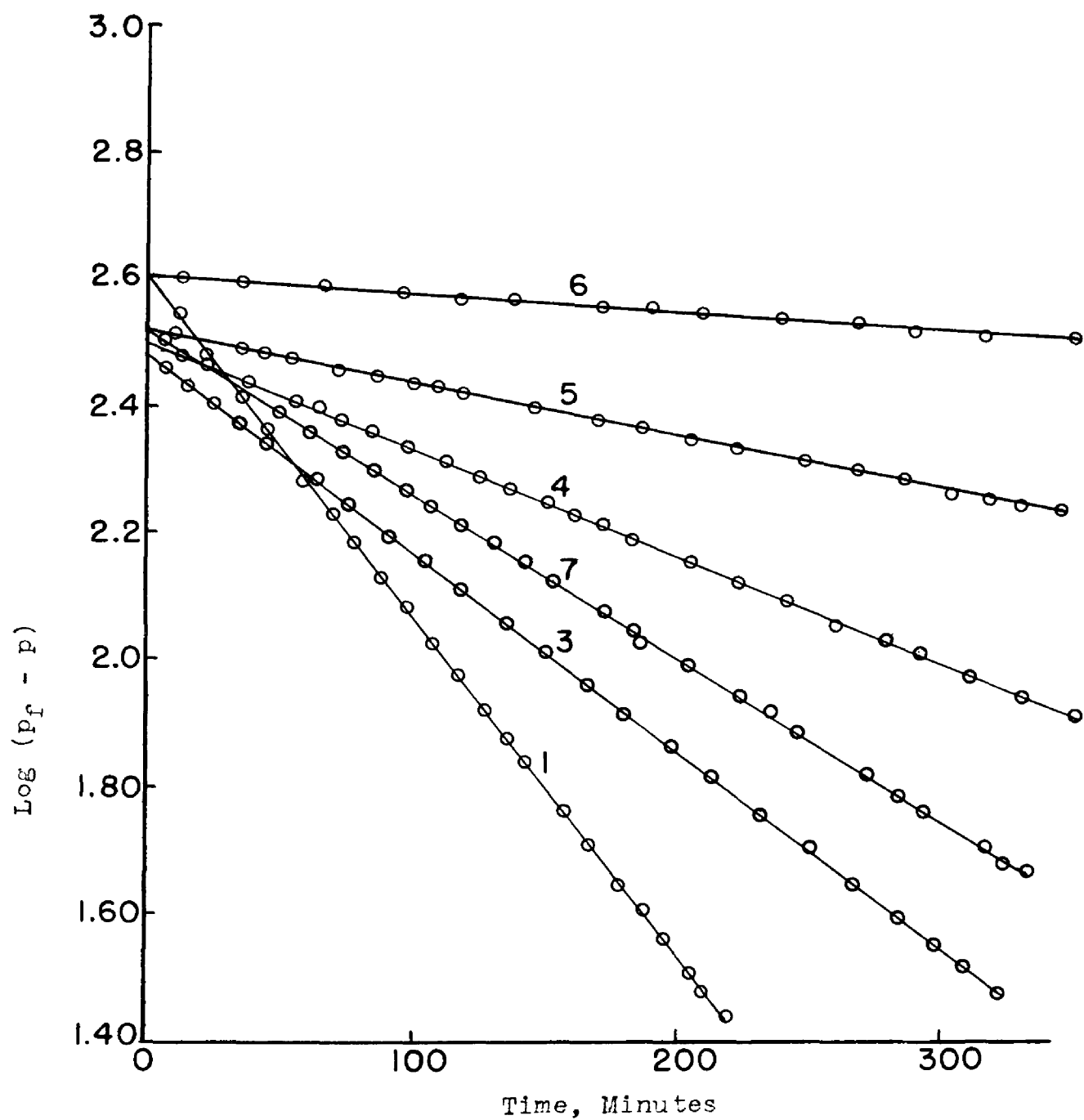


FIGURE 2. Adherence of Observed Data to First Order Rate Law.

obtained by plotting (dp/dt) versus p to $(dp/dt = 0)$. The p_o value shown in column 7, Table 1, represents the vapor pressure of the tertiary halide, plus that of phenol and the oxygenated material used, and was found by extrapolation of the pressure-time curves to zero time. With these data available, it was then possible to calculate the values of $t_{1/2}$ given in column 9, Table 1.

It was then necessary to calculate the half times, $t_{1/2}$, which one would expect under varying assumptions concerning the actual role of the oxygenated material in the alkylation reaction. This was done in the following manner:

Bordeaux and Hart (9) derived the equation

$$[(t_{1/2})/(t_{1/2o})] = [M^o/M]^n$$

in which $t_{1/2o}$ represents the reaction half time when no oxygenated material is present, $t_{1/2}$ the half time for the reaction under observation, M^o the molarity of phenol in the reaction with no oxygenated material, M the phenol molarity in the reaction being studied, and n is the order of the reaction with respect to phenol.

From Table 1, the reference values are seen to be $t_{1/2o} = 54.0$, and $M^o = 10.57$ at 50° . The calculated $t_{1/2}$ values are shown in Table 2, and have the following significance:

TABLE 2

SUMMARY OF CALCULATED AND OBSERVED HALF-TIMES FOR
THE VARIOUS ALKYLATION EXPERIMENTS*

Expt.	$t_{1/2}$ obs. (min.)	$t_{1/2}^a$ (min.)	$t_{1/2}^b$ (min.)	$t_{1/2}^c$ (min.)	Mole Ratio (oxygenated compound/ phenol)
1	55.2				
2	53.1				
3	96.7	65.5	78.7	95.4	0.02868
4	178.6	84.7	118.2	174.3	0.06205
5	457.8	103.1	217.6	497.7	0.11320
6	1497.3	134.0	461.3	1654.7	0.16751
7	119.0	85.9	118.4	165.7	0.05635
8	268.8	111.3	247.6	557.4	0.11598
9	423.7	137.2	400.2	1433.4	0.16198
10	146.1	144.5			0.15252

* The symbols $t_{1/2}^a$, $t_{1/2}^b$, and $t_{1/2}^c$ are defined on p. 112.

The values of $t_{1/2}^a$ (column 3, Table 2) were calculated assuming that the oxygenated material serves only to decrease the phenol concentration by dilution of the reaction mixture. For example, data from Experiment 5 are considered:

$$[(t_{1/2}^a)/54.0] = [10.57/9.46]^6; t_{1/2}^a = 103.1 \text{ minutes}$$

The order n was taken as 6 because Hart and Simons (2) pointed out that the apparent reaction order with respect to phenol was sixth.

The values of $t_{1/2}^b$ (column 4, Table 2) were calculated with the assumption that each mole of added oxygenated compound combined with one mole of phenol, and thus decreased the available phenol for alkylation. Using the same Experiment as above, $t_{1/2}^b$ is found to be:

$$[(t_{1/2}^b)/54.0] = [10.57/8.36]^6; t_{1/2}^b = 217.6 \text{ minutes}$$

The values of $t_{1/2}^c$ (column 5, Table 2) were obtained in the same manner from the assumption that each mole of oxygenated material combined with two moles of phenol, to decrease the phenol concentration for alkylation even further. Experiment 5 is used again as an example.

$$[(t_{1/2}^c)/54.0] = [10.57/7.29]^6; t_{1/2}^c = 497.7 \text{ minutes}$$

In the case of the experiments involving tetrahydropyran as the oxygenated material, the latter assumption is omitted, of course,

since only one oxygen atom is present for complex formation with the phenol molecule.

Figures 3 and 4 show plots of these calculated half times against the oxygenate-phenol concentration ratio, as compared to the same curves for the experimental half times (column 2, Table 2).

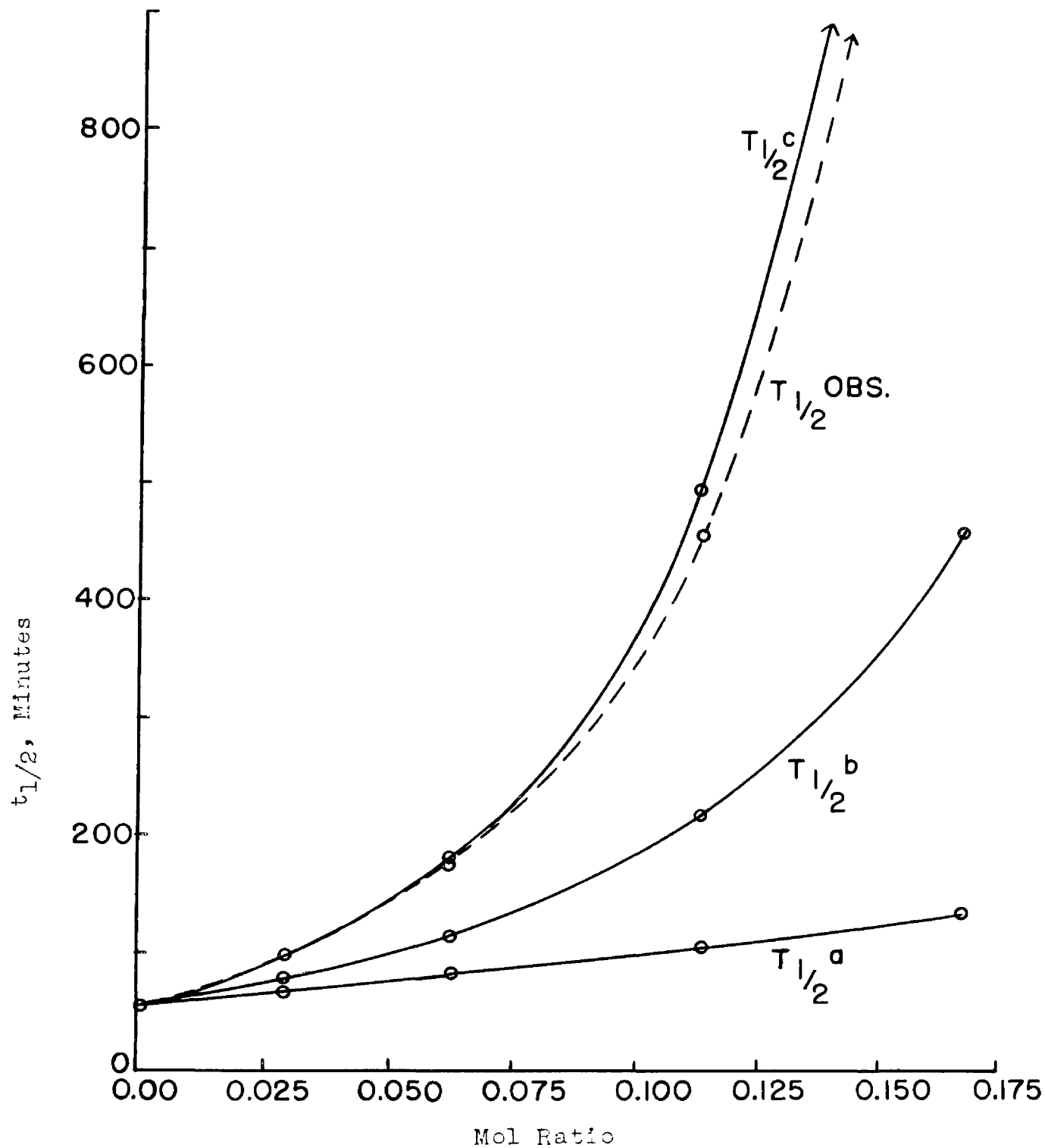


FIGURE 3. Half-Time Values vs. Mol Ratio of Dioxane to Phenol.

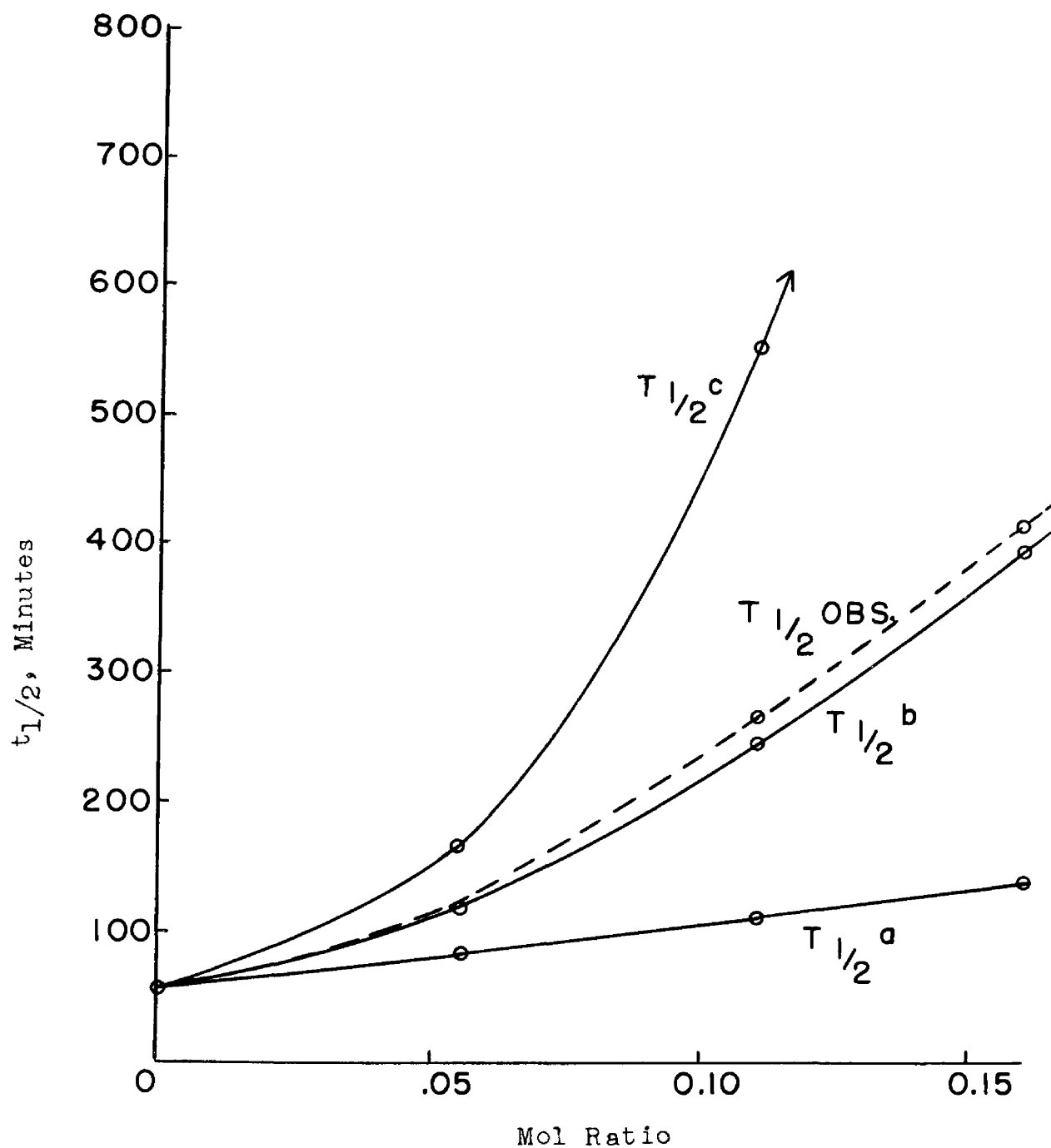


FIGURE 4. Half-Time Values vs. Mol Ratio of Tetrahydropyran to Phenol.

Discussion

The mechanism postulated by Hart and Simons (2) for the uncatalyzed alkylation of phenol with tertiary halides was based upon several experimental observations. Among these was the complete inhibition of the reaction by the addition of approximately 21 mol percent of 1,4-dioxane. In view of the fact that other diluents of equivalent dielectric constant had no such marked effect on the reaction rate, it was suggested that the dioxane inhibition was due to a hydrogen bonding effect which reduced the available hydroxyl groups for participation in a concerted reaction.

In an effort to firmly establish the role of the dioxane in the reaction, Bordeaux (9) conducted a kinetic investigation of the reaction using varying amounts of dioxane. Once again the results indicated that the inhibition was too great to be due to a dilution effect, and it was suggested that the dioxane formed a 1:1 oxonium-type complex with the hydroxyl group of the phenol. This suggestion is supported by the work of Bartlett and Dauben (35), which showed that dioxane was basic enough to form oxonium compounds with acidic substances such as phenol.

In view of the rather crude experimental technique used by Bordeaux, however, it was felt that more precise quantitative

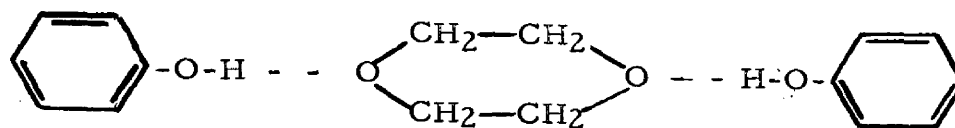
measurements of the stoichiometry of the inhibition would be of value. With the aid of a rate measuring apparatus such as that described in Part II, it was possible in this investigation to make a more accurate study of the effect of oxygenated compounds on the alkylation rate.

It was pointed out by Hart and Simons (2) that the uncatalyzed reaction proceeded by virtue of the presence of a large excess of phenol. As was seen from their kinetic data, any significant decrease in phenol concentration resulted in a large decrease in reaction rate. Therefore, the addition of any inert material would be expected to cause a rate decrease. The results tabulated in Table 1 verify this, but the decrease observed is far greater than would be expected for only dilution of the reaction mixture (column 3, Table 2). For example, consider Experiment 4, in which dioxane was used as the inhibitor. The experimentally determined half time was 178.6 minutes; the calculated half time for dioxane dilution is 84.7 minutes, while the half time based on the assumption that one mole of phenol is complexed per mole of dioxane is 118.2 minutes. When the half time was calculated for the assumption that each mole of dioxane complexed two moles of phenol, it was found to be 174.3 minutes. The latter value corresponds quite well to the experimentally

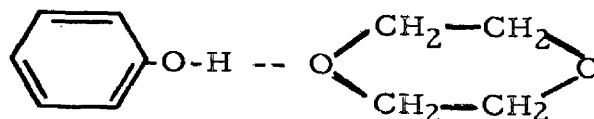
determined value in Experiment 4, and it can be seen that the other dioxane Experiment 3 through 6 coincide in the same manner. This correlation is illustrated in Figure 3, where it is seen that the experimental half time curve follows quite closely the calculated curve for a 2:1 oxonium complex between phenol and dioxane.

If an inhibition of this type is general and if the results obtained above are fairly accurate, then it follows that an oxygenated material similar to dioxane, but having only one available oxygen for oxonium formation, should inhibit the reaction by the formation of a 1:1 oxonium complex. Tetrahydropyran was chosen for this work because the ring size is the same as in dioxane except that one dioxane oxygen is replaced by a methylene group. Experiments 7 to 9, Table 1, and Figure 4 show that this reasoning is substantiated.

The results of this study add additional evidence to the postulation by Hart and Simons (2) and in Parts A and B of this thesis that the uncatalyzed alkylation of phenol proceeds by a mechanism involving the availability of the phenolic hydroxyl group, and that the effective concentration of phenol is decreased by the formation of complexes such as:



and



Experiment 10 was carried out using *p*-xylene in place of the oxygenated material. Comparing this experiment with Experiments 6 and 9, where comparable amounts of oxygenated material were added, it is seen that the observed half time is much lower in the *p*-xylene experiment, where the rate decrease is caused only by dilution.

Another possible explanation of the inhibition studied here, which has not been mentioned, is that the addition of an oxygenated material such as dioxane might cause increased solubility of the evolved hydrogen chloride in the phenol-dioxane mixtures. Since the rate was followed by the increase in hydrogen chloride pressure, this could give the effect of apparent inhibition. This possibility was eliminated by Hart and Simons (2), who carried out two experiments with a constant mol ratio of dioxane to phenol. In the first experiment the reaction was conducted in the usual manner and no alkylation occurred. In the second experiment, the reactants were first saturated with hydrogen chloride and then the reaction carried

out as before. Once again the result was the same; there was complete inhibition of the reaction. Since hydrogen chloride was not evolved even when the reaction medium was already saturated with the gas, it was concluded that the inhibition was not an artifact.

SUMMARY

2,6-Di-*t*-butylphenol, a compound exhibiting maximum steric hindrance of the hydroxyl group, was synthesized by the method of Hart (15) in 44 percent yields. This compound was characterized by its alkali insolubility, sensitivity to the phosphomolybdic test for hindered phenols, and its characteristic ultraviolet and infrared absorption spectra.

The action of sulfuric acid caused this phenol to rearrange to 2,4-di-*t*-butylphenol, while nitration at 25° to 35° in glacial acetic acid (1:1) gave cleavage of a *t*-butyl group to yield 4,6-dinitro-2-*t*-butylphenol. Under milder nitrating conditions the phenol was oxidized to 3,3',5,5'-tetra-*t*-butyldiphenoquinone.

2,6-Di-*t*-butylphenol gave negligible rates of para bromination, diazonium coupling, and alkylation when compared to 2,6-xylenol. This is attributed to steric inhibition of the usual hydroxyl resonance with the aromatic ring, by the bulky *t*-butyl groups.

Relative rates of para *t*-butylation of several phenols were determined at 50°, using the phenol to be alkylated as the reaction solvent. The alkylation rate was found to decrease with an increase

in size and/or number of ortho alkyl groups. The observed rate decrease, under the reaction conditions employed, could result from several factors, all of which, however, could be attributed to steric hindrance of the hydroxyl group by the bulky ortho substituents.

Precise kinetic studies of the alkylation of phenol and *o*-cresol were made in *o*-dichlorobenzene at 88°, using triphenylmethyl chloride. The reaction was found to be auto catalyzed by hydrogen chloride formed during the alkylation, and third-order kinetics were obtained when the hydrogen chloride gas was present initially in the reaction.

A kinetic study of the inhibition of this reaction by dioxane and tetrahydropyran was carried out at 50° in excess phenol. Evidence was presented to show that phenol forms 2:1 and 1:1 complexes, respectively, with these materials, thus decreasing the phenol available for alkylation.

A carbonium mechanism involving preliminary solvation of the halide by the phenol or hydrogen chloride, followed by a rate-determining electrophilic attack by the carbonium ion on the phenol, is proposed to account for the facts observed here and in several previous investigations.

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