MECHANISTIC STUDIES OF ELECTROPHILIC SUBSTITUTION ON THIOPHEN COMPOUNDS

being a Thesis

presented by

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ABSTRACT

The mechanism of electrophilic substitution on thiophen has been investigated. A study of salt effects and activation parameters for the bromination of thiophen and mesitylene, in 15% aqueous acetic acid, indicates a similar mechanism for the two reactions. There is an isotope effect of $k_H/k_D = 1.35 \pm 0.05$ in the bromination of thiophen. This is shown to be a secondary isotope effect and does not represent slow proton loss.

The effect of substituents at the 2- position on the rate of bromination of thiophen, in 15% aqueous acetic acid, has been studied, and using substituent constants derived from benzene compounds, a linear Hammett free energy correlation was obtained with a ρ value of -10. A similar study of the chlorination of 2- substituted thiophens, in glacial acetic acid, gave a ρ value of -6.5. Bromination of deactivated thiophens has been analysed in terms of simultaneous second and third order processes. The activation parameters for various substituted thiophens show that the rate of bromination is controlled by changes in enthalpy, while the entropy of reaction remains essentially constant. In the bromination of 2,3-benzothiophen, in 15% aqueous acetic acid, evidence of complex formation between 2,3-benzothiophen and bromine was obtained.

The variation in the rate of protodetritiation of 2- and 3-tritiothiophen with acidity and temperature has been measured. Activation parameters were found to be independent of acidity. General acid catalysis has been detected in the protodetritiation of 2-methoxy-5-tritiothiophen. The mechanism of hydrogen exchange is discussed.

The rates of nitration of thiophen and some substituted thiophens in sulphuric and perchloric acids have been measured. The mechanism of nitration is shown to be the same as that for benzene compounds. The difficulties experienced with the nitration of thiophen on a preparative scale are attributed to the extreme susceptibility of thiophen to nitrosation and subsequent reactions of the nitroso intermediate. The success of nitric acid in acetic anhydride as a nitrating agent for thiophen is due to the preferential oxidation of the nitroso product to nitrothiophen under these conditions.

DECLARATION

I declare that this thesis is based on the results of experiments carried out by me, that it is my own composition and has not previously been presented for a Higher Degree.

The work was carried out in the Department of Chemistry of the United College in the University of St. Andrews, under the direction of Dr. A.R. Butler.

CERTIFICATE

I hereby certify that Mr. James Buchanan Hendry, B.Sc., has spent eleven terms at research work under my supervision, has fulfilled the conditions of Ordinance No. 16 (St. Andrews), and is qualified to submit the accompanying thesis in application for the degree of Ph.D.

Director of Research.

UNIVERSITY CAREER

I entered the University of St. Andrews as an undergraduate in October 1963 and graduated B.Sc. with Second Class Honours in Chemistry in July 1967.

The research described in this thesis was carried out between October 1967 and July 1970, during which time I held a Research Studentship awarded by the University of St. Andrews.

PUBLICATIONS

(1) Electrophilic Substitution on the Thiophen Ring.

Part I. Bromination of Thiophen and Deuteriated Thiophen.

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(2) Part II. Halogenation of Substituted Thiophens.

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J. Chem. Soc.(B), 1970, 848.

(3) Part III. Hydrogen Exchange in Acidic Media.

Anthony R. Butler and James B. Hendry

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(4) Part IV. Kinetics and Mechanism of the Nitration of Thiophen.

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" A Man would do nothing, if he waited until he could do it so well that no one would find fault with what he had done."

CARDINAL NEWMAN

PART I

INTRODUCTION

1. REACTION KINETICS AND REACTION MECHANISMS

The stoicheiometric equation for any chemical reaction indicates the nature and quantity of the reactants and products but gives no information concerning the mechanism by which the change occurs. Such information is obtained only by a consideration of other features of the reaction. The study of reaction kinetics has been widely used in this connection and is the principal topic of this work. There are however certain limitations to which the method is subject. The interaction of molecules during a reaction may according to the theory of absolute reaction rates, be represented by a potential energy curve. The portion of the curve at the maximum is known as the "transition state" or "activated complex". The determination of the order of reaction, i.e. the mathematical form of the rate equation, gives only the stoicheiometric composition of the transition state and not its structure. A more detailed study of the kinetics may disclose the form of the reacting species but, again, not the way they interact in the transition state.

In some instances the reactants may form an unstable intermediate which decomposes to give the products of the reaction. This intermediate is represented by a depression in the potential energy curve but an investigation of reaction orders cannot detect its formation.

However, in spite of these limitations, the study of reaction kinetics has proved a valuable method in the elucidation of reaction mechanisms.

2. STRUCTURE OF THIOPHEN

The planar structure of the thiophen ring appears to be generally accepted with the four carbon atoms and sulphur atom spaced about an axis of symmetry which passes through the sulphur nucleus.

Dimensions established by Schomaker and Pauling[1] from electron diffraction data are subject to uncertainties as assumed values for C=C and C-C bond lengths were used because values of bond distances in heterocyclic molecules containing only light atoms cannot be determined by electron diffraction.

A more recent study by Bak et al. on the microwave spectra of thiophen, deuteriated thiophens[2] and 2- and 3-C^{13} enriched thiophen[3], has resulted in the dimensions of thiophen being known with very high precision (TABLE 1).

Fig. 1 Numbering of carbon atoms of the thiophen molecule.

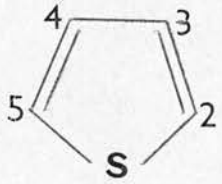


TABLE 1

The dimensions of the thiophen molecule[a]

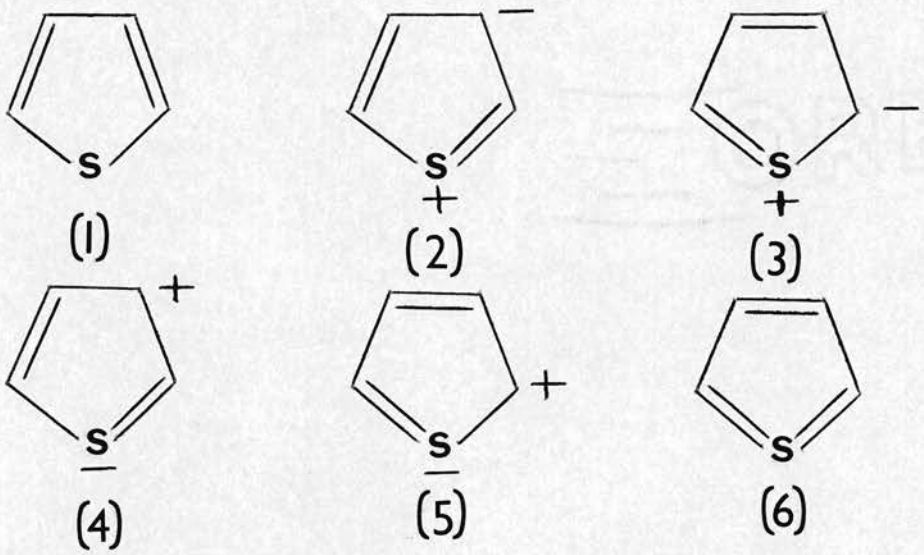
Bond	Distance Å
C(2)H(2)	1.0776 ± 0.0015
C(3)H(3)	1.0805 ± 0.0014
C(2)S	1.7140 ± 0.0014
C(2)C(3)	1.3696 ± 0.0017
C(3)C(4)	1.4232 ± 0.0023

Bond	Angle
C(5)SC(2)	92°10' ± 6'
SC(2)C(3)	111°28' ± 14'
C(2)C(3)C(4)	112°27' ± 11'
SC(2)H(2)	119°51' ± 47'
C(4)C(3)H(3)	124°16' ± 4'

[a] see ref. 4

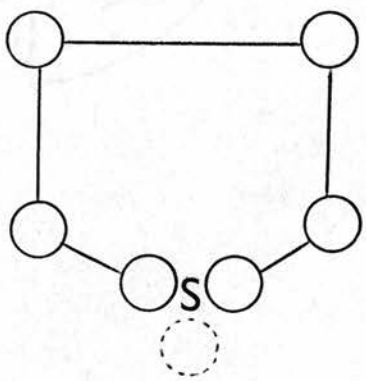
The high double bond character of the C-S bond is especially striking and shows clearly how badly the classical formula alone represents the true structure of the thiophen molecule. According to Bak, the higher double bond character of the C-S bond, as compared to the bond between C-3 and C-4, is probably the cause of the greater chemical reactivity of the 2- position in electrophilic reactions.

Up to 1939, it was believed that the sulphur atom in thiophen participates in conjugation by the use of its two 3p electrons, similarly to the use of the two 2p electrons of oxygen in furan. Resonance structures in which the sulphur atom has expanded its valence shell to 10 electrons were first proposed by Schomaker and Pauling[1]. By considering bond lengths, resonance energies and dipole moments these authors concluded that the following were important contributing structures:-



Structures (4), (5) and (6) must involve sulphur d orbitals because the sulphur atom has a decet of electrons in its valence shell. Since the energy difference between 3p and 3d orbitals is small, the participation of such 3d orbitals in the bonding process is reasonable.

In 1949, Longuet-Higgins[5] introduced a theory of the electronic structure of thiophen in which the sulphur atom contributes two hybrid pd^2 orbitals to the π-electron system. The geometry of these orbitals makes them a good substitute for two p orbitals of two adjacent carbon atoms in a benzene ring. The sulphur atom in thiophen can therefore be considered to replace a -CH=CH- fragment of benzene. Actually three pd^2 hybrid orbitals are formed, but only two of these have the right symmetry and energy for conjugation with the p orbitals of the adjacent carbons. The third pd^2 hybrid orbital is too high in energy for it to be occupied in the ground state. Longuet-Higgins' description of the electronic structure of thiophen may be illustrated as follows:-



The six solid circles representing the four carbon p orbitals and the two sulphur pd^2 orbitals, and the dotted circle refers to the high energy unoccupied sulphur pd^2 orbital.

Moreover, since the same electronegativity value is assigned to sulphur and carbon[6] Longuet-Higgins implied that there would be no difference in the net electrical charge between the different atoms of thiophen, as in the case of benzene. The difference in chemical behaviour between thiophen and benzene is accounted for by the difference in the resonance integral between adjacent carbon and sulphur orbitals as compared to that between two adjacent carbon orbitals. Longuet-Higgins was able to show that the resonance integrals between adjacent carbon and sulphur orbitals are approximately 80% of the corresponding resonance integral where only carbon atoms are involved. Since two of the resonance integrals in thiophen are 20% less than the corresponding ones in benzene, the electronic structure of thiophen should be intermediate between those of benzene and butadiene, but closer to that of benzene (the stabilization energies are 29.1 and 36 k cals./mole for thiophen[7] and benzene[8], respectively, as determined for heats of combustion). Hence Longuet-Higgins accounts for preferential attack at the 2-position and the greater susceptibility of thiophen to electrophilic substitution than benzene on the basis of

butadiene character, the two double bonds in thiophen resembling the butadiene system.

However, no agreement has been reached on the pd-hybridization of the sulphur atom. This is considered by some workers an essential feature in the electronic structure of thiophen, making the sulphur atom similar to a -CH=CH- group, and being responsible for some of the differences between thiophen, furan, and pyrrole[9]; whereas others have suggested that most of the properties of thiophens may be accounted for without invoking pd-hybridization at all[10]. The Longuet-Higgins approach has been criticised for the use of nonorthogonal hybrid orbitals[11] and Mangini and Zauli[12] claim that, for thiophen with a C-S-C angle of about 90°, the three pd^2 hybrid orbitals have mainly d character and so have an impossibly high energy.

Many attempts have been made to try and calculate the electron densities, resonance energies and dipole moments both by valence bond and LCAO-MO approaches. Theoretical calculations concerning the electron density on the 2- and 3-positions of thiophen have not given consistent results. Using molecular orbital calculations, Kikuchi[13] concluded that the electron density is higher in the 3- position. The calculations of Kreevoy[10] also by the molecular orbital method showed a partial negative charge on both the 2- and 3- carbon

atoms of thiophen, with the charge on the 3- carbon being slightly larger than the charge on the 2- carbon, in agreement with Kikuchi's results. However, Mangini and Zauli[12], using the valence bond method, found the calculated charge distribution at the 2- position to be the more negative one.

The study of the N.M.R. spectra of thiophens has attracted considerable interest, partly because the spectra of substituted thiophens containing only a few ring hydrogens are quite suitable for complete analysis and partly because in a series of related compounds the chemical shifts observed are related to differences in the electron distribution about the molecules. The electron densities at the 2- and 3- positions of thiophen have been compared in a study by Gronowitz and Hoffman[14] of the N.M.R. of 2,5- and 3,4- dibromothiophen. They concluded that the electron density is higher at the 3- position as the resonance of the hydrogens in the 2,5- dibromothiophen occurs at a higher field than that of the hydrogens in 3,4- dibromothiophen.

A comparison of the N.M.R. spectra of furan, pyrrole and thiophen indicates differences in their electronic structure. At 60 mc/sec the resonances of the alpha hydrogens of furan, pyrrole[15] and thiophen[16] appear at 66, 31 and 12 c.p.s. respectively, at lower fields than the resonances of the beta hydrogens. These results may be interpreted by assuming that

the electron attracting hetero atoms unshield the alpha hydrogen more than the beta hydrogen and based on electronegativity consideration,[a] this effect should be greatest for oxygen and least for sulphur. This agrees with the observed results. The alpha and beta hydrogens of thiophen, in contrast to those of furan and pyrrole, have similar values and, presumably, similar electron densities. The results may partially confirm Longuet-Higgins' conclusions that there is no difference in the net electrical charge between the different atoms of thiophen.

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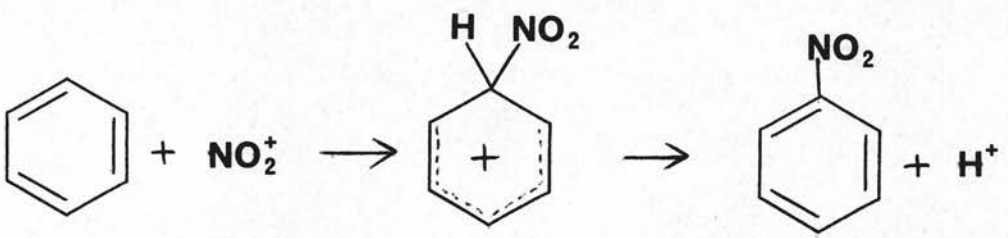
[a]The following electronegativity values are assigned to C, S, N, O; C = 2.5, S = 2.5, N = 3.0, O = 3.5[6].

3. THE MECHANISM OF ELECTROPHILIC SUBSTITUTION

The mechanism of electrophilic substitution in benzenoid compounds is now well established.[17] In such reactions the two electrons which form the covalent bond between the aromatic compound and the reagent are both supplied by the former. This may be illustrated from the nitration of benzene by the nitronium ion, NO_2^+. The aromatic ring supplies two electrons to form a covalent bond with the nitrogen atom of the reagent, causing a temporary electron deficiency which is accommodated in the π orbitals of the residual aromatic system, and reaction is completed by the removal of a proton from the nucleus.



Neutral species may also be electrophilic. For instance, in the reaction of chlorine with a benzene ring the new C-Cl bond is formed by the supply of two electrons from the aromatic compound, molecular chlorine behaving as an

electrophile because of the ability of one chlorine atom to be displaced as chloride ion.

Attack of an electrophile, E, and loss of a proton must occur in one of three ways;

1) Synchronous formation of the C-E bond with both the incoming and leaving groups partially bonded to the aromatic nucleus in the transition state.
2) Addition of the electrophile to the nucleus followed by loss of a proton in a slow step.
3) Slow attack of the aromatic nucleus by the electrophile and rapid loss of a proton.

In all cases for which enough evidence is available to distinguish between these possibilities, the reaction is known to follow 3) (an S_E2 mechanism) unless there are steric reasons making loss of the proton rate determining[18].

4. KINETIC HYDROGEN ISOTOPE EFFECTS

One method of distinguishing between the above mechanisms for electrophilic substitution is by measurement of kinetic hydrogen isotope effects.

It should be pointed out that isotopic replacements in the substrate are possible for almost any element and in no way limited to hydrogen. Since the isotope effect is brought about by the difference in mass of the isotopes it is consequently largest for the isotopes of hydrogen.

The term "hydrogen isotope effect" signifies the change in reaction rate obtained on replacing protium by deuterium (or possibly tritium) in a reacting system.

Four different hydrogen isotope effects are recognised, which may be observed in the following ways:-

1) by substituting a protium atom of the substrate, which is replaced during the reaction, by a deuterium (or tritium) atom,
2) by substituting a protium atom, not at the seat of reaction, by a deuterium (or tritium) atom,
3) by replacing normal water by heavy water in solvolytic reactions, and
4) by changing the isotopic composition of the medium in non-solvolytic reactions.

It is the first of these effects which is most useful in

elucidation of the mechanism of electrophilic substitution. An order of bond strengths, C-T > C-D > C-H, obtains when the carbon atom is in the same structural environment, so that the rates at which these bonds are broken in a given reaction increase in the opposite order, i.e. C-T < C-D < C-H. Normally when a carbon-hydrogen bond is broken in the rate determining step of a reaction a positive hydrogen isotope effect is observed: that is $k_H > k_D > k_T$. The absence of a positive isotope effect therefore indicates that the C-H bond is not ruptured during the rate determining synchronous mechanism but is consistent with the two step mechanism:-

$$ArH + E^+ \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} {}^+Ar\begin{smallmatrix}H\\E\end{smallmatrix} \xrightarrow{k_2} ArE + H^+$$

provided that the rate of reaction is determined solely by the rate of the first step, which does not involve C-H bond rupture, i.e. $k_2 \gg k_{-1}$. If, however, this condition were not to hold, the intermediate would be partitioned between product formation and reversion to the starting material. Since the rate at which the intermediate loses a proton is greater than that at which it loses D^+ or T^+ but the rate at which it reverts to starting material is independent of the nature of the hydrogen isotope, the effect of partitioning

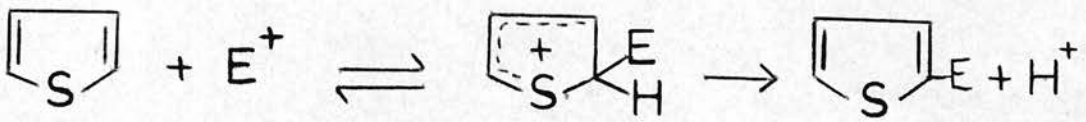
would be to increase the rate of formation of the hydrogen substituted product relative to the deuterium or tritium substituted products.

The absence of isotope effects, therefore, not only shows that the synchronous mechanism cannot apply but also that formation of the intermediate adduct is the rate determining step of the substitution and that this reacts essentially completely to form the product.

A positive isotope effect is consistent with synchronous displacement and the two step mechanism in which k_2 is comparable with or less than k_{-1}, the observed isotope effect then arising from the partitioning principle enunciated above. A distinction between these possibilities can only be made if some further evidence is available.

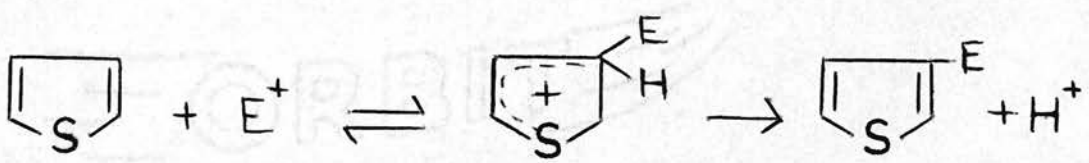
5. ELECTROPHILIC SUBSTITUTION OF THIOPHEN

If one assumes a mechanism for thiophen analogous to the two step mechanism now generally accepted for electrophilic substitution of benzenoid compounds, then electrophilic substitution at the 2- position of thiophen may be pictured to take place as follows:-

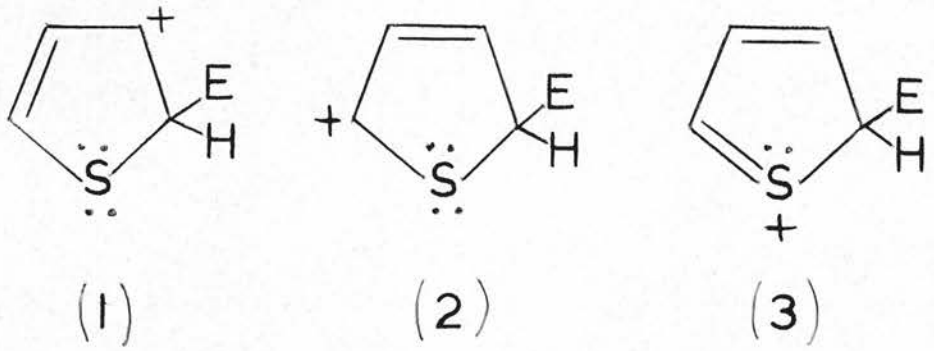


The attacking group, E^+, is pictured as being a cation, but may be neutral as explained above.

The following scheme is postulated for electrophilic substitution at the 3- position:-

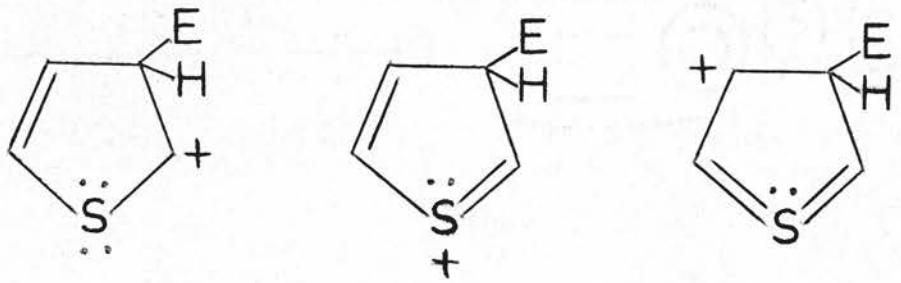


The following structures may be assigned to the intermediate for electrophilic substitution at the 2-position:-



(1) (2) (3)

and for electrophilic substitution at the 3- position:-



(4) (5) (6)

However, both Schomaker and Pauling[1] and Melander[19] assign low weights to structures with a π bond between carbon and sulphur due to the decreased overlap between sulphur pd^2 and carbon p orbitals. Thus structures (3), (5), and (6) have a higher energy and are regarded as unstable. Considering only the energetically favourable structures (1) and (2)

stabilizing the complex for electrophilic substitution in the 2- position and one structure (4) for electrophilic substitution in the 3- position.

The lower energy of the transition state and predominant substitution at the 2- position can therefore be accounted for by the increased stabilization of the intermediate which is similar in structure and energy to the transition state of the reaction.

Electrophilic substitution of thiophens with an ortho / para directing substituent

It is important to note that the use of " ortho / para " terminology has no real theoretical significance when one is referring to the thiophen ring. It is tempting however to compare orientation in a thiophen derivative to a similarly substituted benzene. Future references to orientation in thiophen will be made with the above limitations in mind.

An " ortho / para " directing group in the 2- position of thiophen would be expected to activate the 3- and the 5- positions towards electrophilic attack. Coupled with the directing effect of the sulphur atom one would expect the 5- position to be the more reactive. In a typical reaction, the chlorination of 2-chlorothiophen, the products consist of

99% of 2,5-dichloro- and 1% of 2,3-dichlorothiophen.[20, 21]

By similar arguments one would expect an "ortho / para" directing group in the 3- position to activate the 2- position towards electrophilic attack. It is reported by Steinkopf and Kohler[22] that bromination of 3-methylthiophen yields 100% of the 2-bromo product. However metallation of 3-methyl--thiophen occurs exclusively at the 5- position[23], possibly for steric reasons.

Electrophilic substitution of thiophens with a meta directing substituent.

When thiophen is substituted in the 2- position by a meta directing group, there is a tendency to overcome the directive influence of the sulphur atom, and a mixture of 5- substituted and 4- substituted thiophen results, with the former predominating. The nitration of 2-nitrothiophen yields 90 - 95% of 2,5-dinitrothiophen and 10 - 5% of 2,4-dinitrothiophen[24], depending on experimental conditions. However, Marino[25] reports that bromination of thiophen-2-carboxylic acid ethyl ester in acetic acid gives the 5-bromo product exclusively.

6. HAMMETT AND RELATED LINEAR FREE ENERGY RELATIONSHIPS

The Hammett and related equations are empirical correlations of reactivity and structure. Such correlations are generally linear relationships involving the logarithms of rate or equilibrium constants of reactions. Since the logarithm of a rate constant (k) is proportional to the standard free energy of activation ($\Delta G^{\ddagger}$) and that of an equilibrium constant (K) to the standard free energy change of reaction (ΔG°)[26], the term free energy relationship is appropriate.

The Hammett equation was formulated in 1937[27] to describe the influence of polar meta- or para- substituents on the side chain reactions of benzene derivatives. The simple equation cannot be applied to the influence of ortho substituents owing to the occurrence of steric effects.

The Hammett equation can take two forms:-

$\log \frac{k_x}{k_o} = \rho\sigma$ referring to reaction rates

e.g.

$$C_6H_5CH_2\text{-}Cl \xrightarrow[H_2O]{k_o} C_6H_5CH_2OH + HCl$$

$$X\text{-}C_6H_4CH_2\text{-}Cl \xrightarrow[H_2O]{k_x} X\text{-}C_6H_4CH_2OH + HCl$$

or $\log \frac{K_x}{K_o} = \rho\sigma$ referring to equilibria

$$C_6H_5CH_2NH_3^+ \overset{K_o}{\rightleftharpoons} C_6H_5CH_2NH_2 + H^+$$

$$X\text{-}C_6H_4CH_2NH_3^+ \overset{K_x}{\rightleftharpoons} X\text{-}C_6H_4CH_2NH_2 + H^+$$

where k_o and K_o are the rate constant and equilibrium constant respectively of the unsubstituted or "parent" compound and k_x and K_x are the rate constant and equilibrium constant respectively of a meta- or para- substituted benzene. The substituent constant, σ, measures the polar effect of the substituent (relative to hydrogen), and is, in principle, independent of the nature of the reaction. The reaction constant, ρ, depends on the nature of the reaction, including conditions such as solvent and temperature and is a measure of the susceptibility of a reaction to polar effects.

In order to obtain σ values for substituents, Hammett chose the ionization of benzoic acids in water at 25° as a standard reaction and defined $\rho = 1$ for this reaction:-

$$C_6H_5COOH \overset{K_o}{\rightleftharpoons} C_6H_5COO^- + H^+$$

$$X\text{-}C_6H_4COOH \overset{K_x}{\rightleftharpoons} X\text{-}C_6H_4COO^- + H^+$$

$$\sigma_x = \log \frac{K_x}{K_o}$$

The substituent constant of a meta substituent is a measure of inductive effects only as the negative charge cannot resonate with the meta position whereas the substituent constant of a para substituent is a measure of both inductive and resonance effects. If σ is positive then the substituent withdraws electrons more than hydrogen and is a weaker electron attractor than hydrogen if the substituent constant is negative.

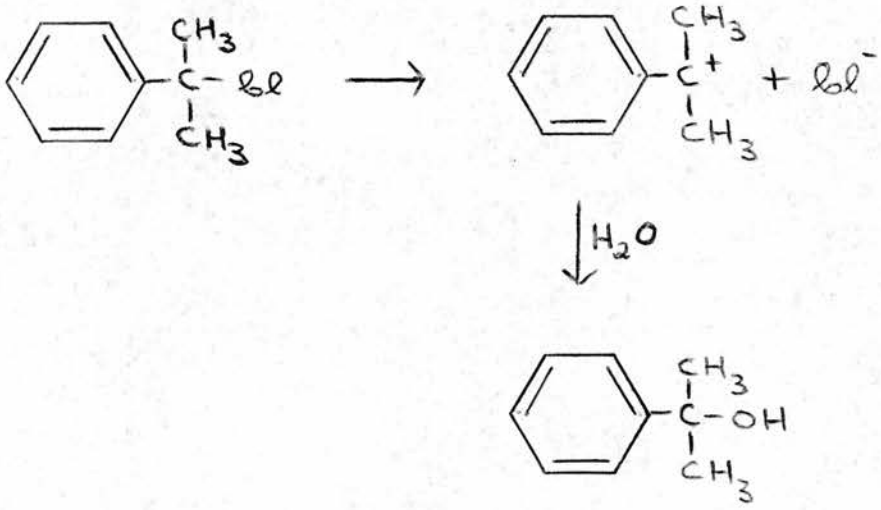
Once the substituent constants have been measured then the value of the reaction constant can be obtained as the slope of a plot of the logarithm of the relative rate of reaction (or relative equilibrium constant) against σ. It is also possible, once ρ has been established, to obtain σ values for substituents where the ionisation constant of the appropriate benzoic acid is not available.

It was found on applying the simple Hammett equation to the mass of data available in the literature that the idea that σ is "independent of the nature of the reaction" was only approximately true. The difficulty arising mainly from the importance of conjugative effects varying from reaction to reaction.

In 1953, Jaffé carried out a massive survey of the

literature[28] finding further examples of the "duality of substituent constants". He advocated using the ionization of benzoic acid as a standard only as a starting point and suggested that σ values should be adjusted to give the best statistical fit for all available data. The disadvantage of this procedure being that it has to be repeated every few years to incorporate new results, and that it tends to obscure deviations. For these reasons McDaniel and Brown[29] reaffirmed the ionization of benzoic acid as the standard process.

Brown and Okamoto[30, 31] extended the Hammett equation to highly electron demanding reactions, notably electrophilic substitution in the aromatic ring. They suggested that the solvolysis of substituted phenyldimethylcarbinyl (cumyl) chlorides might serve as a suitable defining reaction for σ^+ values:-



Since resonance effects are not transmitted to the meta positions, σ^+ values for meta substituents were equated with their σ values and by using those meta substituents whose values had been precisely established, ρ^+ was computed (this procedure brings ρ^+ values on to the same scale as ρ values and $\rho^+ = \rho$). The σ^+ values for all substituents were then derived from their log $\frac{k}{k_o}$ values for the reaction. The σ^+ values were shown to correlate rates of electrophilic substitution with greater success than the σ values[32].

Several workers have suggested modifications to the Hammett equation in the way of improving correlation. Wepster's[33] view was that the resonance interaction of para substituents depends both on the mesomeric effect of the para substituent and of the reaction centre and hence would vary from reaction to reaction. He advocated the use of a "sliding scale" of σ values with certain σ values for substituents, considered to be free from any resonance interaction factors, to be used to evaluate ρ.

Taft's[32] approach was through a quantitative separation of substituent effects into inductive and resonance contributions. He found that the resonance portion was reaction dependent, his conclusions being similar to those of Wepster.

Other workers such as Exner[34] and Yukawa[35] have refined the equation still further and both show the importance of

variable resonance effects in determining the substituent constants. The substituent constants are still the subject of much work mainly in trying to decide how the substituents transmit their effect to the reaction centre. The nature of that part of the polar effect which is not mesomeric is by no means clear and increasing attention has been paid to the role of field effects as well as the polarization of σ and π bonds in the transmission of these effects. Dewar and Grisdale[36] have devised a treatment of field, π-inductive and resonance effects in which a dipolar substituent is considered to behave as a unipole situated at the ring carbon to which the substituent is attached. The relative importance of field and inductive effects is the subject of much debate and model systems which should prove illuminating are being devised and studied[37].

The reaction constant, ρ, can be used to shed light on the reaction mechanism, as it is a measure of the way the reaction is affected by dispersal or concentration of electronic charge in the vicinity of the reaction centre. Thus, if the reaction constant is positive then the reaction is aided by electron withdrawal and vice versa. The relative roles of inductive, field effects and solvent effects on the reaction constant are not well understood.

The application of the Hammett equation to other than

benzenoid compounds has been tested. The application to heterocyclic compounds was reviewed by Jaffé[38] who pointed out the scarcity of reliable data to test the equation and related theories. More recently Eaborn[39], Katritzky[40] and Butler[41] have set about compiling the necessary data and Butler[42] has also determined a set of σ constants for thiophen from the dissociation constants of thiophen carboxylic acids and finds the values agree closely with those predicted by the Dewar-Grisdale theory[36].

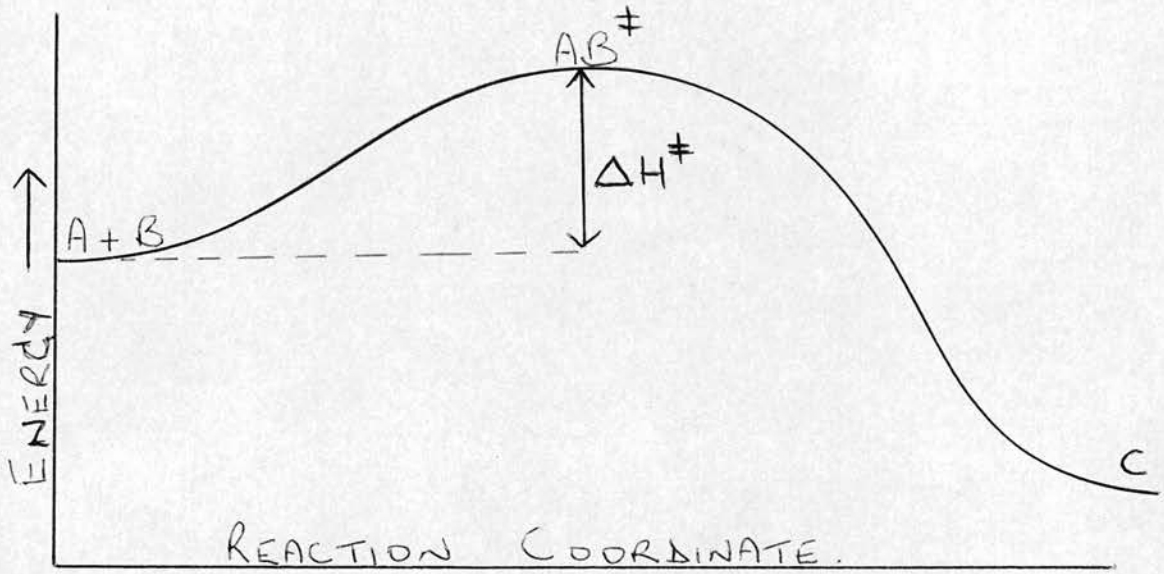
Despite the simplicity and empirical nature of the Hammett equation it remains a valuable means of predicting and correlating reactivity, its widespread applicability still remains to some extent a mystery.

7. THE ROLE OF ENTHALPIES AND ENTROPIES OF REACTION IN THE ELUCIDATION OF REACTION MECHANISMS.

An understanding of the importance of enthalpy and entropy factors in terms of reaction mechanisms can be obtained from the transition state theory or theory of absolute reaction rates enunciated by Eyring[43], Evans and Polanyi[44]. During the course of a reaction molecules may be thought of as ascending an energy hill, the summit of which is known as the transition state and molecules which reach this point are known as an activated complex, which can then pass down to the products side of the energy hill. The rate of a reaction is then related to the number of molecules that pass from reactant side to product side in a given time. Raising the temperature increases the concentration of molecules with sufficient energy to make the ascent and more conversions from reactants to products then occur.

Considering a reaction between molecules A and B going to products C one can represent the activated complex as $AB^{\ddagger}$ and the reaction as:-

$$A + B \rightleftharpoons AB^{\ddagger} \longrightarrow C$$



The activated complex is treated as a chemical species in equilibrium with the reactants and consequently one can write an equilibrium constant:-

$$K^{\ddagger} = \frac{(AB^{\ddagger})\ f_{AB^{\ddagger}}}{(A)(B)\ f_A f_B}$$

$$= \frac{[AB^{\ddagger}]}{[A][B]}$$ if we consider only dilute solutions where the activity coefficients approach unity. The transition state theory assumes the rate of reaction to be proportional to $[AB^{\ddagger}]$, which in turn is proportional to $K^{\ddagger}$ and it can be shown, by a consideration of statistical mechanics, that the proportionality constant approximates to $\frac{kT}{h}$, where k is Boltzmann's constant, T is

the absolute temperature, and h is Planck's constant.[43]

It is also possible to define quantities analogous to the thermodynamic functions used in connection with ordinary equilibrium constants.

The free energy of activation:-

$$\Delta G^{\ddagger} = -RT\ln K = -RT\ln \frac{k_r h}{kT}$$ where k_r is the rate constant for reaction,

and the heat of activation:-

$$\Delta H^{\ddagger} = RT^2 \frac{d\ln K}{dT} = RT^2 \frac{d\ln k_r}{dT} - RT$$ for a reaction in solution, and the entropy of activation:-

$$\Delta S^{\ddagger} = \frac{(\Delta H^{\ddagger} - \Delta G^{\ddagger})}{T}$$

It is important to note that the values of $\Delta G^{\ddagger}$, $\Delta H^{\ddagger}$, and $\Delta S^{\ddagger}$ are values for standard states. The standard states of reactants and activated complex are unit concentrations where the concentration unit corresponds to whatever is used in evaluating the rate constant for the reaction k_r. $\Delta H^{\ddagger}$ may be considered as the difference in enthalpy between the activated complex and reactants, all substances being in their standard states.

The relationship between the enthalpy of reaction and the Arrhenius energy of activation, its experimental

determination and subsequent determination of the entropy of reaction will be dealt with in the experimental section. The enthalpy of reaction, or to a first approximation the Arrhenius activation energy, can be regarded as the difference in energy between the reactants and the activated complex and taken in conjunction with the entropy of activation, which is a measure of the degree of order or "freedom of restraint from motion", an increase in order bringing a decrease in entropy, can give an insight into the mechanism of the reaction.

Schaleger and Long[45] point out the necessity for care in considering changes in entropy and enthalpy terms, as the experimental errors in their values tend to be larger than is often anticipated.

The relationship between entropy and enthalpy is the subject of some debate.[46-48] The terms often vary systematically for a series of structurally similar compounds undergoing the same reaction[47]. Generally $\Delta H^{\neq}$ and $\Delta S^{\neq}$ tend to vary in a compensating manner, i.e. a large change in $\Delta H^{\neq}$ is accompanied by a large change in $T\Delta S^{\neq}$ in the same direction. This phenomenon has been termed the compensation law or isokinetic relationship[47]. However, reaction series are known in which either $\Delta H^{\neq}$ or $\Delta S^{\neq}$ is constant or in which $\Delta H^{\neq}$ and $\Delta S^{\neq}$ vary independently[49-51].

There are certain generalisations that can be made as

regards the size and sign of the entropy term, and mechanism. Any reaction which results in a decrease in freedom of motion of molecules or which involves an increase in order of molecules will be accompanied by a negative entropy of activation. Thus a decrease in the number of molecules from reactants to products e.g. dimerisations, Diels-Alder reactions, all exhibit negative entropies of activation, and similarily if a cyclic transition state is formed from non cyclic reactants[52]. Long[53, 54] has used the entropy of activation as a criterion for deciding whether the mechanism of hydrolysis reactions are unimolecular or bimolecular. He argues that in the bimolecular reaction a water molecule is involved in the activated complex and that the loss of translational and rotational freedom of a water molecule should result in a lower energy of activation relative to the unimolecular case. He justifies the theory with examples, but again warns of the danger of placing too much importance on isolated entropy values. The increase in orientation, mainly through the formation of solvation sheaths of molecules, brought about by the production of ions from neutral molecules, also results in a negative entropy of activation[55].

A negative entropy of activation means some degree of orientation is necessary in the activated complex. The result being that the rate of reaction is controlled by both

the entropy and enthalpy of activation, as molecules may have the necessary energy for reaction but not the correct orientation.

Although of considerable theoretical interest, activation parameters have a limited usefulness in the elucidation of reaction mechanisms.

8. ACIDITY FUNCTIONS

The problem of finding a suitable method of measuring the acidity of concentrated acids has received much thought and experimental study[56]. Since the invention of the H_o acidity function by Hammett and co-workers[57] nearly 40 years ago, there has been a proliferation of related acidity scales.

Hammett defined an acidity function H_o using the ionization equilibria of nitrated primary anilines,

i.e. $$B + H^+ \rightleftharpoons BH^+ \qquad \text{with}$$

$$H_o = -\log a_{H^+} f_B / f_{BH^+}$$

$$= pK_{BH^+} + \log [B]/[BH^+]$$

where a_{H^+} ≡ activity hydrogen ion

f_B ≡ activity coefficient of base

f_{BH^+} ≡ activity coefficient of protonated base

K_{BH^+} ≡ thermodynamic ionization constant of the base and conjugate acid in terms of molar concentrations.

$[B]/[BH^+]$ ≡ concentration ratio of the indicator in its two forms.

The fact that these Bronsted bases differ widely in size and structure has led to the suggestion that they might follow different acidity functions[58].

The acidity functions H_+ and H_- referring to equilibria

$$B^+ + H^+ \rightleftharpoons BH^{++} \qquad \text{and}$$

$$B^- + H^+ \rightleftharpoons BH \qquad \text{respectively}$$

were defined by Hammett[59] as

$$H_+ = -\log a_{H^+} f_{B^+}/f_{BH^{++}} \qquad \text{and}$$

$$H_- = -\log a_{H^+} f_{B^-}/f_{BH} \qquad \text{(the symbols}$$

having the same meaning as for H_o). Despite the criticism of Hinman and Lang[60], who suggested that the effect of charge would be overshadowed by the indicator structure, and make the use of H_+ and H_- meaningless as acidity functions when the structure differed from those used for defining H_o, they have been measured and used with some success[61, 62].

Gold and Hawes[58] defined an acidity function J_o, in order to apply the Hammett idea to the equilibria between alcohols and carbonium ions. However, it was found to be not generally valid throughout the entire range of sulphuric acid concent--ration, which led Deno[63] to define C_o using arylmethanols such that

$$C_o - J_o = \log (f_{R^+}/f_{ROH_2^+})$$

A similar acidity function H_R was defined by Lowen, Murray and Williams[64] for a carbinol indicator, computing values relative to an arbitrary zero and not in absolute

terms. More recently Kresge and Chiang[65] have shown that there is a linear relationship between log k_{obs} and H_R - log a_w for the detritiation of 1,3,5-trimethoxybenzene.

Because many deviations have been detected, general agreement seems to have been reached that the original idea of a universally applicable indicator based acidity function is not feasible. Even the idea of two acidity functions, corresponding to two general classes of bases (those that protonate on carbon correlated by H_o and those that protonate on nitrogen or oxygen correlated by H_R - log a_w, where a_w is the activity of water,) is only approximately true. Bunnett[66] has suggested that a series of acidity functions representing protonation equilibria is more correct, perhaps providing some justification for the many new acidity function scales that have appeared recently[67, 68].

The use of acidity function data for mechanistic interpretation is difficult[69]. Ideally the actual acidity function for the series of bases under kinetic investigation should be measured, and the rates and equilibria measured in the same media[70, 71], before any definite conclusions can be reached. This matter is considered in some detail in the Results and Discussion section.

9. REVIEWS OF THIOPHEN CHEMISTRY

No attempt has been made here to review electrophilic substitution reactions of thiophens. The reviews of Hartough[72], Gronowitz[73], and more recently Hurd[74] provide comprehensive and up to date coverage of thiophen chemistry, and it was felt that any further contribution would merely be a reiteration of these excellent works.

PART II

RESULTS AND DISCUSSION

1. MECHANISM OF THE BROMINATION OF THIOPHEN.

Soon after the discovery of thiophen, it was shown by Meyer[75] that this compound and bromine react readily to give a mixture of 2,5-dibromo- and 2-bromothiophen. Better yields of the latter product are obtained by using acetic acid[76], or benzene[77], as solvent. The rate of reaction was first determined by Lauer[78], and Marino[25] has studied the rates of bromination of 2- substituted thiophens.

Aromatic bromination by molecular bromine in acetic acid is kinetically a rather complicated reaction[79]. The production of hydrogen bromide during the reaction inhibits further attack by complexing with bromine to give tribromide ion, a non-brominating species[80]. The problem is overcome by the addition of an excess of bromide ion, which then remains essentially constant during the course of the reaction.

The kinetic expression for bromination in acetic acid, contains as well as a simple second order term (i.e. first order in substrate and bromine), higher order terms in bromine due to the role played by one or two bromine molecules, whose function is to assist the breaking of the bromine-bromine bond in the formation of the Wheland type intermediate:-

$$ArHBr_2 + Br_2 \longrightarrow ArHBr^{+} + Br_3^{-}$$

The importance of these higher order terms is reduced by

working with aqueous acetic acid, by higher temperatures, and by added salts[81], all of which increase the ease of heterolysis of the bromine-bromine bond without the aid of other bromine molecules. Reducing the concentration of reactants also lowers the relative importance of the higher order terms in the rate expression[79].

The reaction scheme for the bromination of an aromatic (ArH) may be represented as follows, (assuming no contribution from terms of higher than first order in bromine).

$$Br_2 + Br^- \underset{}{\overset{K}{\rightleftharpoons}} Br_3^-$$

$$K = \frac{[Br_3^-]}{[Br_2][Br^-]}$$

$$Br_2 + ArH \xrightarrow{k'} ArBr + HBr$$

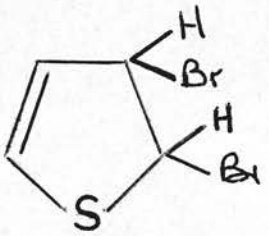
$$\text{Rate} = k[Br_2][ArH]$$

$$= \frac{k}{K[Br^-]}[Br_3^-][ArH]$$

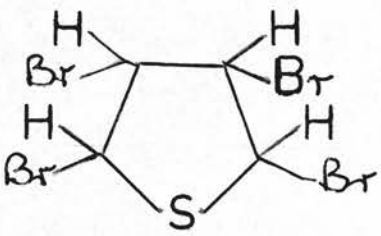
$$k_2 = \frac{k}{K[Br^-]} = \frac{k_{obs}}{[ArH]}$$

SCHEME 1

Hartough[72], in describing the preparation of 2-bromo- and 2,5-dibromothiophen, gives experimental details for converting the addition products, (1) and (2), to the corresponding substituted compound.



(1)



(2)

However, although the corresponding chlorinated compounds have been isolated[21], Lawesson[82] was unable to detect their formation in the case of bromination. One of the objects of this investigation was to look for kinetic evidence for the formation of these addition compounds.

Under the conditions indicated (TABLE 2) the bromination of thiophen was found to follow simple kinetics of the first order, and the term $k_2K[Br^-]$ (= k, see SCHEME 1) is constant. These results are consistent with either rate determining addition of bromine, to give an addition product, or normal electrophilic substitution. In an attempt to distinguish between these possibilities, the bromination of thiophen was compared (in terms of salt effects and activation parameters)

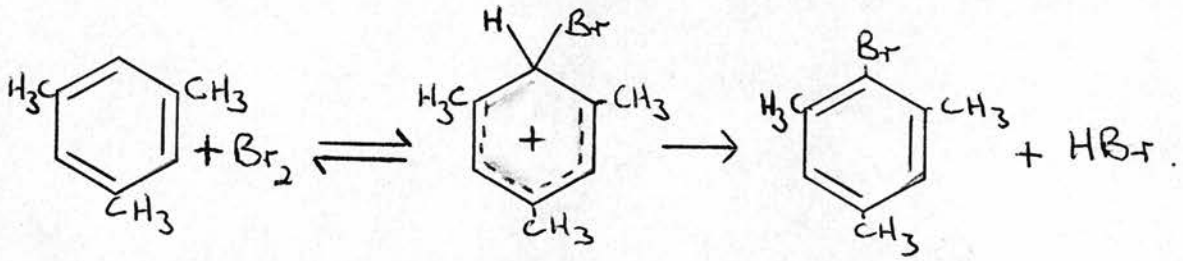
to that of mesitylene. The reactivity of the latter is similar to that of thiophen, and the mechanism of reaction is well established[83] (SCHEME 2).

TABLE 2

Summary of rate constants for the bromination of thiophen at 25° in 15% aqueous acetic acid.[a]

[LiBr] M	[$LiClO_4$] M	k_2 l. $mole^{-1}$	$10^{-2}k_2KBr^-$ $min.^{-1}$
0.06	0.04	337	24.26
0.07	0.03	300	25.20
0.08	0.02	254	24.38
0.09	0.01	219	23.65
0.10	0.00	204	24.48

[a] $[thiophen]_o$ ca 1 x 10^{-3}M.



SCHEME 2

(1) Salt effects. Owing to the highly charged transition state the bromination of mesitylene is greatly affected by the addition of salts. However, it was found that addition of lithium perchlorate affects the bromination of thiophen the same way (see TABLE 3).

TABLE 3

Effect of addition of lithium perchlorate on the rate of bromination of mesitylene and thiophen at 25° in 15% aqueous acetic acid.

$[LiClO_4]$ M	k_2 l. mole^{-1} min.$^{-1}$	
	Mesitylene	Thiophen
0	11.9	270
0.04	16.9	326
0.08	20.9	383
0.10	21.7	394
0.12	24.0	410

[LiBr] = 0.06M

The similarity in the size of the salt effect suggests[84] that thiophen bromination involves an intermediate similar in structure to that occurring in the reaction of mesitylene.

(2) Activation Parameters. It is generally the case that the rate of a reaction increases with temperature, and that a plot of log rate versus the reciprocal of the absolute temperature is nearly linear with a negative slope, which is equivalent to

$$\frac{d\ln k_r}{dT} = \frac{E_a}{RT^2}$$ the Arrhenius equation,

where E_a is an empirical energy of activation and, since for a reaction in solution,

$$\Delta H^{\neq} = \frac{RT^2 d\ln k_r}{dT} - RT$$

then $\Delta H^{\neq} = E_a - RT$, which allows for the experimental determination of $\Delta H^{\neq}$, the enthalpy of reaction. The determination of rate constants at various temperatures for the bromination of thiophen and mesitylene enabled the enthalpy and entropy of reaction to be calculated for the two substrates (TABLE 4).

The size of the entropy terms strongly suggests that the structure of the activated complex is similar for the two reactions. The difference in reactivity towards bromine, between thiophen and mesitylene, being accounted for by the higher enthalpy of reaction in the mesitylene case.

TABLE 4

Activation parameters for the bromination of thiophen and mesitylene at 25° in 15% aqueous acetic acid.

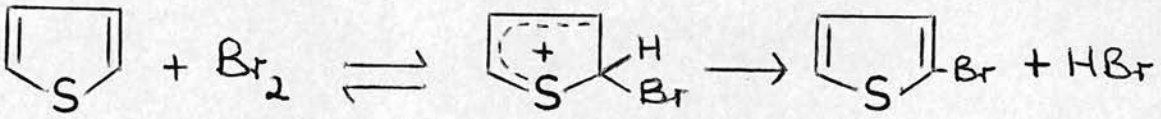
$\Delta H^{\ddagger}_{thiophen} = 12.4$ kcal. mole^{-1}

$\Delta H^{\ddagger}_{mesitylene} = 9.40$ kcal. mole^{-1}

$\Delta S^{\ddagger}_{thiophen} = -19.5$ e.u.

$\Delta S^{\ddagger}_{mesitylene} = -15.5$ e.u.

The combination of salt effects and activation parameters suggest formation of a highly charged Wheland type intermediate and subsequent expulsion of a proton, as opposed to addition of bromine across a thiophen double bond followed by elimination of hydrogen bromide, as the mechanism of bromination. Thus the reaction scheme is:-



The ultraviolet spectrum of the reaction of bromine and thiophen, in 15% aqueous acetic acid, was monitored, in an attempt to find spectroscopic evidence for the formation of an intermediate.

No evidence of an intermediate was found, the rate of disappearance of absorption due to tribromide ion and thiophen was equal to the rate of appearance of absorption due to product (2-bromothiophen).

Any intermediate that is formed must be present at such low concentration as to be undetectable by U.V.

Having decided that the bromination of thiophen exhibits a similar type of mechanism to bromination of benzene compounds the remaining problem was to ascertain whether formation or decomposition of the Wheland type intermediate is the rate determining step.

Bromination of benzene type compounds occurs in general without an isotope[85, 86] effect, except as a result of steric congestion at the reaction site.[87, 18]

The isotope effect in the bromination of thiophen.

The rate of bromination of 2,5-dideuteriothiophen (TABLE 5) was compared to that of thiophen (TABLE 2). As predicted from SCHEME 2, a plot of k_2 versus $1/[Br^-]$ was found to be linear for both compounds (Figure 2), with gradient

of k/K, giving an isotope effect of k_H/k_D of 1.35 $\pm$ 0.05.

TABLE 5

Summary of rate constants for the bromination of 2,5-dideuteriothiophen at 25° in 15% aqueous acetic acid.

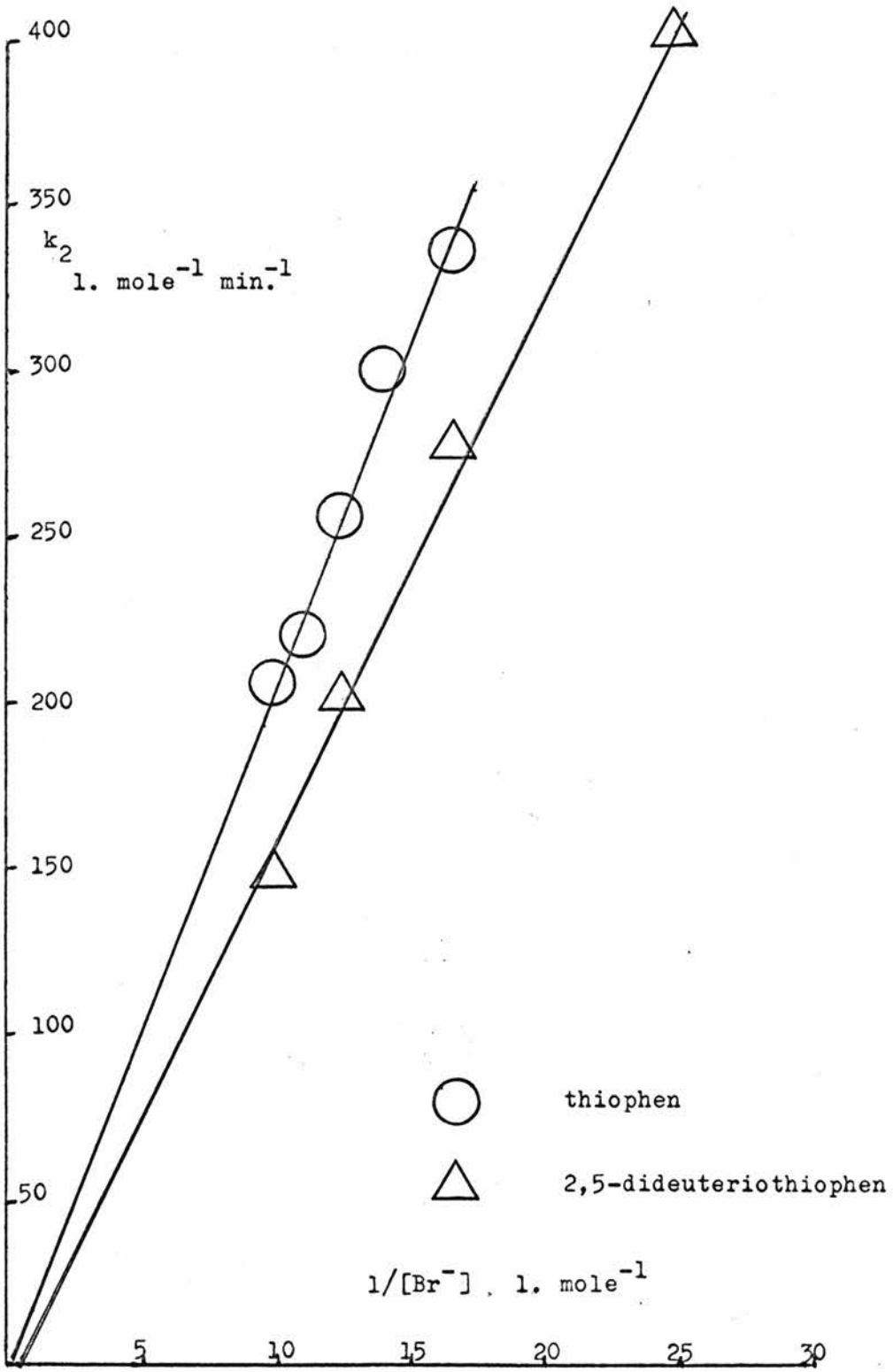
[LiBr] M	[$LiClO_4$] M	k_2 l. $mole^{-1}$ min^{-1}	$10^{-2}k_2KBr^-$
0.04	0.06	402	19.3
0.06	0.04	277	19.9
0.08	0.02	201	24.1
0.10	0.00	147	17.6

Berliner[88], in the bromination of 2,5-dimethylnaphthalene, has shown that if the removal of a proton is rate determining then the reaction should be catalysed by acetate ion, acting as a base.

It was found that sodium acetate has a smaller accelerating effect than lithium perchlorate (TABLE 6, Figure 3), which is inconsistent with a primary isotope effect.

Berliner[88] has also analysed the kinetics of the situation where loss of the proton is rate determining, and shows that a plot of k_2 versus the reciprocal of the bromide ion concentration should be curved. A linear relationship,

Fig. 2 The isotope effect in the bromination of thiophen.



as obtained for thiophen, indicates a secondary isotope effect.

TABLE 6

Effect of addition of lithium perchlorate and sodium acetate on the rate of bromination of thiophen in 15% aqueous acetic acid at 25°.

[NaOAc] M	k_2 l. mole^{-1} min.$^{-1}$
0.00	277
0.04	305
0.06	312
0.10	342
0.12	353

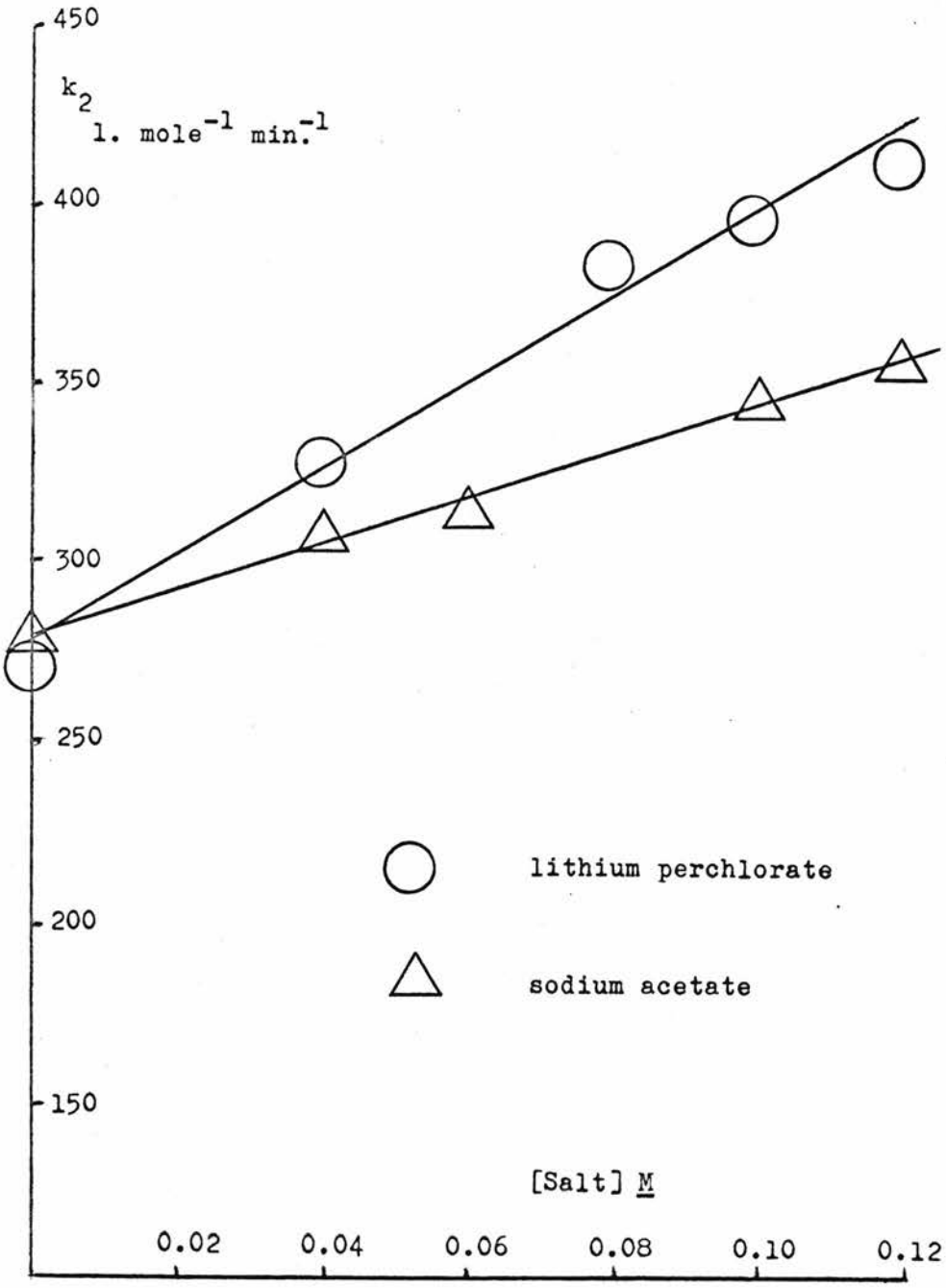
[$LiClO_4$] M	k_2 l. mole^{-1} min.$^{-1}$
0.00	270
0.04	326
0.08	383
0.10	394
0.12	410

[LiBr] = 0.06M.

All runs were followed by U.V. at 290 nm. under pseudo first order conditions.

Figure 3.

Fig. 3 Effect of salts on the rate of bromination of thiophen



The isotope effect was also examined at an ionic strength of 0.2M in order to determine whether it was independent of the bromide ion concentration (TABLE 7).

TABLE 7

Effect of varying the bromide ion concentration on the isotope effect for bromination of thiophen and 2,5-dideuteriothiophen at 25°.

	[LiBr]	[$LiClO_4$]	k_2 l. $mole^{-1}$ $min.^{-1}$
Thiophen	0.20	-	122
	0.06	0.14	451
2,5-Dideuteriothiophen	0.20	-	81
	0.06	0.14	320

It has been shown by Baliga and Burns[89], that an increase in bromide ion concentration should affect partitioning of the intermediate between reactants and products, and hence should influence the extent to which the second step (loss of a proton) contributes to the overall reaction rate, giving rise to a variation in the isotope effect.

The isotope effect of 1.45 $\pm$ 0.05 was judged to be independent of the bromide ion concentration. It must be concluded therefore, that the isotope effect is in fact

secondary and that the rate determining step of the reaction is the attack of bromine on thiophen.

The similarities between thiophen and benzene have been pointed out by Longuet-Higgins and others[1, 5], and the present work has established a similar mechanism for bromination. The effect of substituents on the rate of bromination was studied in order to ascertain whether this similarity could be extended to include substituent effects.

2. BROMINATION OF 2- SUBSTITUTED THIOPHENS.

Marino[25] has measured the relative reactivities of a number of 2- substituted thiophens. However, the method of measuring reactivity he employed has been criticised by Keefer and Andrews[90]. He measured the relative reactivities in terms of the time taken for 10% reaction to occur. This is of doubtful validity as the kinetic equation is complex and includes a third order term as well as a second order one:-

$$\text{rate} = k[ThX][Br_2] + k'[ThX][Br_2]^2$$

It has to be assumed that the relative importance of the two terms in the rate expression will not vary with the substituent, and the marked increase in the importance of k' with increase in bromine concentration is overlooked. The technique can at best be regarded as only a semiquantitative measure of reactivity.

In this study the rate of bromination was measured under conditions where (with the exception of the acid and the ester) there was no interference from terms of higher than second order.

Substitution is known to occur exclusively at the 5-position. This has been shown by Marino[25] (G.L.C. on the products) for 2-methyl-, 2-chloro-, 2-bromo-, and thiophen itself, and for 2-phenylthiophen by Kosak[91]. There is no reason to suppose that 2-tert-butylthiophen and 2-ethylthiophen

should behave differently.

Rate constants for the bromination of 2-bromo- and 2-bromo-5-deuteriothiophen are given in TABLE 8. The isotope effect for this reaction (assumed to be secondary as with thiophen itself) is 1.5 ± 0.1.

TABLE 8

Summary of rate constants for the bromination of 2-bromo- and 2-bromo-5-deuteriothiophen in 15% aqueous acetic acid at 25°.

[BrTh] M	[LiBr] M	k_2 l. mole^{-1} min.$^{-1}$
1.934×10^{-2}	0.1	15.1
3.686×10^{-2}	0.1	15.7
[BrDTh] M	[LiBr] M	k_2 l. mole^{-1} min.$^{-1}$
2.018×10^{-2}	0.1	9.27
4.036×10^{-2}	0.1	8.91

Bromination of 2-chlorothiophen in 15% aqueous acetic acid.

Some of the runs were followed by titration of unreacted bromine. The reaction scheme differs from that when following the disappearance of tribromide ion by U.V. and may be represented as shown in SCHEME 3.

$$Br_2 + Br^- \underset{}{\overset{K}{\rightleftharpoons}} Br_3^-$$

$$K = \frac{[Br_3^-]}{[Br_2][Br^-]}$$

$[Br_2]_{St} \equiv$ stoicheiometric concentration of bromine determined by titration.

$$[Br_2]_{St} = [Br_2] + [Br_3^-]$$

$$= [Br_2] + K[Br_2][Br^-]$$

$$= [Br_2](1 + K[Br^-])$$

$$\text{rate} = k[ThX][Br_2]$$

$$= \frac{k}{(1 + K[Br^-])}[ThX][Br_2]_{St}$$

$$k = \frac{k_{obs}(1 + K[Br^-])}{[ThX]}$$

SCHEME 3

TABLE 9

Summary of rate constants for bromination of 2-chlorothiophen in 15% aqueous acetic acid at 25°.

[LiBr] M	[$LiClO_4$] M	k_2 l. $mole^{-1}$ min^{-1}	k
0.06	0.04	25.5	209[a]
0.08	0.02	19.5	207[a]
0.10	0.00	15.4	200[a]
0.10	0.00	15.9	191[b]

[a]Obtained by titration $k = k_2(1 + K[Br^-])$

[b]Obtained by spectroscopy $k = k_2K[Br^-]$

The agreement of values of k obtained by titration and by spectroscopy is within experimental error.

TABLE 10

Summary of rate constants for bromination of 2-chlorothiophen in 15% aqueous acetic acid at 0° and 15°.

Temp.	[LiBr] M	[$LiClO_4$] M	k_2 l. $mole^{-1}$	k $min.^{-1}$
0°	0.05	0.05	3.56	37.4
0°	0.06	0.04	2.88	35.7
0°	0.07	0.03	2.52	35.9
0°	0.10	0.00	1.95	39.0
15°	0.06	0.04	11.64	110.8
15°	0.08	0.02	8.32	102.8
15°	0.10	0.00	6.81	103.5

all runs by titration.

TABLE 11

Summary of rate constants for the bromination of 2-methyl--thiophen in 15% aqueous acetic acid at 25°.

[LiBr] M	[$LiClO_4$] M	$10^{-4}k_2$ l. $mole^{-1}$ $min.^{-1}$	$10^{-5}k$
0.06	0.04	13.4	9.65[a]
0.08	0.02	9.86	9.47[a]
0.10	0.00	8.00	9.60[a]
0.10	0.00	7.95	9.54[b]

[a]Second order conditions.

[b]Pseudo first-order conditions.

The agreement of k values obtained by two methods is within the experimental error.

TABLE 12

Summary of rate constants for the bromination of 2-ethylthiophen in 15% aqueous acetic acid at 25°.

[LiBr] M	[$LiClO_4$] M	$10^{-4}k_2$ l. $mole^{-1}$ $min.^{-1}$	$10^{-5}k$
0.10	0.00	8.20	9.84[a]

[a]Average of three determinations

TABLE 13

Summary of rate constants for the bromination of 2-tert-butylthiophen in 15% aqueous acetic acid at 25°.

[LiBr] M	[$LiClO_4$] M	$10^{-4}k_2$ l. $mole^{-1}$ $min.^{-1}$	$10^{-5}k$
0.08	0.02	6.43	6.17[a]
0.10	0.00	5.93	7.12[a]
0.08	0.02	6.58	6.32[b]
0.10	0.00	5.80	6.96[b]

[a]Under second order conditions

[b]Under pseudo first order conditions.

TABLE 14

Summary of rate constants for the bromination of 2-phenyl--thiophen in 15% aqueous acetic acid.

Temp.	[LiBr] M	$10^{-3}k_2$ l. $mole^{-1}$ $min.^{-1}$	$10^{-4}k$
8°	0.10	6.57	10.6
11.8°	0.10	8.22	12.4
16.5°	0.10	9.80	13.5

$k_{25°} = 19.1 \times 10^4$ l. $mole^{-1}$ $min.^{-1}$

(estimated from a plot of log k versus $1/T°$)

Bromination of thiophen-2-carboxylic acid and its ethyl ester in 15% aqueous acetic acid.

The deactivating effect of the carboxylic acid and ester groups towards electrophilic reagents requires the use of higher substrate and bromine concentrations to obtain a measurable rate of reaction. The result being that the relative importance of the third order term in the rate equation increases.

The data was analysed by the procedure given by Keefer and Andrews[92, 93]. The kinetic equation being:-

$$\text{rate} = \frac{k}{(1 + K[Br^-])}[ThX][Br_2]_{St} + \frac{k'}{(1 + K[Br^-])^2}[ThX][Br_2]^2_{St}$$

where [ThX] ≡ concentration of the thiophen in moles/litre

and $[Br_2]_{St}$ ≡ stoicheiometric concentration of bromine in moles/litre.

The rate at various values of $[Br_2]_{St}$ was taken as the gradient of the tangent to the curve representing the variation of $[Br_2]_{St}$ with time. A plot of rate/$[ThX][Br_2]_{St}$ versus $[Br_2]_{St}$ has a slope of $k'/(1 + K[Br])^2$ and an intercept of $k/(1 + K[Br^-])$.

The method of analysing the data by the drawing of tangents (or normals) to a curve is an inaccurate procedure. Consequently the values of k and k' (TABLE 15) are subject

to a degree of uncertainty. The general trends, however, are clear. The third order term is slightly more important for the acid than the ester, and in both cases the ratio of k'/k increases with decreasing temperature, in common with other reactions exhibiting simultaneous second and third order terms[94].

TABLE 15

Summary of rate constants for the bromination of thiophen-2-carboxylic acid and its ethyl ester in 15% aqueous acetic acid.

	Temp.	k $l.\ mole^{-1}\ min.^{-1}$	k' $l.^2\ mole^{-2}\ min.^{-1}$
Acid	25°	6×10^{-3}	22
	35°	2×10^{-2}	59
	45°	7×10^{-2}	96
Ester	25°	1×10^{-3}	2.2
	35°	6×10^{-3}	3.0
	45°	5×10^{-2}	12

[LiBr] = 0.1M

It should be pointed out, that although third order terms were not evident in the rate expression of any of the

substituted thiophens, except the acid and ester, there is no evidence that the third order processes do not occur. The $k'[ThX][Br_2]^2$ term becomes vanishingly small as the bromine concentration is reduced. No information can be obtained about the relative changes in k and k' with substituents. To obtain such information it is necessary to work under conditions where third order terms can be observed, and to keep the concentration of reactants constant for all the substituted thiophens. Owing to the wide range of reactivity of the substituted thiophens this was found to be experimentally impossible.

Bromination at the 5- position of 2- substituted thiophens in 15% aqueous acetic acid at 25°.

The values of the second order rate constants for the bromination of the 2- substituted thiophens gave a linear correlation with the σ_p^+ values obtained from para substituents in benzene compounds (TABLE 16, Fig.4). The result is good by normal free energy correlation standards.

TABLE 16

Summary of relative rate constants for the bromination of 2- substituted thiophens.

Substituent	k_{rel} [a]	k_{rel} [b]	σ_p^+ [c]
2-Et	8.04×10^{2}	-	-0.30
2-Me	7.84×10^{2}	6.31×10^{2}	-0.31
2-Bu^t	5.82×10^{2}	-	-0.26
2-Ph	1.56×10^{2}	-	-0.18
H	1.00	-	0.00
2-Cl	1.63×10^{-1}	5.20×10^{-1}	+0.11
2-Br	1.50×10^{-1}	3.76×10^{-1}	+0.15
2-COOH	5.90×10^{-6}	3.34×10^{-5}	+0.42
2-COOEt	8.16×10^{-7}	1.07×10^{-5}	+0.48

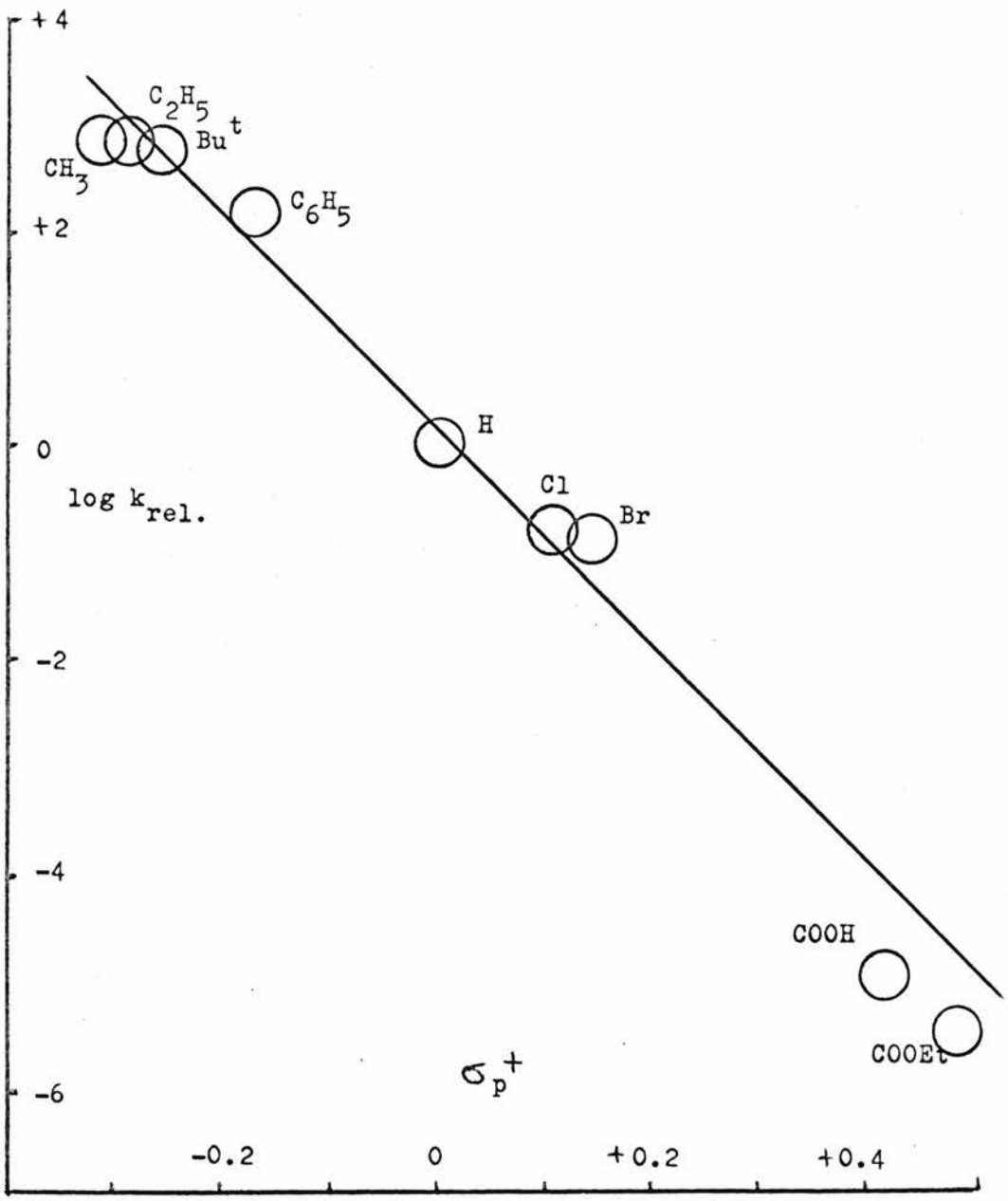
[a] In calculating k_{rel} a statistical factor has been used to allow for the fact that there are two possible sites of substitution in thiophen whereas the 2- substituted thiophens have only one position.

[b] Values from ref. 25.

[c] Values from ref. 95.

Figure 4.

Figure 4 Bromination of 2- substituted thiophens.



The reason why the acid and ester values lie below the line is not clear. However, application of a Hammett relationship over such a range of reactivity (the range of k values is of the order of 10^8) is not firmly established. The plot is superior to that of Marino[25], but this is not surprising as his kinetic method makes no allowance for the inclusion of third order terms in the rate expression.

The fact that the 2-methyl substituent activates the thiophen ring towards electrophilic attack more than the 2-tert-butyl substituent is as predicted by the Baker-Nathan rule[96]. The higher activity of the methyl group has been attributed to a form of mesomeric delocalisation of an electron pair from a carbon hydrogen bond of the methyl group, increasing the reactivity of the 5- position towards electrophilic attack. The tert-butyl group cannot enter into a similar delocalisation of bonding electrons over the thiophen ring, which accounts for the decrease in reactivity compared to the 2-methyl substituent.

The ρ value of -10 obtained from the Hammett plot is identical to the value quoted by Marino and similar to the value of -12 for the bromination of substituted benzenes in in aqueous acetic acid.[97]

3. CHLORINATION OF 2- SUBSTITUTED THIOPHENS IN ACETIC ACID AT 25°.

The chlorination of 2- substituted thiophens in glacial acetic acid has also been studied (see TABLE 17, Figure 5).

The reaction is not subject to the kinetic complications of higher than first order terms in chlorine in the rate expression, nor by any inhibition from hydrogen chloride produced during the reaction as the trichloride ion is much less stable than tribromide[98].

Higher reactant concentrations were necessary for following the reaction by the U.V. absorption due to chlorine than with the tribromide ion, and consequently only thiophen and deactivated thiophens could be studied (TABLE 17).

Substitution of thiophen[99], 2-chlorothiophen[20] and thiophen-2-carboxylic acid methyl ester[100] occurs exclusively at the 5- position and was assumed to be the same for 2-bromothiophen and thiophen-2-carboxylic acid.

The correlation of relative rates with σ_p^+ for benzene compounds is again good (Figure 5). The value of ρ, the reaction constant, is -6.5 which is less negative than the value (-9.8)[101] reported for the chlorination of substituted benzenes in glacial acetic acid, and may indicate a smaller positive charge on the thiophen ring in the transition state.

TABLE 17

Chlorination at the 5- position of 2- substituted thiophens in anhydrous acetic acid at 25°.

Substituent	k l. mole^{-1} min.$^{-1}$	k_{rel} [a]	σ_p^+ [b]
H	1740	1.000	0.00
2-Cl	312	3.586×10^{-1}	0.11
2-Br	414	4.758×10^{-1}	0.15
2-COOH	96×10^{-3}	1.103×10^{-4}	0.42
2-COOEt.	120×10^{-3}	1.379×10^{-4}	0.48

[a] In calculating k_{rel} a statistical factor has been used to allow for the fact that there are two possible sites of substitution in thiophen whereas the 2- substituted thiophens have only one position.

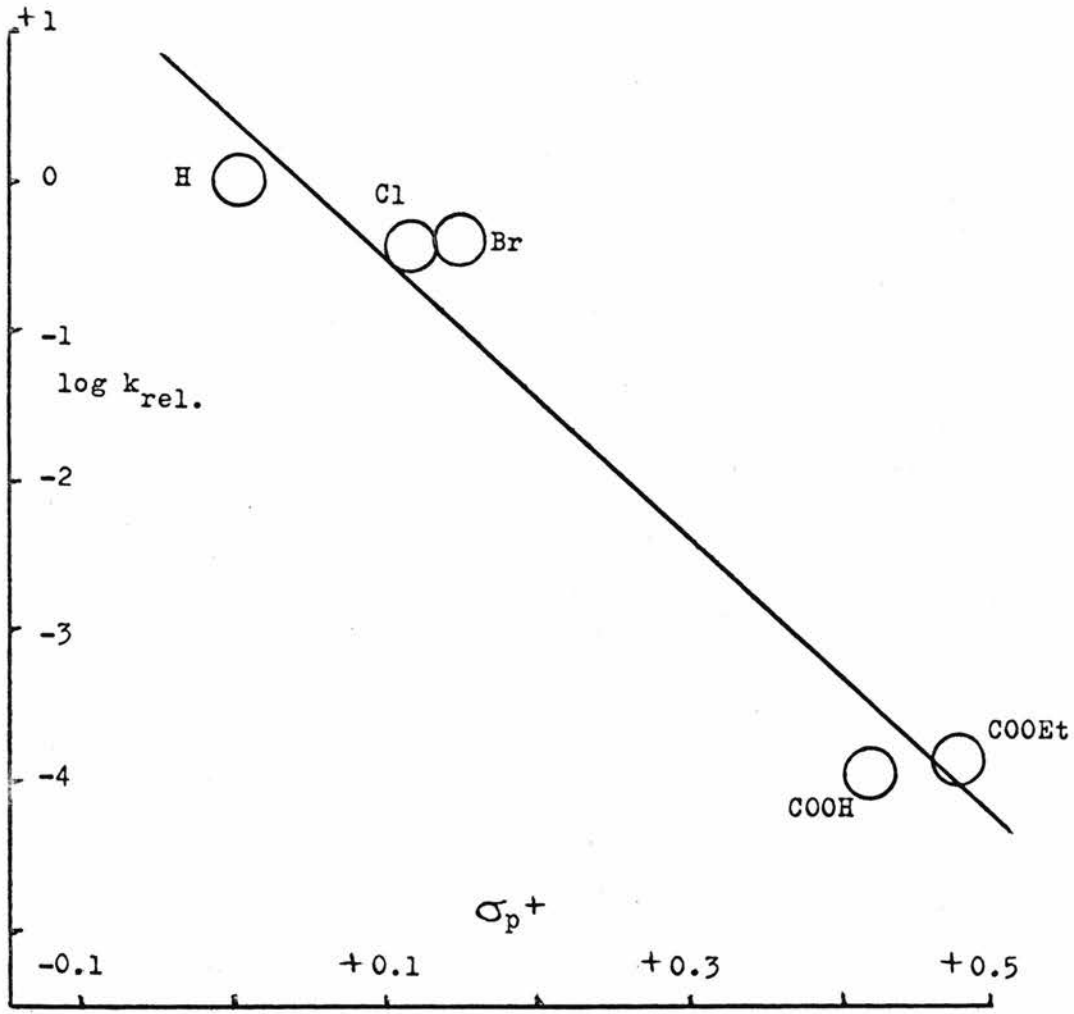
[b] Values from ref. 95

A similar trend is noticed between the ρ value for the bromination of substituted thiophens and the corresponding reaction in substituted benzenes.

The effect of substituents at the 2- position of thiophen on the rate of detritiation at the 5- position also correlates well with σ_p^+ values for benzene[41].

The interesting conclusion that can be drawn from the

Figure 5 Chlorination of 2- substituted thiophens.



above results is that a substituent at the 2- position of thiophen affects the rate of electrophilic substitution at the 5- position in a similar way to a para substituent in benzene.

Further evidence of similarities between substituted thiophens and benzenes is the determination by Butler[42] of a series of σ constants from substituted thiophen carboxylic acids, which were found to differ very little from the values obtained from the corresponding benzene carboxylic acids.

Comparison of activation parameters for substituted thiophens.

Since the bromination of 2-phenylthiophen and 2-chloro--thiophen was performed at various temperatures it was possible to calculate enthalpies and entropies of reaction for the two substituted thiophens and to compare the values with those already obtained for thiophen (TABLE 18).

TABLE 18

Summary of activation parameters for the bromination of 2- substituted thiophens at 25° in 15% aqueous acetic acid.

Substituent	$\Delta H^{\ddagger}$ kcal. mole^{-1}	$\Delta S^{\ddagger}$ e.u.
2-Ph	5.9 ± 0.2	-24 ± 2
H	9.4 ± 0.2	-20 ± 2
2-Cl	10.7 ± 0.2	-20 ± 2

The values are similar to those obtained by Baciocchi and Mandolini[50] for the chlorination of polymethylbenzenes, where variations in reactivity are accounted for by changes in $\Delta H^{\ddagger}$ and the $\Delta S^{\ddagger}$ term remains essentially constant. This result is to be expected as the substituents will not sterically interfere with the site of reaction.

4. BROMINATION OF 2,3-BENZOTHIOPHEN.

The bromination of 2,3-benzothiophen in 15% aqueous acetic acid was examined with an excess of bromide ion present. The U.V. spectrum obtained on mixing the reactants did not correspond to the sum of the reactant spectra. There was an initial rapid decrease in absorption followed by a slower, first-order decrease in absorption in the tribromide ion region of the spectrum.

The formation of an adduct is reported by Baciocchi and Mandolini[102] for the chlorination of 2,3-dimethylbenzothiophen in acetic acid, and it is considered likely that a similar complex is formed between bromine and benzothiophen prior to reaction by the complex (SCHEME 4), or by reaction between uncomplexed bromine and benzothiophen (SCHEME 5).

$$[BzTh] + Br_2 \underset{}{\overset{K}{\rightleftharpoons}} [C]$$

$$[C] \xrightarrow{k_1} \text{products}$$

SCHEME 4

$$[BzTh] + Br_2 \overset{K}{\rightleftharpoons} [C]$$

$$[BzTh]_{free} + Br_{2_{free}} \xrightarrow{k_2} \text{products}$$

SCHEME 5

Both schemes, if K is sufficiently large predict first-order kinetics with the first-order rate constant = k_1 (SCHEME 4) or k_2/K (SCHEME 5)[102]. An approximate value of 3×10^3 l. $mole^{-1}$ was obtained for K (see Experimental).

TABLE 19

Variation in optical density fall off with 2,3-benzothiophen concentration.

[BzTh] x 10^4 M	Initial $D_{Br_3^-}$	Initial $D_{1st\ order}$	D_{fall}	$\frac{D_{fall}}{[BzTh]}$
9.597	1.023	0.748	0.275	287
9.597	0.860	0.618	0.242	253
13.44	0.879	0.502	0.377	281
17.27	0.876	0.478	0.398	231
19.19	0.859	0.419	0.440	229

The fall off in the initial optical density was directly proportional to the benzothiophen concentration (TABLE 19) confirming the idea of formation of a 1:1 complex, and the variation in complex concentration was proportional to uncomplexed tribromide ion when the benzothiophen concentration was kept constant (TABLE 20, Figure 6). The

Figure 6 Variation in complex concentration with tribromide ion concentration.

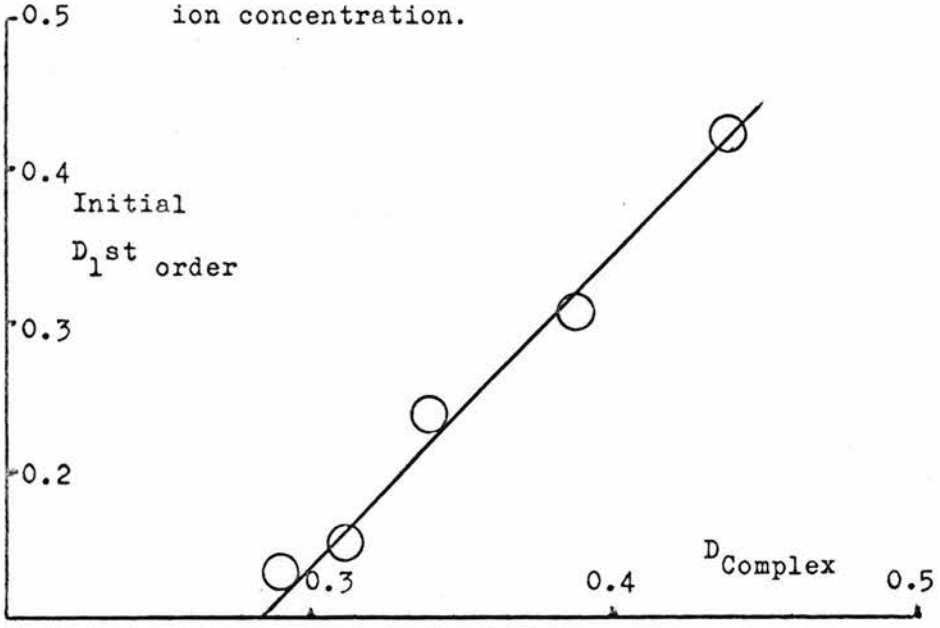
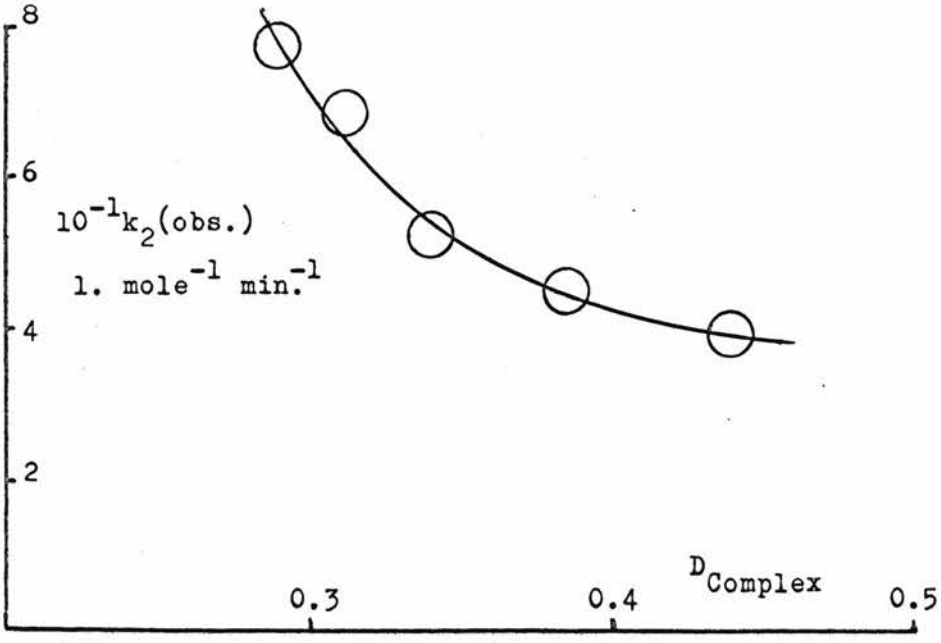


Figure 7 Variation in rate of bromination with complex concentration.



variation in reaction rate with complex and tribromide ion concentration is more difficult to explain (TABLE 20, Figure 7). Since the kinetic situation is extremely complicated and the method of analysis an approximate one no attempt will be made at a quantitative treatment. The important point being that some interaction takes place between benzothiophen and bromine before formation of 3-bromobenzothiophen.

TABLE 20

Variation in the rate of bromination with complex formation.[a]

$D_{Br_3^-}$	Initial $D_{1^{st}\ order}$	$D_{Complex}$	$k_2(obs) \times 10^{-1}$ l. mole^{-1} min.$^{-1}$
0.859	0.419	0.440	3.82
0.691	0.303	0.388	4.44
0.577	0.237	0.340	5.03
0.461	0.148	0.313	6.78
0.423	0.132	0.291	7.65

[a] [BzTh] = 1.919×10^{-3}M.

Figures 6 and 7.

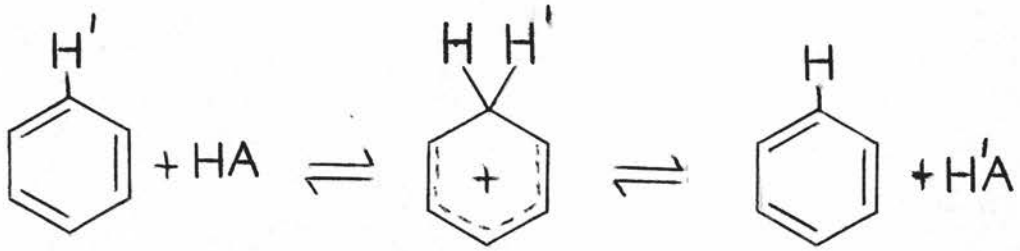
The addition of halogens across the 2,3 double bond has been suggested for substrates similar to the benzothiophen system[103], and addition compounds have been isolated for the nitration of 1-acetyl-2,3-dimethylindole[104] and suggested as intermediates in the bromination of 2,3-dimethylindole[105]. The suggestion of a similar mechanism for the bromination of 2,3-benzothiophen is therefore reasonable. Another possibility is the formation of a charge transfer complex[17]. The results of the present investigation do not distinguish between the possible types of complex formed.

5. HYDROGEN EXCHANGE ON THIOPHEN.

Hydrogen exchange where, under acidic conditions, one isotope of hydrogen is replaced by another is the simplest form of electrophilic aromatic substitution.

The reaction is valuable in several ways. It is possible, by suitable synthetic means, to "label" one position of a molecule and study its reactivity separately and by carrying out hydrogen exchange under widely differing conditions the exchange rates of both reactive, and relatively inactive, positions in a molecule can be studied. Hydrogen exchange is free from steric factors, which simplifies comparisons of reactivities of different positions in a molecule.

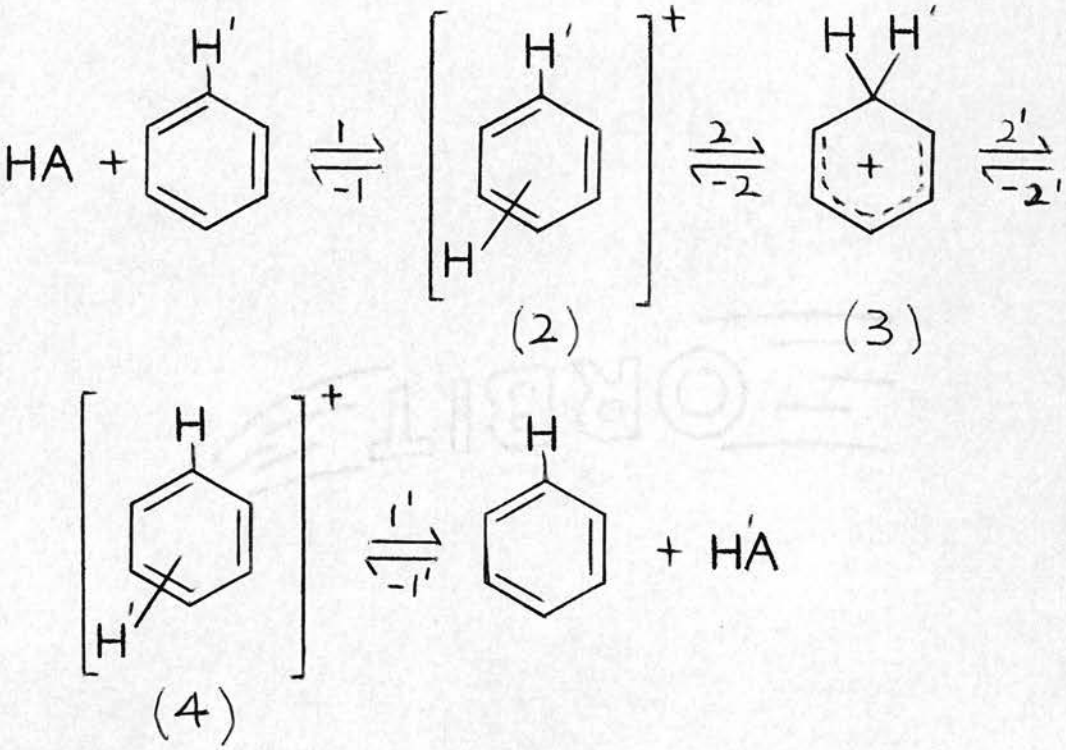
Two mechanisms have been suggested for hydrogen exchange. The first is that common to many electrophilic aromatic substitution reactions:-



and consists of a bimolecular process between an acid, HA, and the aromatic ring, which results in the transfer of a hydrogen

ion to form a Wheland intermediate, followed by loss of a hydrogen ion. This bond breaking and making taking place in essentially identical steps with a reaction energy profile symmetrical about the intermediate except for a small isotope effect. The mechanism is designated A-S_E2.

The second mechanism is that proposed by Gold and Satchell[106]:-



Steps 1 and 1' are fast and 2 and 2' are rate determining; (2) and (4) are outer, or π-complexes and (3) is an inner or σ-complex; and in (2) - (4) the species A^- has lost its association with the exchanging proton. The mechanism is

designated A-1.

The formation of a Wheland intermediate, common to both mechanisms, has been demonstrated by N.M.R. studies which have shown the presence of aliphatic CH_2 groups[107].

Gold and Satchell[106] report that there is a linear relationship between log k (the first order rate constant) and $-H_o$ (the Hammett acidity function) for the dedeuteriation of anisole, some phenols, toluene and benzene. These results imply, according to the Zucker Hammett hypothesis[108], that a water molecule cannot be covalently bound in the transition state of the reaction, which would be the case if HA is present as H_3O^+ and the mechanism was A-S_E2. It is claimed that this observation supports an A-1 mechanism, where A^- has separated from the aromatic system before the slow step.

Eaborn and Taylor have questioned the linear relationship between log k and $-H_o$ and plots for the dedeuteriation of deuterobenzene and detritiation of tritiobenzene are curved[109].

The detection of general acid catalysis by Kresge and Chiang[110] for the protodetritiation of 1,3,5-trimethoxybenzene, and also in indoles[111], and the dedeuteriation of azulenes[112], has been put forward as support for an A-S_E2 mechanism. The reaction is catalysed by the various A^- species present, which is inconsistent with an A-1 mechanism and confirms an A-S_E2 mechanism for the reaction.

Hydrogen exchange takes place at both the 2- and the 3-position of the thiophen ring, the former being the more reactive[113, 114]. The rate of exchange has been studied at both these positions, at various temperatures and acid concentrations (TABLES 21 - 24) to determine whether the reaction exhibits characteristics of an A-S_E2 or A-1 mechanism.

TABLE 21

Variation in the rate of protodetritiation of 2-tritiothiophen with acidity at 25°.

$[H_2SO_4]$ M	$-H_o$ [a]	10^4k $min.^{-1}$
1.94	0.81	2.15
3.32	1.50	9.79
4.65	2.13	47.9
5.81	2.67	236
6.58	3.09	675

$[HClO_4]$ M	$-H_o$ [b]	10^4k $min.^{-1}$
3.70	1.57	11.2
4.44	1.95	29.9
4.92	2.20	56.7
6.15	2.97	383

[a] see ref. 115. [b] see ref. 116.

Figure 8 Variation in rate of protodetritiation of 2-tritiothiophen with acidity at 25°.

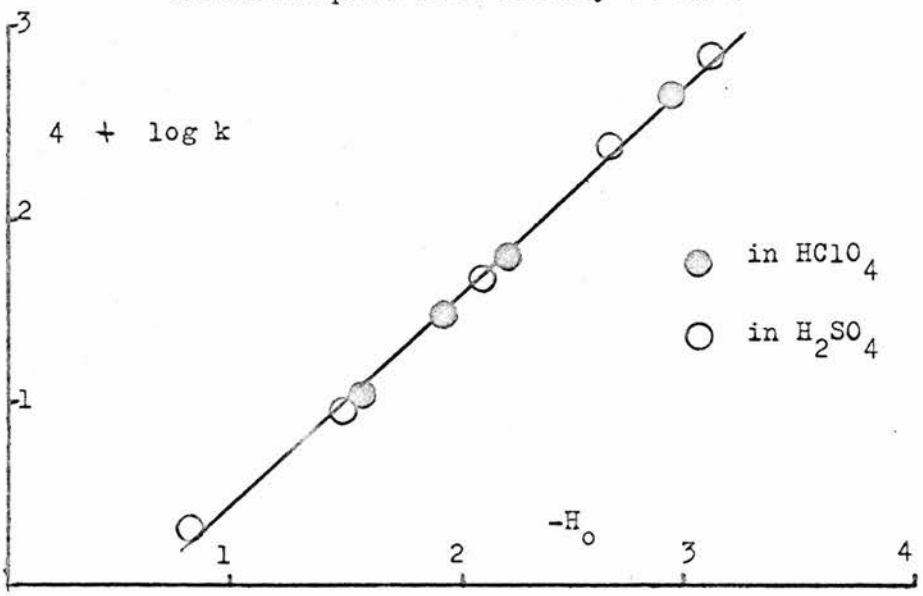


Figure 9 Variation in rate of protodetritiation of 2-tritiothiophen with acidity at 1.9°.

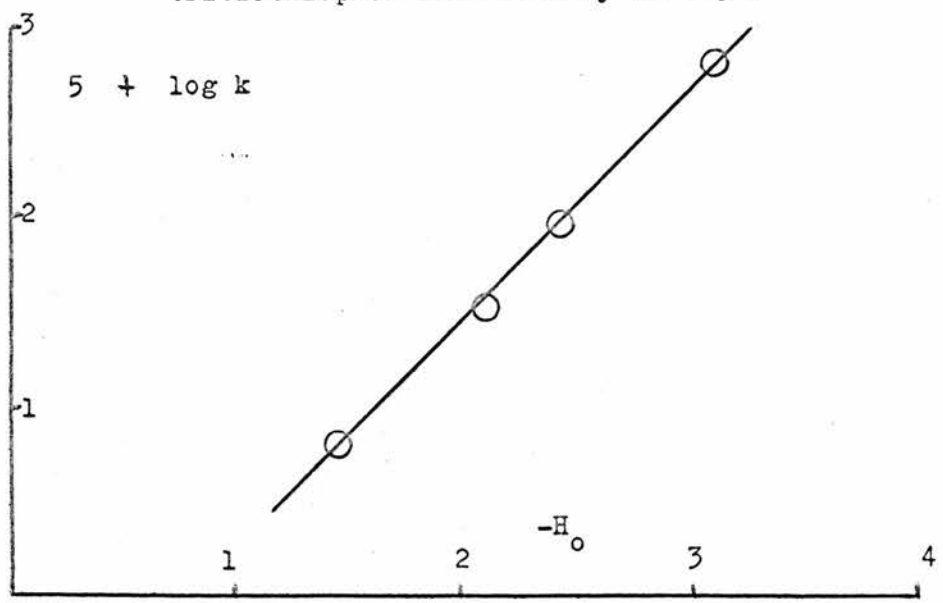


TABLE 22

Variation in the rate of protodetritiation of 2-tritiothiophen with acidity at 1.9°.

$[H_2SO_4]$ M	$-H_o$ [a]	10^4k $min.^{-1}$
3.24	1.48	0.64
4.54	2.13	3.08
5.28	2.47	8.58
6.60	3.13	60.4

[a] see ref. 117.

Figure 9.

TABLE 23

Variation in the rate of protodetritiation of 3-tritiothiophen with acidity at 25°.

$[H_2SO_4]$ M	$-H_o$	10^4k $min.^{-1}$
7.92	3.80	5.21
8.67	4.20	14.2
9.24	4.49	37.8
10.6	5.17	317

Figure 10.

Figure 10 Variation in rate of protodetritiation of 3-tritiothiophen with acidity at 25°.

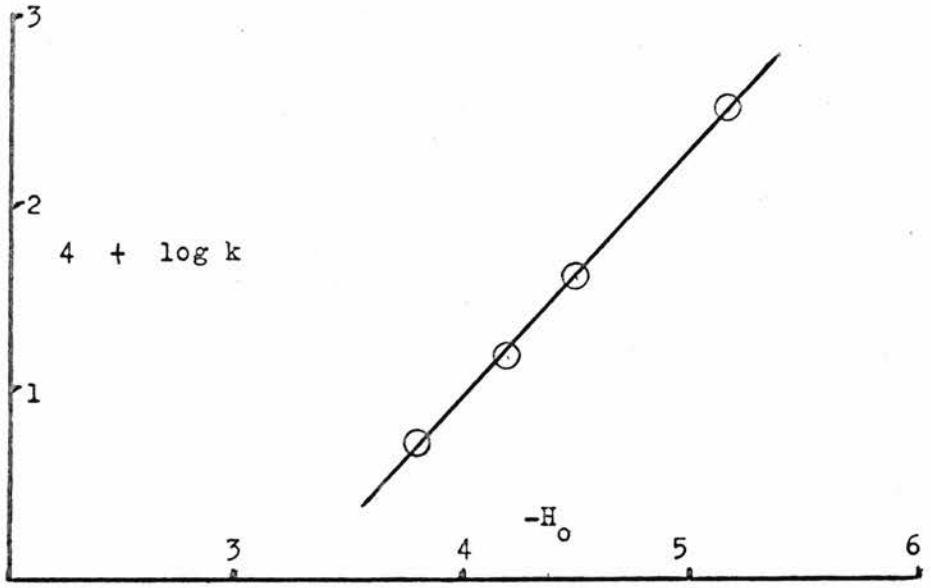


Figure 11 Variation in rate of protodetritiation of 3-tritiothiophen with acidity at 1.9°.

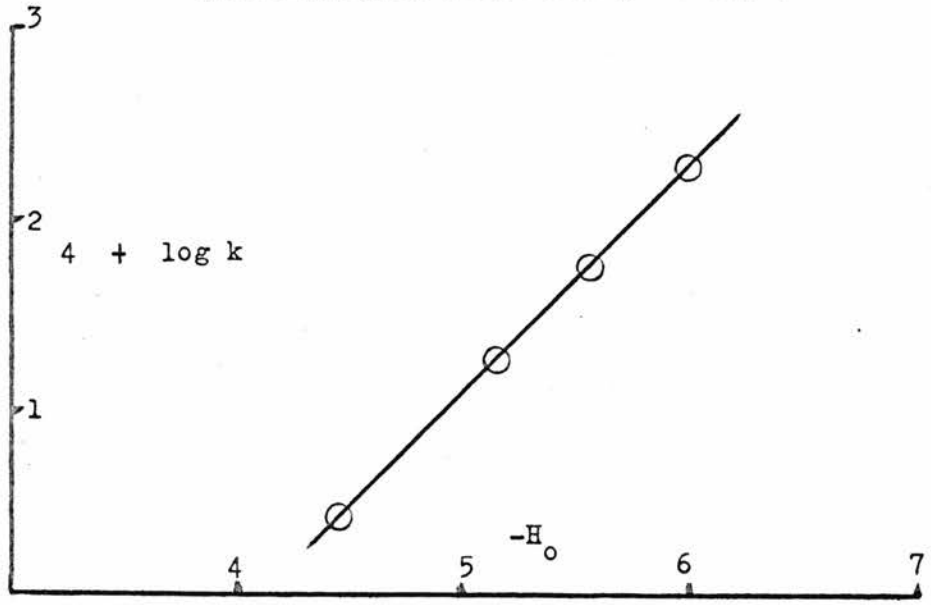


TABLE 24

Variation in the rate of protodetritiation of 3-tritiothiophen with acidity at 1.9°.

$[H_2SO_4]$ M	$-H_o$	$10^4 k$ $min.^{-1}$
9.24	4.49	2.15
10.56	5.17	17.7
11.22	5.56	60.6
11.88	6.00	203

Figure 11

There is a linear relationship between log k and $-H_o$, over approximately two H_o units, for the reaction at the 2- and 3- position at both 25° (Figures 8 and 10) and 1.9° (Figures 9 and 11). The gradient of the lines should be unity to support an A-1 mechanism, but deviations (TABLE 25) are similar to those reported for benzene compounds[106, 109].

TABLE 25

Gradients of plots of log k versus $-H_o$ for protodetritiation of thiophen.

Position	Temperature	Gradient
2-	25°	1.17
2-	1.9°	1.24
3-	25°	1.30
3-	1.9°	1.25

The variation in rate of reaction with acidity being the same for thiophen and benzene suggests a similar mechanism. Thus hydrogen exchange in thiophen becomes one of a number of reactions[118] which have an $A\text{-}S_E2$ mechanism and also a linear relationship between log k and $-H_o$ with a slope different from unity. The Zucker-Hammett hypothesis[108] is now so doubtful that it can no longer be evoked in order to reject an $A\text{-}S_E2$ mechanism.

The expected variation in rate for an $A\text{-}S_E2$ mechanism on changing A^-, the anion of the acid, is not observed when detritiation rates in sulphuric and perchloric acids are compared at the same acidity and temperature (TABLE 26). The differences in values are small and cannot be taken as

diagnostic considering the fact that the rates in sulphuric acid were obtained by interpolation of a log-log plot and are subject to considerable error.

TABLE 26

Comparison of rates of protodetritiation of 2-tritiothiophen in sulphuric and perchloric acids at 25°.

$-H_o$	$10^4 k$ [a] $min.^{-1}$	$10^4 k$ [b] $min.^{-1}$
1.57	11.2	11.8
1.95	29.9	32.4
2.20	56.7	64.6
2.97	383	513

[a] perchloric acid [b] sulphuric acid.

The protodetritiation, in a series of acetate buffers, of 2-methoxy-5-tritiothiophen was studied to determine whether the reaction was subject to general acid catalysis (TABLE 27).

TABLE 27

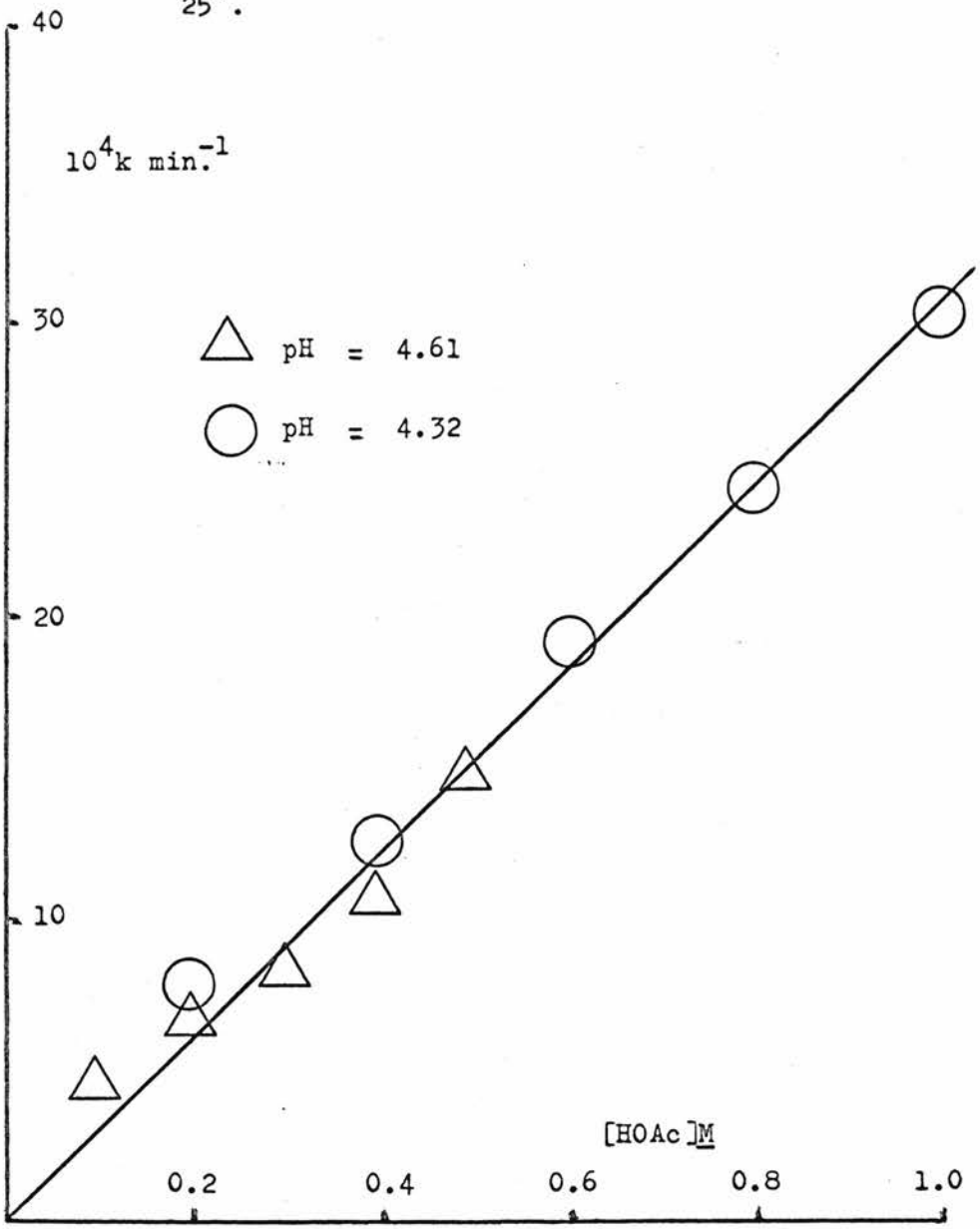
Protodetritiation of 2-methoxy-5-tritiothiophen in acetate buffer at 25°.

Buffer conc.[a] M	[NaOAc]/[HOAc]	[HOAc] M	pH	$10^4 k$ $min.^{-1}$
0.20	1.00	0.1	4.61	4.41
0.40	-	0.2	-	6.64
0.60	-	0.3	-	8.07
0.80	-	0.4	-	10.3
1.00	-	0.5	-	14.6
0.30	0.50	0.2	4.32	7.77
0.60	-	0.4	-	12.5
0.90	-	0.6	-	19.4
1.20	-	0.8	-	24.4
1.50	-	1.0	-	30.3
0.98	0.11	0.9	3.62	33.0
1.96	-	1.8	-	53.5
2.94	-	2.6	-	73.5

[a]Ionic strength = 0.5M.

Figure 12.

Figure 12 Variation in rate of protodetritiation of 2-methoxy-5-tritiothiophen with acetic acid concentration at 25°.



A plot of the first-order rate constant versus the acetic acid concentration is linear, (Figure 12) confirming general acid catalysis. The mechanism of hydrogen exchange in 2-methoxythiophen, like that of 1,3,5-trimethoxybenzene, is therefore A-S_E2. However, Melander[119] has suggested the possibility of a change of mechanism from A-S_E2 to A-1 depending on the acid strength and the reactivity of the aromatic substrate, and Gold[120] has reached a similar conclusion. The possibility still remains, therefore, on moving from aqueous buffer to fairly strong acid conditions and from 2-methoxythiophen to the less reactive thiophen, of a change of mechanism occurring.

Further evidence was obtained by performing the proto--detritiation of the 2- and 3- position at constant acidity and various temperatures and calculating the activation parameters (TABLE 28). Since the slopes of the plots of log k versus $-H_o$ are the same at 25° and 1.9° (TABLE 25) the activation parameters are independent of acidity. This is true for both the 2- and 3- position and is surprising, as the hydration of the hydronium ion will change considerably over the acidity range studied and it might be thought that this would affect both the entropy and enthalpy of reaction.

TABLE 28

Activation parameters for the protodetritiation of thiophen at 25°.

Position	$\Delta H^{\ddagger}$ kcal. mole^{-1}	$\Delta S^{\ddagger}$ e.u.
2-[a]	17.0 ± 2	-15 ± 2
3-[b]	18.6 ± 2	-15 ± 2

[a] $[H_2SO_4]$ = 6.67M [b] $[H_2SO_4]$ = 9.34M.

The similarity in entropy values for the two positions reflects a similarity in the activated complex for both positions and the absence of steric effects in hydrogen exchange.

The value of $\Delta S^{\ddagger}$ is higher than that reported by Kresge, Chiang and Sato[121] for the protodetritiation of 1,3-dimethoxy--benzene, but the difference may be explained by a medium effect.

The entropy of reaction value is inconsistent with an A-1 mechanism[45] and lies within the range of values found for known A-S_E2 reactions and fits on to a plot of log k versus $\Delta S^{\ddagger}$ for such reactions given by Matesich[122].

The relative reactivities of the 2- and 3- positions were calculated at different acidities and temperatures (TABLE 29).

TABLE 29

Relative reactivities of the 2- and 3- position of thiophen in protodetritiation.

Temperature	$-H_o$	k^2/k^3
25°	6.00	440
25°	4.00	900
1.9°	4.00	1200

The values are of interest if only to show the danger of basing too much on partial rate factors measured under one particular set of conditions. Halvarson and Melander[123] report a k^2/k^3 value of 955 for the protodetritiation of thiophen in aqueous sulphuric acid under heterogeneous conditions, and Shatenshtein[113] a value of 3400 for the same reaction with dedeuteriation at the 2- position 1944 times faster than the 3- position in aqueous methanol[124]. Taylor[125] in the pyrolysis of 1-arylethylacetates finds the 2- position more reactive by a factor of 1235. The variation in relative reactivity is probably of little significance when allowances have been made for changes in reaction and reaction conditions.

The conclusion from the above results is that hydrogen exchange or thiophen, like bromination and chlorination, exhibits definite mechanistic similarities to that on benzene compounds.

6. KINETICS AND MECHANISM OF NITRATION.

Nitration is perhaps the most complex of electrophilic aromatic substitution reactions and the reaction that has been investigated most thoroughly.

The classic work of Ingold et al.,[126] and more recently that of Schofield and Moodie[127] has established the mechanism of nitration for benzenoid compounds.

Nitration can be brought about under a variety of experimental conditions, among them being:-

(1) mixtures of nitric acid and sulphuric or perchloric acid.

(2) mixtures of nitric acid and acetic acid or acetic anhydride.

(3) acyl nitrates in organic solvents.

(4) nitrosation followed by oxidation.

Despite the marked difference in experimental conditions the mechanism of nitration is essentially the same in all of the above cases, with the exception of (4).

Although the nitronium ion, NO_2^+, is present under the nitrating conditions described above,[128, 129] this does not establish that it is the reactive nitrating entity, the other possibilities being nitric acid and the nitric acidinium ion, $H_2NO_3^+$. However, nitric acid can be discounted as the effective agent as the variation in the rate of nitration, when water is added, is not related to the change in nitric acid concentration[130]. Acidity function correlations were

used to distinguish between the two remaining possibilities. If the nitric acidinium ion were the nitrating agent the rate of reaction should follow the Hammett acidity function H_o, which is a quantitative measure of the ability of a solvent to donate protons to an uncharged base:-

$$XOH + H^+ \rightleftharpoons XOH_2^+$$

e.g. $$HNO_3 + H^+ \rightleftharpoons H_2NO_3^+$$

whereas it was found the rate followed the J_o acidity function which describes the equilibrium:-

$$XOH + H^+ \rightleftharpoons X^+ + H_2O$$

e.g. $$HNO_3 + H^+ \rightleftharpoons NO_2^+ + H_2O$$

confirming NO_2^+ as the reactive entity, which in some cases is extracted from a species NO_2X by the aromatic substrate.[131]

Nitration by acyl nitrates in organic solvents e.g. benzoyl nitrate in acetonitrile, is believed to occur by formation of dinitrogen pentoxide in a pre-equilibrium[132]:-

$$2BzONO_2 \rightleftharpoons Bz_2O + N_2O_5$$

which normally undergoes heterolysis before reaction[133] with the aromatic substrate, the nitronium ion being the nitrating species[134]. However, with very reactive substrates, it is thought possible that nitration can be effected by the

dinitrogen pentoxide[17].

Active substrates such as amines and phenols can be nitrated by nitric acid / acetic acid mixtures, provided nitrous acid is present[135]. The reaction is believed to be nitrosation, followed by oxidation of the nitroso product by nitric acid:-

$$ArH + HNO_2 \xrightarrow{slow} ArNO + H_2O$$

$$ArNO + HNO_3 \xrightarrow{fast} ArNO_2 + HNO_2$$

and since nitrous acid is produced in the oxidation reaction its concentration remains constant[136]. However, an autocatalytic increase in nitrous acid[137] can occur as oxidative side reactions[138], producing nitrous acid as one of the products, are sometimes observed. However, more recent work has suggested that nitric acid may not be the oxidising agent.

Nitrosation, in comparison to nitration, has received relatively little attention. Since the nitrosating species are weak electrophiles only highly activated nuclei can be studied. Nitrous acid present in nitric acid exists mainly in the form of dinitrogen tetroxide, which gives rise to the following equilibria:-

$$N_2O_4 \rightleftharpoons 2NO_2 , \qquad N_2O_4 \rightleftharpoons NO^+ + NO_3^-$$

$$2N_2O_4 + H_2O \rightleftharpoons N_2O_3 + 2HNO_3$$

$$N_2O_3 \rightleftharpoons NO + NO_2 , \qquad N_2O_3 \rightleftharpoons NO^+ + NO_2^-$$

The most effective nitrosating agent is the nitrosonium ion[139], NO^+, but some of the carriers of this ion e.g. dinitrogen tetroxide[140] and nitrous acid[141], although less reactive, can be present at high concentration and become kinetically significant[142], giving rise to a complex rate equation.

In high concentrations of nitric acid (above 10M), nitration is anticatalysed by nitrous acid[143], probably because nitrous acid exists in nitric acid as dinitrogen tetroxide, which is partially ionised to nitrosonium, NO^+, and nitrate ions, the latter suppressing formation of the nitronium ion from nitric acid.

The kinetics of nitration with excess nitric acid in organic solvents vary depending on the reactivity of the aromatic substrate. The reaction is zero order in the aromatic for a reactive substrate (toluene) and formation of the nitrating species:-

$$H_2NO_3^+ \underset{\text{slow}}{\rightleftharpoons} H_2O + NO_2^+$$

is the rate determining step[144], with a change to second order kinetics, and attack of NO_2^+ on the substrate being rate

determining for unreactive compounds[145], (nitrobenzene). In concentrated sulphuric acid the nitric acid is completely ionised[146] and second order kinetics are observed regardless of the substrate reactivity.

Nitration of Thiophen.

In 1884 Victor Meyer[147] attempted to nitrate thiophen by the standard procedures used for benzene compounds, but without success. Hartough[72], describes his own work on this reaction in these words, "The work was significantly unsuccessful and extremely hazardous. There appeared to be an induction period during which little reaction took place. Only when some critical point was reached in the mixing of reactants or in adjusting the temperature a sudden, rather violent uncontrollable reaction set in which caused profound decomposition of the thiophen or alkylthiophen." Markovitz[16] has carried out a further comprehensive survey of possible routes to nitrothiophens, including such unusual procedures as floating an ethereal solution of 3-methylthiophen on 25% aqueous nitric acid for a week, and adding an alcoholic solution of tetranitromethane to 3-methylthiophen in pyridine, but none of them was successful in giving the product in

anything but insignificant yield. This does not apply to thiophens with a deactivating substituent (such as nitro or cyano) and they[148], together with benzothiophen[149], may be nitrated by normal procedures. For thiophen itself and activated thiophens the only satisfactory synthetic procedures use benzoyl nitrate[150] or acetyl nitrate[151] as the nitrating agent and these, in contrast to other methods, give nitro--thiophens in high yield in a smooth reaction. Considering the similarities between thiophen and benzene compounds described above it is difficult to understand the reluctance of thiophen to undergo nitration.

Coombs, Moodie and Schofield[152] have studied the nitration, in concentrated sulphuric acid, of a number of active aromatic compounds and, at the substrate concentrations (10^{-4} - 10^{-5}M) used in their kinetic investigations, found that thiophen reacted in the same way as benzene compounds. This study has been extended by investigating the variation in the rate of nitration of thiophens with acidity for both sulphuric and perchloric acids. At constant sulphuric acid concentration and with nitric acid present in a ten-fold excess over the substrate the rate of reaction was found to be first-order in thiophen with an experimentally determined rate constant k(obs.). The value of k(obs.) was found to be directly proportional to the concentration of nitric acid

(TABLE 30, Figure 13) and a second order rate constant was defined as k_2(obs.) being k(obs.) divided by the stoicheiometric concentration of nitric acid.

TABLE 30

Variation in the first-order rate constant with nitric acid concentration for the nitration of thiophen in 70.25% sulphuric acid at 25°.

$10^3[HNO_3]$ M	k(obs.) $min.^{-1}$
3.12	0.131
6.24	0.314
9.36	0.465
12.5	0.681
15.6	0.826

Figure 13.

The variation of k_2(obs.) with acid concentration was measured for the nitration of various thiophens in sulphuric and perchloric acids. Moodie, Schofield and Williamson[153] have shown that there is a linear relationship, with a slope of unity, between $-(H_R + \log a_{H_2O})$, where a_{H_2O} is the

activity of the water present, and log k_2(obs.) for a number of benzene compounds. A similar relationship for the nitration of thiophen (TABLE 31, Figure 14), 2-chlorothiophen (TABLE 32, Figure 16), and 2-methylthiophen (TABLE 33, Figure 17) in sulphuric acid and thiophen (TABLE 31, Figure 15) in perchloric acid and in all cases, except that of 2-methyl--thiophen, the slope is unity. In the latter instance it is only 0.8. As Coombes, Moodie, and Schofield[152] remark, the unity slope is fortuitous and no special conclusions can be drawn concerning the nitration of 2-methylthiophen. It must be noted also that, at the same value of $-(H_R + \log a_{H_2O})$, the rate of nitration of thiophen in sulphuric and perchloric acids differs, which is not the case for the nitration of benzene[152]. In general, however, the results indicate that, under the conditions of these experiments, the mechanism for the nitration of thiophen is the same as that of benzene.

Figure 13 Variation in k(obs.) with nitric acid concentration for the nitration of thiophen at 25°.

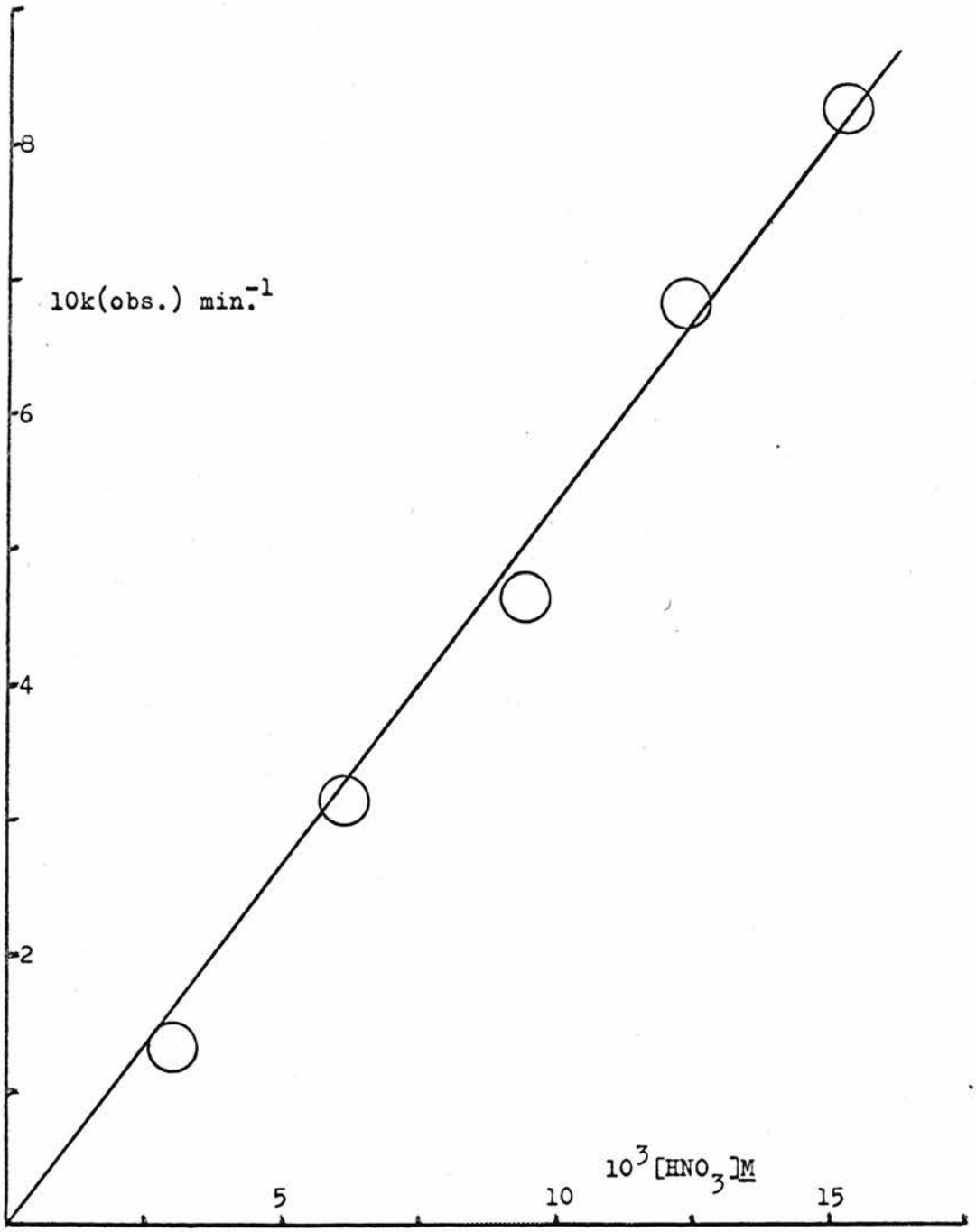


TABLE 31

Variation in the second order rate constant with acidity for the nitration of thiophen at 25°.

H_2SO_4 %	$10^3[HNO_3]$ M	$-(H_R + \log a_{H_2O})$ [a]	$10^{-1}k_2$(obs.) l. mole^{-1} min.$^{-1}$
64.37	15.6	11.03	0.240
66.45	"	11.75	1.06
68.43	"	12.42	5.10
69.61	1.56	12.82	10.3
70.95	"	13.28	30.3
71.59	"	13.48	51.3

$HClO_4$ %	$10^3[HNO_3]$ M	$-(H_R + \log a_{H_2O})$ [b]	$10^{-1}k_2$(obs.) l. mole^{-1} min.$^{-1}$
58.52	15.6	11.49	0.402
59.21	"	11.78	0.774
59.91	"	12.09	1.36
62.09	"	13.13	15.8
65.36	1.56	14.85	460

[a] see ref. 63, 154

[b] see ref. 155

Figures 14 and 15

Figure 14 Variation in k_2(obs.) with sulphuric acid concentration for the nitration of thiophen at 25°.

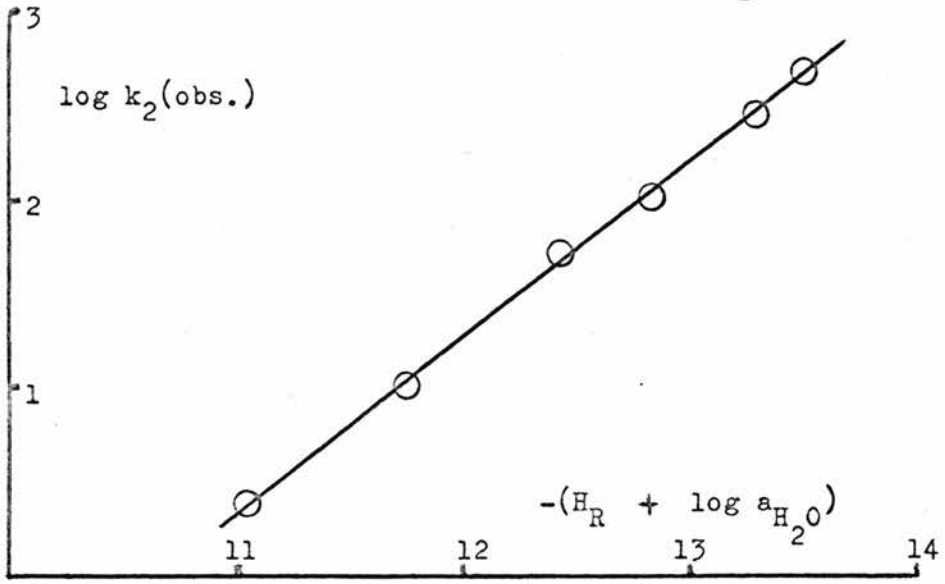


Figure 15 Variation in k_2(obs.) with perchloric acid concentration for the nitration of thiophen at 25°.

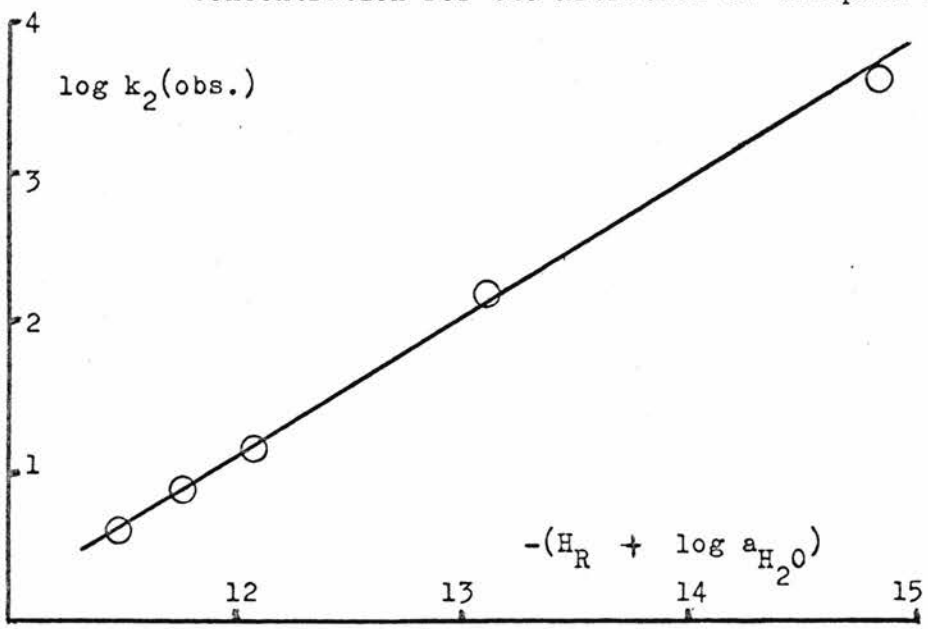


TABLE 32

Variation in the second order rate constant with acidity for the nitration of 2-chlorothiophen at 25°.

H_2SO_4 %	$10^3[HNO_3]$ M	$-(H_R + \log a_{H_2O})$	$10^{-1}k_2$(obs.) l. mole^{-1} min.$^{-1}$
66.45	15.6	11.75	0.384
68.43	"	11.42	1.71
69.61	1.56	12.82	5.05
70.95	"	13.28	10.6
71.59	"	13.48	17.1
72.93	"	13.95	55.1

Figure 16

TABLE 33

Variation in the second order rate constant with acidity for the nitration of 2-methylthiophen at 25°.

H_2SO_4 %	$10^3[HNO_3]$ M	$-(H_R + \log a_{H_2O})$	$10^{-1}k_2$(obs.) l. mole^{-1} min.$^{-1}$
64.37	15.6	11.03	0.666
66.45	"	11.75	2.79
68.43	"	12.42	8.46
69.61	1.56	12.82	21.6
70.95	"	13.28	41.4
71.59	"	13.48	49.2

Figure 17

The variation of k_2(obs.) with temperature was measured for the nitration of thiophen in sulphuric acid and the activation parameters calculated (TABLE 34). The entropy of activation is less negative than in other cases of electrophilic substitution in thiophen compounds (TABLES 18 and 28), but the values of both $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ are similar to those for the nitration of benzene and mesitylene (TABLE 35) calculated from the data of Coombes, Moodie and Schofield[152], confirming the previous statement concerning the mechanism of thiophen nitration.

Figure 16 Variation in k_2(obs.) with sulphuric acid conc. for the nitration of 2-chlorothiophen at 25°.

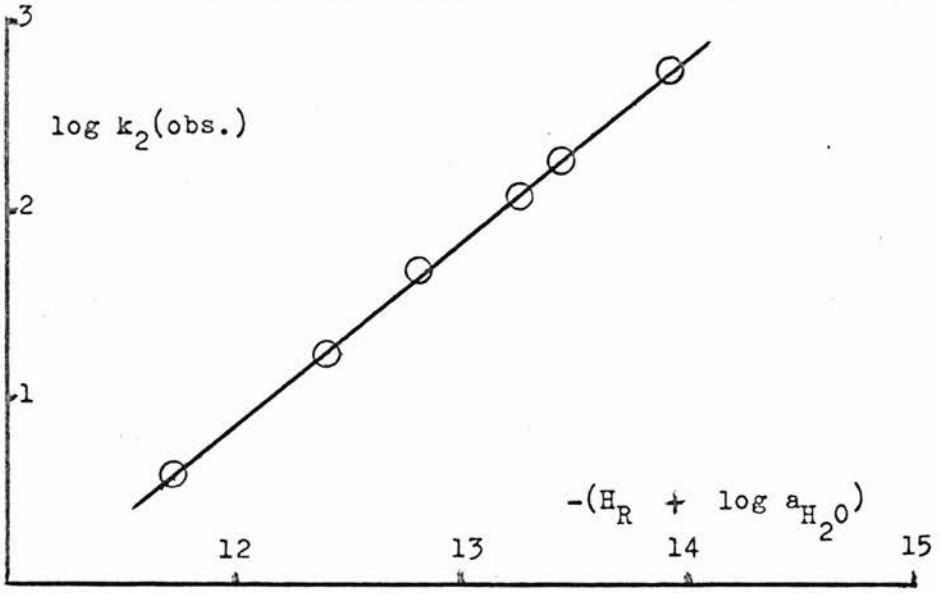


Figure 17 Variation in k_2(obs.) with sulphuric acid conc. for the nitration of 2-methylthiophen at 25°.

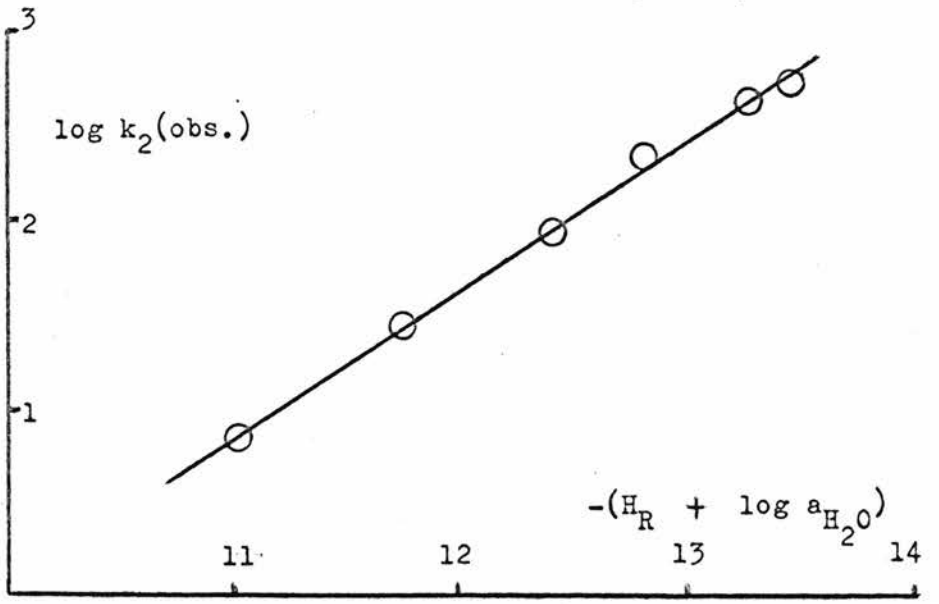


TABLE 34

Activation parameters for the nitration of thiophen at 25° in sulphuric acid.[a]

$[H_2SO_4]$ %	$\Delta H^{\ddagger}$ kcal. mole^{-1}	$\Delta S^{\ddagger}$ e.u.
66.43	18.0 ± 0.3	-1 ± 2
69.15	16.4 ± 0.3	-3 ± 2

[a] $Th_o = 10^{-4}M$, $[HNO_3] = 1.59 \times 10^{-2}M$

TABLE 35

Activation parameters for the nitration of benzene compounds in sulphuric acid at 25°.[b]

Substrate	$[H_2SO_4]$ %	$\Delta H^{\ddagger}$ kcal. mole^{-1}	$\Delta S^{\ddagger}$ e.u.
Benzene	67.1	17.5	-7
	73.2	13.4	-11
Mesitylene	67.1	17.5	-1

[b] Calculated from the results of Coombes, Moodie and Schofield[152].

A much milder nitrating agent is a solution of nitric acid in acetic acid. The reaction was examined using a low initial concentration of thiophen (ca. 10^{-2}M) and, after extraction with iso-octane (see Experimental), the final spectrum indicated about 20% of the theoretical yield of 2-nitrothiophen. However, addition of a small quantity of urea (0.03 mole $l.^{-1}$), to reduce the concentration of nitrous acid present[152], resulted in an almost quantitative yield of product. Under these conditions the reaction was found to be first-order in thiophen and the observed first-order rate constant, k(obs.), independent of the initial thiophen concentration (TABLE 36).

TABLE 36

The effect of initial thiophen concentration on the rate of nitration in acetic acid.[a]

$10^2[Th_o]$ M	10^3k(obs.) $min.^{-1}$
0.52	7.32
1.05	8.16
2.10	7.98

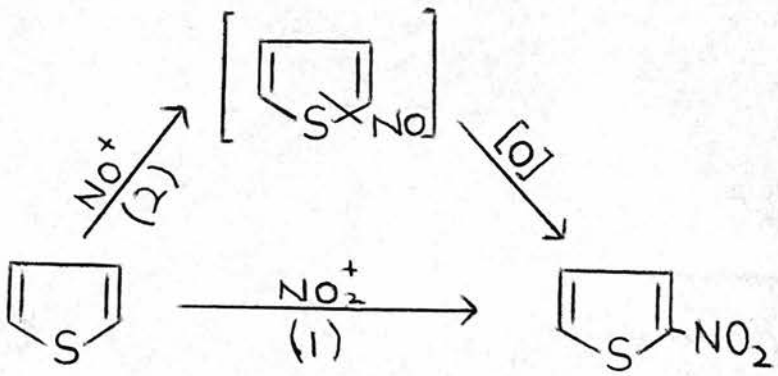
[a] $[HNO_3]$ = 9M.

Under the same conditions the nitration of mesitylene was found to be essentially unaffected by addition of urea. Hughes, Ingold, and Reed[144] report that, under slightly different conditions, the nitration of mesitylene is only weakly anticatalysed by nitrous acid.

From these results it seemed possible that, if all the nitrous acid could be removed, nitric acid in acetic acid would be an effective nitrating agent for thiophen on a preparative scale. When this was attempted, however, the method was found to be unsuccessful and it can only be concluded that even after addition of urea sufficient nitrous acid remains[143] to prevent normal nitration.

The nitrous acid effect is probably only one of the reasons which make sulphuric acid / nitric acid mixtures unsuitable as nitrating agents for thiophen on a preparative scale. At high sulphuric acid concentrations thiophen is known to undergo polymerisation[156], this prevented examination of the reaction at concentrations where protonation of the thiophen might have occurred. If dilute acid is used the reaction mixture is too aqueous for the thiophen to dissolve and a heterogeneous mixture results, an unsatisfactory practical procedure.

Reactive compounds, such as thiophen, may undergo nitration by two pathways:-



direct nitration (1) or nitrosation followed by oxidation (2). The main route to the nitration of phenols and amines appears to be pathway (2)[136, 157], also the nitroso compound may undergo a variety of reactions other than oxidation and these lead to brightly coloured products[158]. For example, the reaction of anisole with nitric acid (containing nitrous acid) in acetic acid gives a purple product which has been identified as the dianisyloxidoammonium ion[136, 159]. Similar highly coloured products were noticed in the attempted nitration of thiophen. These side reactions[136], as well as the oxidation of a nitroso to a nitro compound[137], result in the production of nitrous acid in an autocatalytic process. Now, heteroaromatic compounds are particularly susceptible to nitrosation[160], for reasons which are not yet fully understood,

and it is suggested that this is the reason for the failure to obtain nitrothiophen by normal nitrating methods. At low concentration the preparation succeeds as NO_2^+ is a stronger electrophile than NO^+, the supposed nitrosating agent, and attack by NO_2^+ is more likely than NO^+. By analogy with a benzene compound of similar reactivity (mesitylene), one can predict that nitration, which is first-order at low thiophen concentration, will become zero-order as the substrate concentration is increased. The nitration of mesitylene is known[144] to be zero-order when the substrate concentration is 0.1M. Therefore, at high concentrations of thiophen the rate of nitration is independent of the substrate concentration, but it is not unreasonable to suggest that this is not so for nitrosation, or the subsequent reactions of the nitroso compound producing more nitrous acid in an autocatalytic reaction. Its autocatalytic nature explains the sudden violence of the reaction. Thus, at concentrations used in normal preparations, nitrosation rather than nitration is the predominant reaction. However, it was possible to obtain a good yield of 2-nitrothiophen by adding thiophen very slowly (over 36 hours) to a solution of nitric acid in acetic acid, but this is not a viable synthetic procedure. 2-Nitrothiophen is quite stable in the nitrating medium and there are no complications due to subsequent reactions of that compound.

Thiophen is known to react with nitrous acid[138], although nitrosothiophen does not appear to have been isolated.

The remaining problem is to account for the success of benzoyl nitrate and acetyl nitrate as nitrating agents for thiophen. The exact nature of the nitrating species in these reagents is not certain and for the latter protonated acetyl nitrate[161, 162], nitronium ion[163], and dinitrogen pentoxide[164] have been suggested. The evidence in favour of protonated acetyl nitrate is the formation of acetoxylated products[161], but a spectral examination of the reaction mixture, during the reaction and at completion, produced no evidence for their formation in the case of thiophen and acetyl nitrate. An explanation of the success of acetyl nitrate in nitrating thiophen might be that in a solution of nitric acid in acetic anhydride the concentration of NO_2^+ is much higher than in a solution in acetic acid. Consequently, in the former reagent nitration would be much faster (the rate determining step is encounter between NO_2^+ and the substrate[152]) and would not be overwhelmed by the autocatalytic nitrosation reaction. However, addition of acetic anhydride was found to have a relatively small effect on the rate of production of nitro--thiophen from thiophen and nitric acid in acetic acid solution (TABLE 37, Figure 18) and this cannot be the correct explanation. The kinetics of nitration in acetic anhydride

are too complicated[165] to make any positive deductions from these results.

TABLE 37

The effect of acetic anhydride on the rate of nitration of thiophen in nitric acid / acetic acid mixtures.[a]

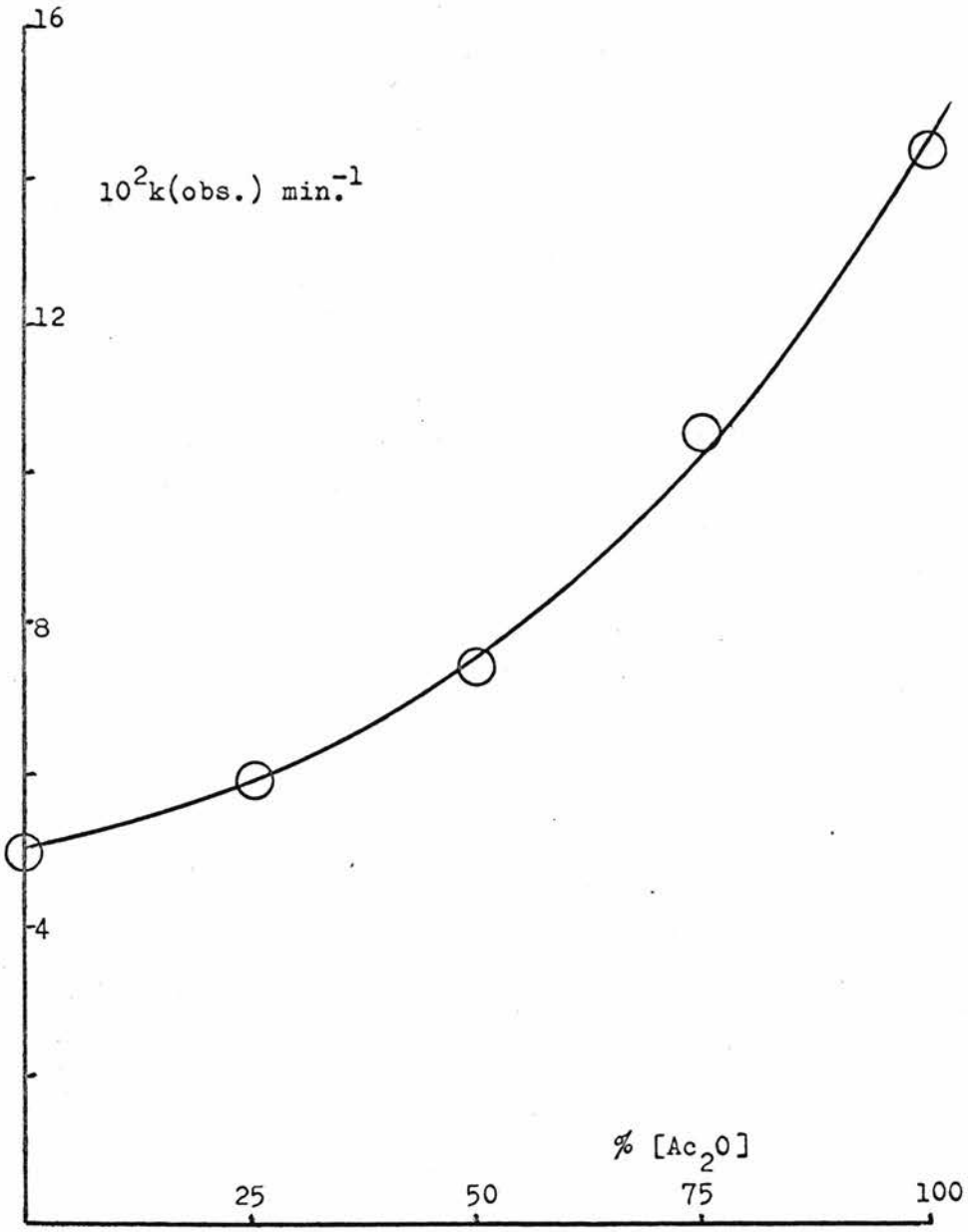
$[Ac_2O]$ %	10^2k(obs.) $min.^{-1}$
0	4.44
25	5.94
50	7.38
75	10.5
100	14.4

[a] $[HNO_3]$ = 9M

Figure 18

It must be concluded that, rather than enhancing the nitration reaction, acetic anhydride affects the competing nitrosation process. Acetic anhydride does not appear to suppress formation of the nitrosating species as Hoggett, Moodie and Schofield[157] report that one pathway for nitration in acetic anhydride is nitrosation followed by oxidation.

Figure 18 Variation in k(obs.) with percentage acetic anhydride for the nitration of thiophen at 25°.



However, oxidation to the nitro compound is only one of the subsequent reactions of the nitroso intermediate and the addition of acetic anhydride may suppress the side reactions and thus enhance formation of nitrothiophen. Confirmation of this comes from observations on the effect of acetic anhydride on the nitration of anisole. Normally the final product is bright purple owing to formation of dianisyloxido--ammonium ion as described previously, but in the presence of acetic anhydride this colour does not appear and the only detectable product is nitroanisole.

The apparent anomaly in the nitration of thiophens is not in the nitration reaction, which is similar to that of benzene compounds, but lies in the greatly enhanced susceptibility of thiophen to nitrosation and subsequent reactions.

PART III

EXPERIMENTAL

1. SOURCES, PREPARATION AND PURIFICATION OF MATERIALS.

Acetic acid. The A.R. material, used for the bromination and chlorination experiments, was further purified by a similar method to that of Orton and Bradfield[166].

The temperature of 2.5 litres of the acid and 50g of chromium trioxide was raised to just below distillation point for 30 mins. and then the acid slowly distilled using a splash head.

Estimation of percentage water in acetic acid. The freezing point of the acid was measured using the normal type of apparatus.

The freezing point of the anhydrous acid was assumed to be 16.6° and the freezing point lowered by 0.2° for every 0.1% water present;

e.g. melting point of acid = 15.6° corresponds to 0.5% water present = 0.5g water per 100g of acid.

Purification of water for halogenations.[167] Potassium permanganate (30g) was added to deionised and distilled water (2 litres). The water was then triply redistilled with the use of a splash head in the final distillation.

Preparation of acetic acid/water mixtures. The mixtures were made up in 500ml. batches. The required amount of water being pipetted into the flask and made up to the mark with acid.

Preparation of anhydrous acetic acid[166]. The freezing point of the acid was measured and the water content calculated. An appropriate amount of A.R. acetic anhydride was added with the chromium trioxide to remove the water present and the purification carried out as above.

e.g. To remove 0.5% water, to each 100g of acid add

$$\frac{0.5 \times \text{mol. wt. of acetic anhydride}}{\text{mol. wt. of water}} \text{ g of acetic anhydride}$$

$$= \frac{0.5 \times 102}{18} = 2.83\text{g before distillation.}$$

Acetic anhydride. The A.R. material was used without further purification.

Bromine. The A.R. material was used without further purification.

Chlorine. Supplied by I.C.I., Mond Division, was passed through concentrated sulphuric acid and phosphorous pentoxide before use.

Heavy water The Koch-Light product, with a stated deuterium content of 99.7%, was used.

Tritiated water The Radiochemical Centre product with an activity of 200mc/ml was used.

Mesitylene The laboratory reagent material was redistilled before use.

Lithium perchlorate The laboratory reagent material was dried under vacuum.

Sodium acetate The A.R. material was dried at 100° for several hours and allowed to cool in a vacuum desicator.

Lithium bromide[168] The laboratory reagent material was purified by recrystallisation from water and from absolute ethanol. The product was dried under vacuum over phosphorous pentoxide.

n-Butyl lithium A solution in hexane, 15% n-butyl lithium, was supplied by Koch-Light.

Thiophen, 2-chlorothiophen, 2-bromothiophen, 2-ethylthiophen, 2-methylthiophen were laboratory reagents which were redistilled immediately before use.

2,3-Benzothiophen (K & K) was sublimed at reduced pressure.

Thienyl-2-carboxylic acid was recrystallised from water (M.P. 129°).

Ethyl ester of thienyl-2-carboxylic acid[169] Thienyl-2-carboxylic acid (10g) was mixed with thionyl chloride (7mls) and refluxed for 30 mins. The product was distilled at atmospheric pressure (B.P. 200 - 203°) yielding 8.8g of acid chloride.

Absolute ethanol (15mls) was mixed with the acid chloride (5g) and refluxed for 30 mins. The product was fractionally distilled at atmospheric pressure collecting the fraction boiling at 215° yielding 3.1g (59%) of the ester.

2-tert-Butylthiophen was prepared by the method of Sy, Buu-Hoi and Xuong[170].

Stannic chloride (126g) was added to a solution of thiophen (35g) and t-butyl chloride (44g) in anhydrous carbon disulphide (600mls), cooled in ice, with stirring during 1 hr. The resulting mixture was warmed to room temperature and allowed to stand for 5 hrs. After pouring into ice cold hydrochloric acid (200mls, 2M), the organic layer was removed, washed with sodium hydroxide and water and dried ($CaCl_2$).

The carbon disulphide was removed and the residue distilled through a Vigreux column and redistilled on a spinning band. Yield 5.6g, (B.P. 165°/760mm.)

2-Iodothiophen[171] To the vigorously stirred thiophen (50mls) benzene (75mls) mixture, cooled to 0° in an ice bath, were added mercuric oxide (112.5g) and iodine (163.5g) alternately in small amounts during 20 mins. The mixture was filtered under suction and the residue washed with 3 x 30mls portions of ether. The ether benzene filtrate was shaken with a 5% solution of sodium thiosulphate (20mls) and dried ($CaSO_4$). The ether and benzene were distilled off and the residue distilled in vacuum. The 2-iodothiophen came over between 85 - 90° (ca. 30mm.). Yield 90g (70%), The product was coloured by traces of iodine.

2-Methoxythiophen[172] Sodium (30.3g) was weighed under benzene after washing in petroleum ether. The sodium was cut into small pieces and added cautiously to the methanol (435mls) over 2 hrs. The 2-iodothiophen (90g) and cupric oxide (17.4g) were added and the mixture stirred and refluxed gently for 30 hrs. The cooled suspension was filtured by suction, poured into two volumes of water and extracted with ether (3 x 50mls). The solvent layer was washed with water, dried, and evaporated. Distillation of the residue gave 30g (60%) of colourless liquid (B.P. 152 - 153°, n^D = 1.5263).

2-Phenylthiophen[91] The preparation involves the reaction of 2-lithiothiophen with cyclohexanone and subsequent dehydrogen--ation of the product with chloranil.

An ethereal solution of 2-lithiothiophen was prepared by adding 0.21 moles of n-butyl lithium (prepared from 82.2g of n-butyl bromide and 12.0g of lithium in 350mls of ether) to 26g of thiophen in 100mls of ether and stirring for 15 mins.

A solution of cyclohexanone (29.5g, 0.3 mole) in 50mls of ether was added rapidly to the 2-lithiothiophen solution (cooled in a Dry Ice-acetone bath). The reaction mixture was left overnight before being hydrolysed by cold hydrochloric acid. The organic layer was washed with water, dried and fractionated to give 15.5g (30%) of 2-(1-cyclohexenyl)-thiophen boiling between 99 - 103° (2mm.).

A mixture of 30g chloranil, 15g of 2-(1-cyclohexenyl)-thiophen and 40mls of benzene was refluxed for 24 hrs. and the product filtered. The filtrate was extracted with 10% sodium hydroxide (3 x 20mls), before the benzene layer was washed with water, dried and distilled. The product (about 5g) was collected at 110° (4mm.) and recrystallised from aqueous methanol (M.P. 37°). The compound was stored in the refrigerator.

2,5-Dideuteriothiophen[173] A solution of CH_3COOD in D_2O was prepared by refluxing 25mls of D_2O and 7g of acetic anhydride for 3 hrs. 2,5-dibromothiophen (8.7g) was added to the cold solution followed by zinc dust (16g) and the mixture refluxed and stirred for 18 hrs. The products were then distilled off until the temperature of the vapour reached 103°. The greater part of the aqueous layer was removed by syringe and the organic layer dried with sodium carbonate and then phosphorous pentoxide. Fractionation gave 1.12g of 2,5-dideuteriothiophen (B.P. 83 - 84°, n^D = 1.5278). The purity was also checked by N.M.R.

2-Bromo-5-deuteriothiophen Fractionation of the products of the 2,5-dideuteriothiophen preparation also yielded 1.25g of 2-bromo-5-deuteriothiophen (B.P. 150 - 151°/760mm.).

2,5-Dibromothiophen[72] An ice cold solution of 32mls of bromine in 160mls of acetic acid was added slowly to 33.6g of

thiophen in 160mls of acetic acid and stirred for 8 hrs. 500mls of water was added and the brominated thiophens extracted with ether (3 x 50mls). The organic extract was washed with 10% sodium hydroxide (3 x 30mls), dried, and the ether removed. The product was heated to about 80° and 20g potassium hydroxide added over 90 mins, before refluxing overnight. After filtering, the mixture was fractionated on a spinning band column. The 2,5-dibromothiophen being collected at 98 - 100° (15mm.).

2-Bromo-5-chlorothiophen[174] Bromine (11mls) was added slowly to 2-chlorothiophen (18.4mls) in 40mls of carbon disulphide at 0°. After 24 hrs. the mixture was decolorised with 5% sodium sulphite solution. The solvent was removed and the residue refluxed for 4 hrs. with 100mls of 5% sodium hydroxide and the steam distilled. The organic layer was separated and fractionated under vacuum. The fraction boiling at 80° (20mm, n^D = 1.5915) was collected, yielding 19.5g (65%) of 2-bromo-5-chlorothiophen.

2-Tritiothiophen[41] A solution of 2-lithiothiophen was prepared by the addition of 100mls of 1.6M n-butyl lithium in hexane to 15mls of thiophen in 100mls of ether under nitrogen. After 30 mins. 2mls of tritiated water (40mc/ml) was added followed by excess aqueous ammonium chloride. The organic layer was separated, washed, dried ($CaCl_2$) and distilled

(B.P. 84°) giving 10.5g 2-tritiothiophen with hexane present as an impurity.

3,4-Ditritiothiophen[175] Thiophen, tritiated in all positions, was prepared by stirring thiophen (12g) with sulphuric acid (4.2mls) and tritiated water (1.8mls, 100mc/ml) for 26.5 hrs. The thiophen was separated, washed, dried and distilled. The product (10g) was stirred with perchloric acid (20mls, 50%) for 19 hrs. to protodetritiate the 2- and 5- positions and 25mls of ether added. Separation, washing, drying (Na_2SO_4) and fractionation of the ether layer gave 3,4-ditritiothiophen (6g)

2-Methoxy-5-Tritiothiophen[41] 1.67M Butyl lithium in hexane (30mls) was added to a solution of 2-methoxythiophen (5.7g) dissolved in ether (10mls) and the mixture refluxed under nitrogen for 30 mins. After cooling, tritiated water (0.9ml, 30mc/ml) was added and allowed to react. Ammonium chloride solution was added and the organic layer separated, washed and dried (Na_2SO_4). The ether and hexane were evaporated off and the residue distilled at reduced pressure (B.P. 66°/ 37mm.) yielding 4.3g of product n^D = 1.5250.

2-Nitrothiophen[176] Thiophen (42g) was dissolved in acetic anhydride (170mls) and nitric acid (Sp. Gr. = 1.51, 40g) in acetic acid (300mls) and each solution divided into two equal parts. One half of the thiophen solution was added

drop by drop to half the nitric acid solution, cooled to 10°, at such a rate to prevent the temperature rising above about 20°. After addition of the first half of the thiophen solution the mixture was again cooled to 10° and the rest of the nitric acid solution added rapidly before continuing the gradual addition of the remaining thiophen solution. The mixture was allowed to stand at room temperature for 2 hrs. before being poured on to 600g of ice and stored in the refrigerator overnight. The product was filtered off under suction, washed with ice water and dried in a desiccator in the dark. Recrystallisation from petroleum ether yielded 38g (60%) of product (M.P. 44°).

Dinitrogen tetroxide[177] 70% nitric acid was added dropwise to sodium nitrate in a stream of oxygen. The gases were passed up a vertical water condenser and passed over a boat containing phosphorous pentoxide and condensed in a trap surrounded by a Dry Ice-acetone bath.

Perchloric acid The A.R. material was used without further purification.

Sulphuric acid The A.R. material was used without further purification.

Nitric acid The A.R. material was used without further purification.

Potassium chloride The A.R. material was dried at 110° for

several hours and allowed to cool in a vacuum desiccator.

Iso-octane (2,2,4-trimethylpentane) B.D.H. "Special for Spectroscopy" was used.

Urea The A.R. material was dried in a vacuum desiccator.

Sodium nitrite The A.R. material was dried in a vacuum desiccator.

Anisole The laboratory reagent was redistilled before use.

Scintillator solution Beckman Fluoralloy T.L.A. Scintillation Cocktail Mix was dissolved in sulphur free toluene (8.51g/litre).

Sodium hydroxide Standard solutions were B.D.H. volumetric solutions.

Sodium thiosulphate Standard solutions were B.D.H. concentrated volumetric solutions (stabilised with a trace of chloroform).

2. DETERMINATION OF K THE EQUILIBRIUM CONSTANT FOR TRIBROMIDE FORMATION IN 15% AQUEOUS ACETIC ACID.[93]

$$Br_2 + Br^- \rightleftharpoons Br_3^-$$

$$K = \frac{[Br_3^-]}{[Br_2][Br^-]}$$

K was evaluated spectrophotometrically from plots of $1/(\epsilon Br_2T + \epsilon Br_2)$ vs. $1/[Br^-]$ where ϵBr_2T represents the apparent extinction coefficient of bromine both free and in the form of tribromide. ϵBr_2 is the extinction coefficient of free bromine and ϵBr_3^- that of the tribromide ion.

A series of solutions of various bromine and bromide concentrations was made up and their optical densities measured on a Unicam SP 700 spectrophotometer using 10mm. cells in a thermostatted cell holder. The extinction coefficient for bromine, (ϵBr_2), was measured separately from a series of bromine solutions of known concentration. Plots of optical density versus bromine concentration have gradient ϵBr_2 (Figure 19).

The determination of K at each temperature was carried out at four wavelengths and the average value used. A stream of dry air was directed on to the cell faces to prevent condensation forming during the determinations at 0°. The

ionic strength was kept constant at 0.1M by the addition of lithium perchlorate.

Specimen Experiment

TABLE 38

Determination of the equilibrium constant for tribromide formation in 15% aqueous acetic acid at 0°.

OD[a]	$10^4[Br_2]$ M	$[Br^-]$ M	$\epsilon Br_2 T$	$\frac{1 \times 10^3}{(\epsilon Br_2 T - \epsilon Br_2)}$	$\frac{1 \times 10^{-2}}{[Br^-]}$
0.99	4.8	0.045	2070	0.493	0.222
0.97	4.8	0.032	2030	0.502	0.317
0.68	3.6	0.023	1880	0.543	0.444
0.65	3.6	0.018	1810	0.564	0.555
0.51	3.0	0.014	1690	0.604	0.740
0.33	3.0	0.005	1100	0.939	2.20
0.35	1.5	0.537	2310	0.441	1.86

[a] at 340nm.

Figure 20

$\epsilon Br_2 = 36$ (Figure 19)

$$\text{Gradient} = \frac{1}{K(\epsilon Br_3^- - \epsilon Br_2)} = 2.54 \times 10^{-6}$$

Figure 19 Variation in optical density at 340nm. with bromine concentration in 15% aqueous acetic acid.

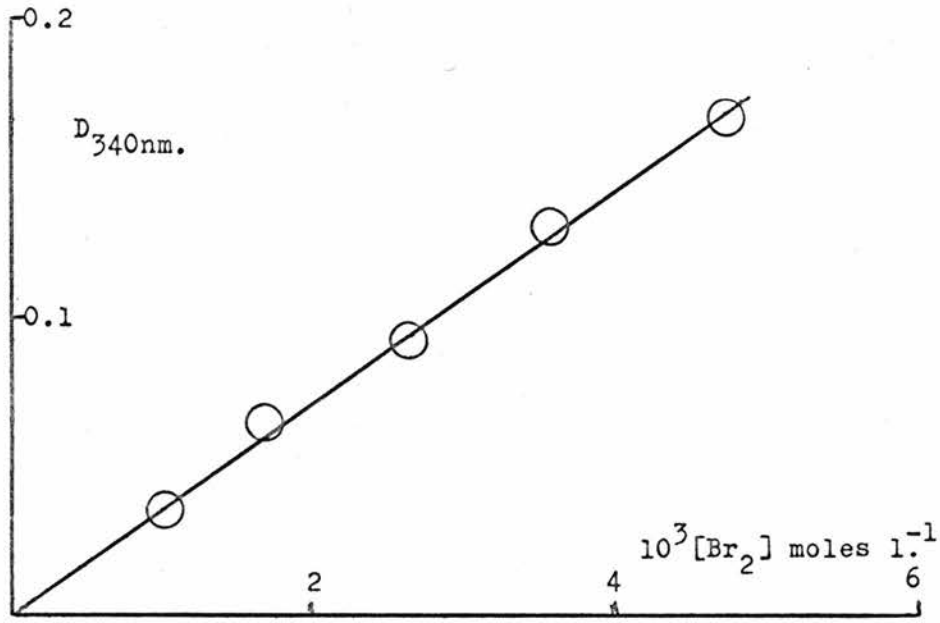
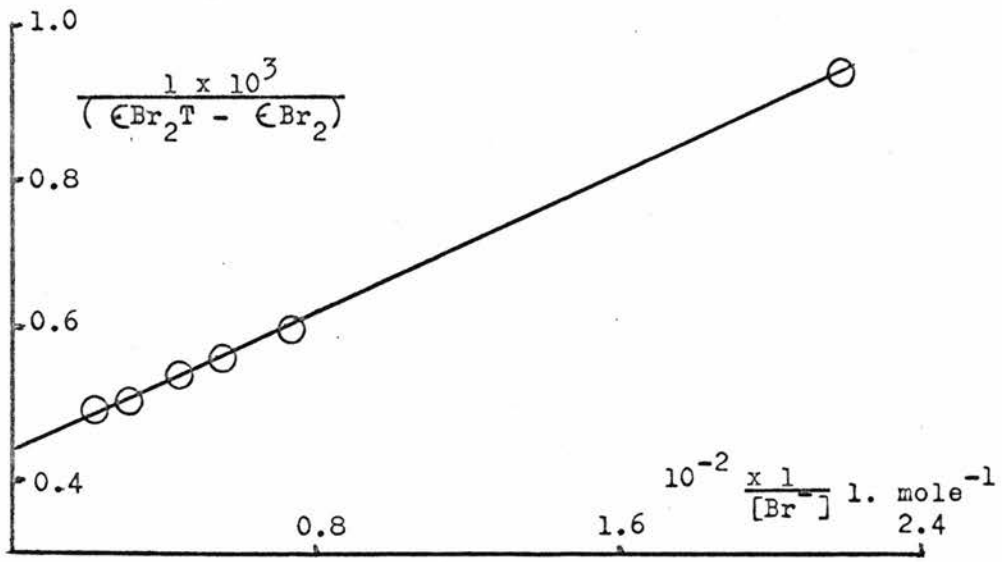


Figure 20 Determination of the equilibrium constant for tribromide formation in 15% aqueous acetic acid.



$$K(\epsilon Br_3^- - \epsilon Br_2) = 0.394 \times 10^6$$

But intercept from Figure 20 $= \frac{1}{\epsilon Br_3^- - \epsilon Br_2}$

$$= 0.45 \times 10^{-3}$$

$$\therefore \epsilon Br_3^- = 2200 - 36$$

$$K = \frac{3940 \times 10^2}{2164} = \underline{183}$$

Summary of K Determinations

Temperature	Average K value
0°	190
10°	157
18°	132
25°	120[a]

[a]Keefer and Andrews value[178]

Determination of the extinction coefficient of the tribromide ion at 25° in 15% aqueous acetic acid.

Three solutions of known bromine concentration (determined by iodine thiosulphate titration) were prepared in 15% aqueous acetic acid. The solutions were placed in 1mm. cells and thermostatted at 25° in a Unicam SP 700, and the optical density measured.

TABLE 39

Determination of the extinction coefficient of the tribromide ion at 25°.

OD[a]	$10^4[Br_2]$ M	$[Br^-]$ M	$10^4[Br_3^-]$ M	ϵBr_3^-
0.369	1.865	0.1	1.72	21,450
0.190	0.933	0.1	0.916	20,740
0.301	1.492	0.1	1.38	21,850

[a] at 340nm.

Wavelength	Average value of ϵBr_3^-
290nm.	21,350
267nm.	45,000

3. BROMINATION OF 2- SUBSTITUTED THIOPHENS AND MESITYLENE

Kinetic procedure

Several different methods were used depending on the reactivity of the substrate.

Bromination of thiophen at 25° by U.V.

The rate of bromination of thiophen in 15% aqueous acetic acid, in the presence of an excess of lithium bromide, was determined by following the disappearance of absorption due to tribromide ion at 290nm.

10mls of solution were made up e.g. 1ml of thiophen solution, 5mls of 0.2M lithium bromide and 4mls of 15% aqueous acetic acid. The solution was placed in a 10mm. cell and allowed to thermostat for 30 mins. A concentrated solution of bromine in 15% aqueous acetic acid was then added by micropipette (0.01ml) and the cell shaken. The fall off in optical density with time was recorded for about three half lives and a residual optical density measured after about ten half lives.

Thiophen was present in at least twenty fold excess over bromine, giving pseudo first-order conditions and the observed rate constants, k(obs.), were calculated from plots of $\log_{10} (D_t - D_\infty)$ against time, where D_t and D_∞ represent the optical densities at time t and infinite time respectively. Such plots were rectilinear over at least three half lives.

Bromination of thiophen in 15% aqueous acetic acid.

Specimen Experiment 2

$[Br_2]_{St}$ = 3.322×10^{-5} M [Thiophen] = 7.357×10^{-4} M

[LiBr] = 0.06 M $[LiClO_4]$ = 0.04 M

25° 290nm.

Time mins.	D_t	$D_t - D_\infty$	$2 + \log (D_t - D_\infty)$
0.00	0.671	0.654	1.816
1.50	0.444	0.427	1.630
3.00	0.316	0.299	1.476
4.50	0.221	0.204	1.310
6.00	0.159	0.142	1.152
7.50	0.115	0.098	0.991
9.00	0.085	0.068	0.830

k_2 = 3.37×10^2 l. mole^{-1} min.$^{-1}$

Figure 21 Bromination of thiophen in 15% aqueous acetic acid.

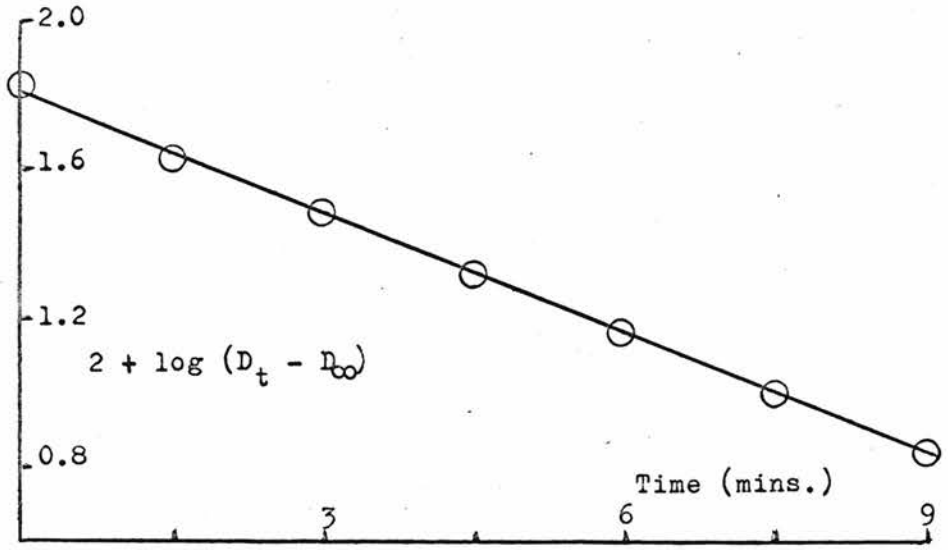
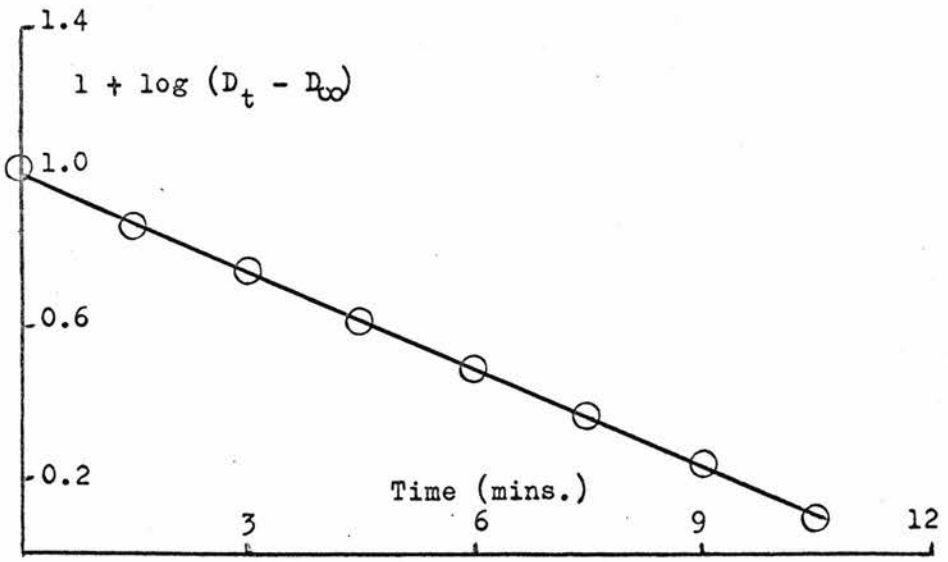


Figure 22 Bromination of mesitylene in 15% aqueous acetic acid.



Bromination of mesitylene in 15% aqueous acetic acid.

The kinetic procedure used for the bromination of mesitylene was identical to that of thiophen.

Specimen Experiment 3

$[Br_2]_{St}$ = 5.449×10^{-5}M [Mesitylene] = 1.197×10^{-2}M

[LiBr] = 0.06M $[LiClO_4]$ = 0.04M

25° 290nm.

Time mins.	D_t	$D_t - D_\infty$	$1 + \log (D_t - D_\infty)$
0.00	1.095	1.054	1.023
1.50	0.790	0.749	0.875
3.00	0.601	0.560	0.748
4.50	0.454	0.413	0.616
6.00	0.352	0.311	0.493
7.50	0.272	0.231	0.364
9.00	0.210	0.169	0.228
10.50	0.163	0.122	0.086

k_2 = 16.89 l. $mole^{-1}$ $min.^{-1}$

Figure 22

TABLE 40

Bromination of thiophen in 15% aqueous acetic acid at various temperatures.

Temp.	K l. mole^{-1}	k x 10^{-2} l. mole^{-1} min.$^{-1}$	1 + log $\frac{k}{60}$	10^3 $\frac{1}{T}$°$_A$
0.0°	190	4.90	1.935	3.660
6.9°	165	7.62	2.104	3.570
13.4°	146	12.2	2.310	3.490
18.4°	134	15.9	2.423	3.430
25.0°	120	24.5	2.611	3.354

Figure 23

The plot of 1 + log $\frac{k}{60}$ vs. $\frac{1}{T}$°$_A$ has gradient = $-\frac{E_A}{RT}$

= -2.195 x 10^3.

$\Delta H^{\ddagger}$ = 12.4 kcal. mole^{-1} and $\Delta S^{\ddagger}$ = -19.5 e.u. were calculated from $\Delta H^{\ddagger} = E_A - RT$ and

$\Delta S^{\ddagger} = \frac{\Delta H^{\ddagger} - \Delta G^{\ddagger}}{T}$ where $\Delta G^{\ddagger} = RT \ln \frac{k_r h}{kT}$

the symbols having the same meaning as previously.

TABLE 41

Bromination of mesitylene in 15% aqueous acetic acid at various temperatures.

Temp.	K l. mole^{-1}	k x 10^{-2} l. mole^{-1} min.$^{-1}$	1 + log $\frac{k}{60}$	$10^3 \frac{1}{T^oA}$
6.9°	165	0.29	0.682	3.570
13.4°	146	0.46	0.889	3.490
18.4°	134	0.70	1.068	3.430
32.6°	105	2.04	1.531	3.271

Figure 24

The plot of 1 + log $\frac{k}{60}$ vs. $\frac{1}{T^oA}$ has gradient = -2.845×10^3

The values of $\Delta H^{\neq}$ and $\Delta S^{\neq}$ were calculated as for thiophen.

Bromination of thiophen

The purpose of the following experiment was to ascertain whether the rate of appearance of products equalled the rate of disappearance of reactants.

An investigation of the rate of disappearance of absorption due to thiophen and tribromide ion with appearance of absorption due to 2-bromothiophen and tribromide at different wavelengths was carried out for the bromination of thiophen in 15% aqueous acetic acid.

Figure 23 Arrhenius plot for the bromination of thiophen.

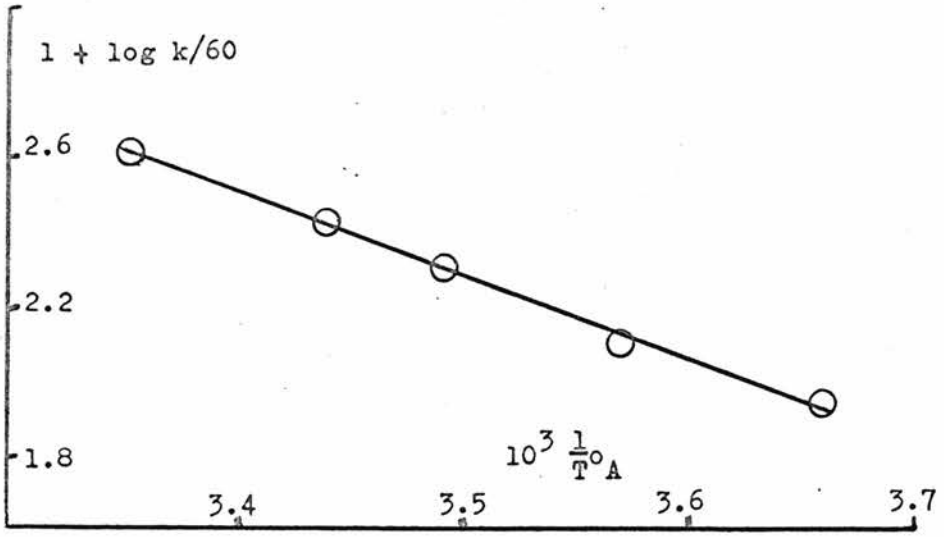
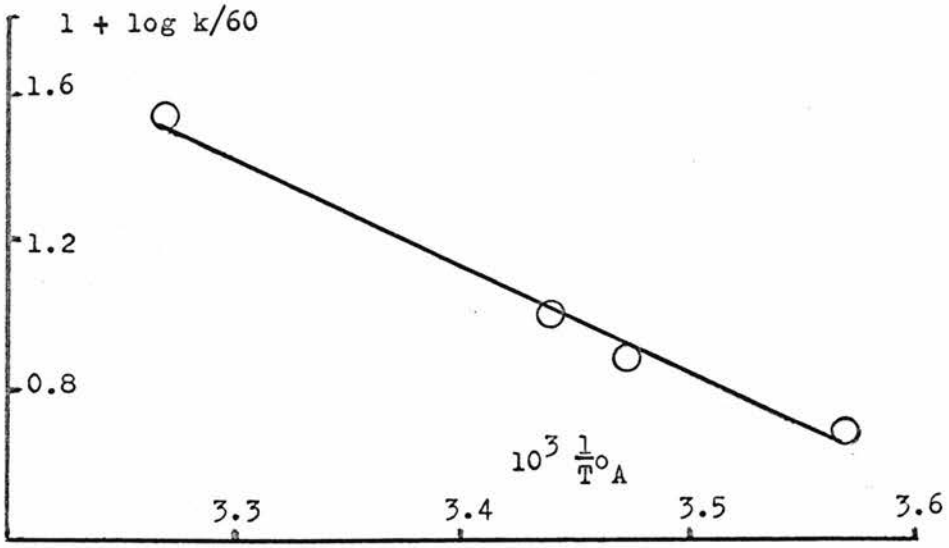


Figure 24 Arrhenius plot for the bromination of mesitylene.



The extinction coefficients of thiophen and 2-bromothiophen in 15% aqueous acetic acid were measured separately:-

	$\lambda_{nm.}$	ϵ
Thiophen	250	435
	267	300
2-Bromothiophen	250	3,330
	267	360

The reaction was followed on a Unicam SP 500 at 25° at 250nm. and 267nm. The change in optical density being plotted against time (Figures 25 and 26).

TABLE 42

Comparison of the rate of disappearance of reactants and appearance of products in the bromination of thiophen.

[Thiophen] = 3.051×10^{-4}M [LiBr] = 3.00×10^{-3}M

$[Br_2]$ = 3.12×10^{-4}M

Time mins.	$D_{267nm.}$	$D_{250nm.}$
3.0	1.82	1.21
4.5	1.44	1.16
5.8	1.18	1.12
8.3	0.87	1.09
11.5	0.64	1.05

Figures 25 and 26

Figure 25 Variation in optical density with time at 267nm. for the bromination of thiophen.

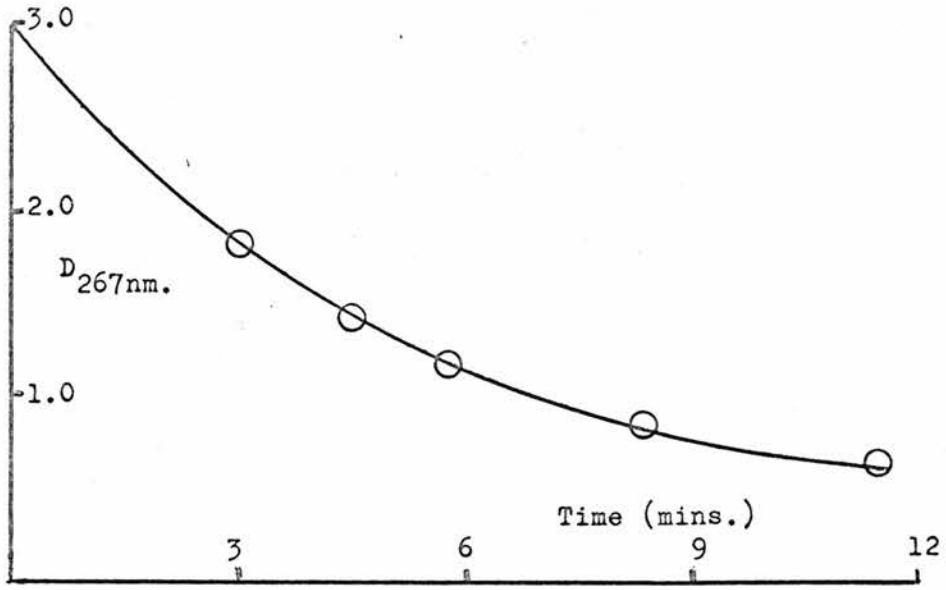
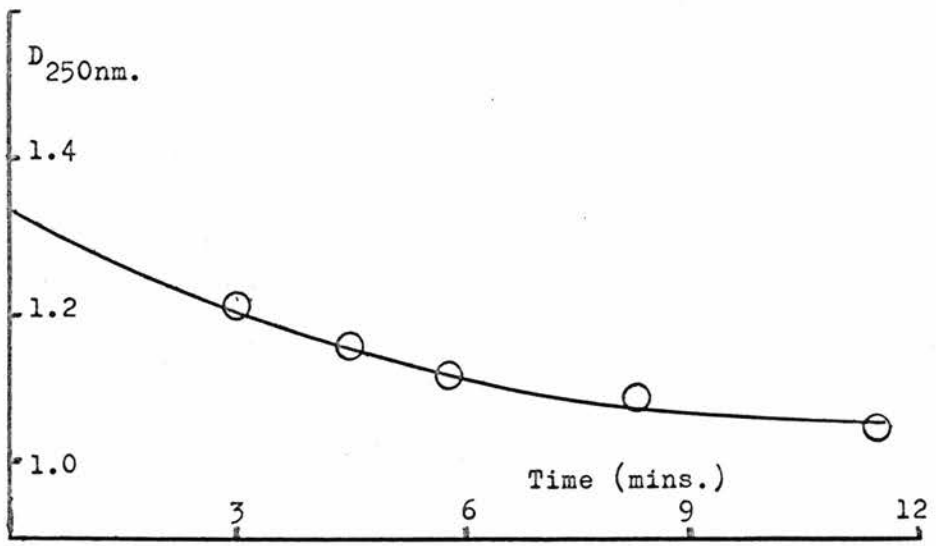


Figure 26 Variation in optical density with time at 250nm. for the bromination of thiophen.



Final O.D. due to 2-bromothiophen at 250nm.

$$= 3,330 \times 3.05 \times 10^{-4} = 1.0$$

Initial O.D. due to thiophen at 250nm.

$$= 435 \times 3.05 \times 10^{-4} = 0.13$$

Final O.D. due to 2-bromothiophen at 267nm.

$$= 360 \times 3.05 \times 10^{-4} = 0.11$$

But initial O.D. at 267nm. (estimated from Figure 26) = 3.00

and initial O.D. due to thiophen at 267nm.

$$= 300 \times 3.05 \times 10^{-4} = 0.10$$

$\therefore$ initial O.D. due to tribromide = 3.00 - 0.10 = 2.90

At half reaction $O.D._{267nm.} = O.D._{Br_3^-} + O.D._{Th} + O.D._{BrTh}$

$$= 1.45 + 0.05 + 0.05 = 1.55$$

estimated from Figure 26 to occur at 3.9 mins.

Now initial O.D. at 250nm. (estimated from Figure 25) = 1.34

and initial O.D. due to tribromide = $1.34 - O.D._{Th} = 1.21$

At half reaction $O.D._{250nm.} = O.D._{Br_3^-} + O.D._{Th} + O.D._{BrTh}$

$$= 0.61 + 0.07 + 0.5 = 1.18$$

The optical density at 3.9 mins. at 250nm. is in fact 1.18 (from Figure 25).

Bromination of 2,5-dideuteriothiophen at 25° in 15% aqueous acetic acid.

The kinetic method was identical to that used for thiophen.

Specimen Experiment 4

$[Br_2]_{St}$ ca. 5×10^{-5}M [LiBr] = 0.10M

[2,5-dideuteriothiophen] = 9.624×10^{-4}M $[LiClO_4]$ = 0.00M

25° 290nm.

Time mins.	D_t	$D_t - D_\infty$	$2 + \log (D_t - D_\infty)$
0.00	0.508	0.445	1.658
1.50	0.420	0.367	1.565
3.00	0.347	0.294	1.468
4.50	0.289	0.236	1.373
6.00	0.247	0.194	1.288
7.50	0.208	0.155	1.190
9.00	0.175	0.122	1.086
10.5	0.149	0.096	0.982
12.0	0.135	0.082	0.914

$k_2 = 1.47 \times 10^2$ l. mole^{-1} min.$^{-1}$

Figure 27

Figure 27 Bromination of 2,5-dideuteriothiophen in 15% aqueous acetic acid.

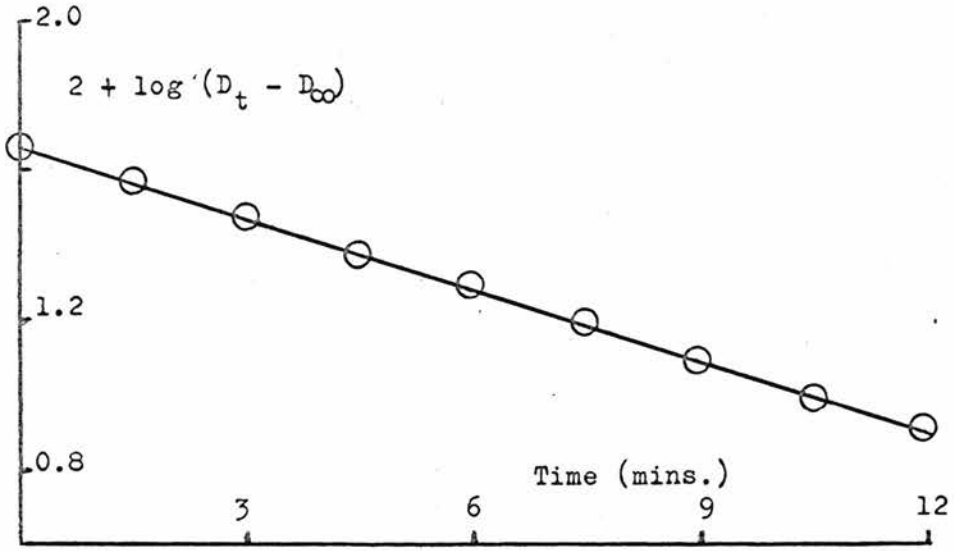
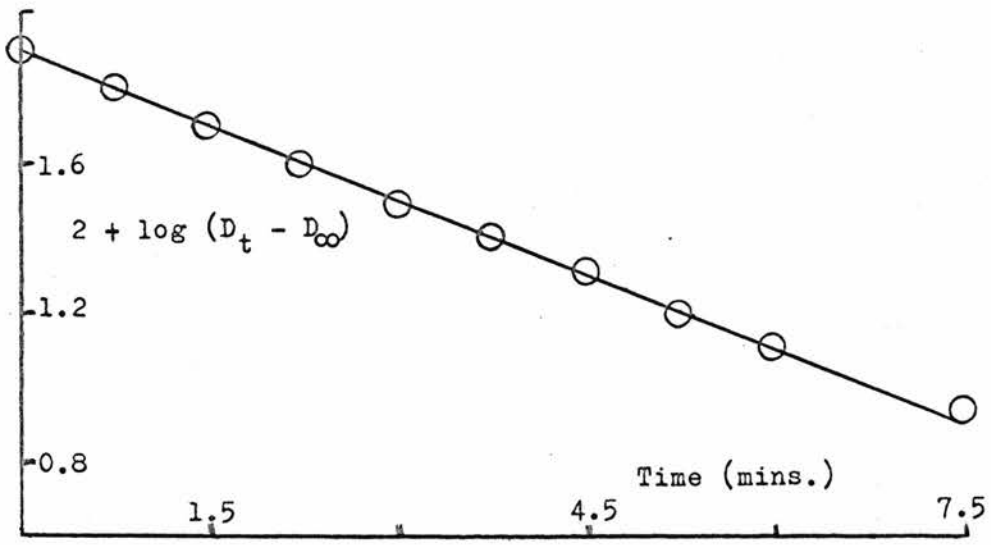


Figure 28 Bromination of 2-bromothiophen in 15% aqueous acetic acid.



Bromination of 2-bromothiophen and 2-bromo-5-deuteriothiophen at 25° in 15% aqueous acetic acid.

The kinetic method was identical to that used for thiophen.

Specimen Experiment 5

$[Br_2]_{St}$ ca. 1×10^{-4}M [2-bromothiophen] = 1.934×10^{-2}M

[LiBr] = 0.10M $[LiClO_4]$ = 0.00M

25° 345nm.

Time mins.	D_t	$D_t - D_\infty$	$2 + \log (D_t - D_\infty)$
0.00	0.768	0.763	1.883
0.75	0.616	0.611	1.786
1.50	0.490	0.485	1.686
2.25	0.390	0.385	1.586
3.00	0.317	0.312	1.494
3.75	0.257	0.252	1.401
4.50	0.208	0.203	1.308
5.25	0.163	0.158	1.199
6.00	0.135	0.130	1.114
7.50	0.090	0.085	0.929

k_2 = 15.10 l. $mole^{-1}$ $min.^{-1}$

Figure 28

Bromination of 2-chlorothiophen at 25° in 15% aqueous acetic acid.

Two methods for following the rate of reaction were used.

1) The method was similar to that used for thiophen i.e. following the rate of disappearance of absorption due to tri--bromide ion by U.V. The 2-chlorothiophen was in at least ten fold excess over tribromide giving pseudo first-order conditions.

Specimen Experiment 6

$[Br_2]_{St}$ ca. 1×10^{-4}M [2-chlorothiophen] = 2.004×10^{-2}M

[LiBr] = 0.10M $[LiClO_4]$ = 0.00M

25° 345nm.

Time mins.	D_t	$D_t - D_\infty$	$2 + \log (D_t - D_\infty)$
0.00	0.787	0.777	1.890
0.75	0.618	0.608	1.784
1.50	0.489	0.479	1.680
2.25	0.389	0.379	1.579
3.00	0.307	0.297	1.473
4.50	0.192	0.182	1.260
6.00	0.129	0.119	1.076
7.50	0.092	0.082	0.914

k_2 = 15.94 l. mole^{-1} min.$^{-1}$

Figure 29

Figure 29 Bromination of 2-chlorothiophen in 15% aqueous acetic acid under pseudo first-order conditions.

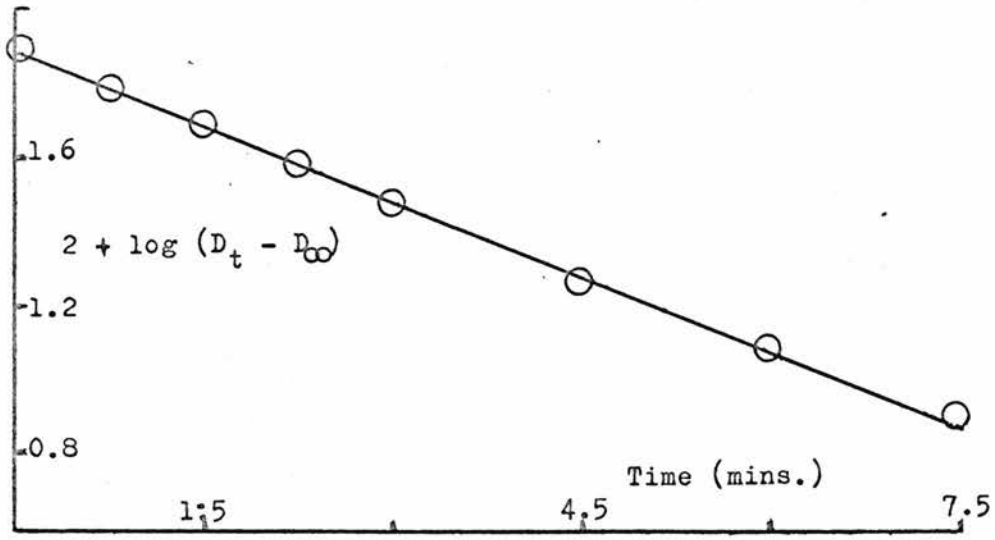
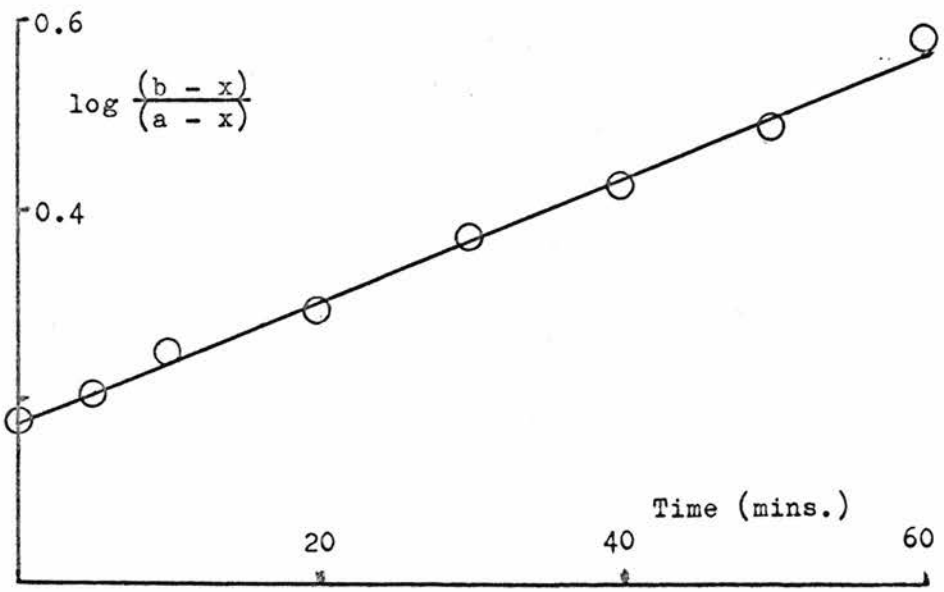


Figure 30 Bromination of 2-chlorothiophen in 15% aqueous acetic acid under second order conditions.



2) The reaction was also followed under second order conditions by titration. The unreacted bromine, present as free bromine and tribromide, was titrated by removing aliquots of the reaction mixture by pipette at timed intervals and running into acidified potassium iodide solution. The liberated iodine was titrated with standard sodium thiosulphate solution using starch as indicator.

Specimen Experiment 7

a = [2-chlorothiophen] = 2.061×10^{-3}M [LiBr] = 0.10M

b = $[Br_2]_{St}$ = 3.01×10^{-3}M $[LiClO_4]$ = 0.00M

25°

Time min.	mls. of $\frac{N}{100}$ thio.	$(b - x) \times 10^3$ M	$(a - x) \times 10^3$ M	$\log \frac{(b - x)}{(a - x)}$
0.0	6.02	3.01	2.06	0.163
5.1	5.05	2.53	1.59	0.202
10.0	4.49	2.25	1.31	0.235
19.8	3.86	1.93	0.99	0.289
30.8	3.34	1.67	0.73	0.359
40.0	3.03	1.52	0.58	0.420
50.2	2.78	1.39	0.45	0.489
60.0	2.58	1.29	0.35	0.565

k_2 = 16.17 l. $mole^{-1}$ $min.^{-1}$

Figure 30

Bromination of 2-methylthiophen at 25° in 15% aqueous acetic acid.

The reactivity of 2-methylthiophen is such that it required working in more dilute solutions in order to reduce the rate to a value that could be followed.

1) The first method adopted was to work under second order conditions using cells with 100mm. path length. The bromine/bromide solution was placed in the cell and allowed to thermostat. These dilute solutions were found to react with minute traces of impurity present in the solvent. The optical density of the tribromide ion was therefore checked before the start of each run. The run was commenced by adding a concentrated solution of 2-methylthiophen in 15% aqueous acetic acid by micropipette (0.1ml.).

The products of the reaction absorb in the same region as the tribromide ion. The following procedure was therefore adopted:-

The reaction can be represented as

$$Br_2 + 2\text{-MeTh} \longrightarrow \text{MeThBr} + HBr$$

at time = 0, b moles + a moles $\longrightarrow$ 0

at time = t_1, (b - x) moles + (a - x) moles $\longrightarrow$ x moles

$\therefore$ Optical density at time t_1

$$= D_1 = \epsilon_1(b - x)d + \epsilon_2 xd$$

assuming no absorption due to 2-methylthiophen, where

b = initial concentration of bromine

a = initial concentration of 2-methylthiophen

x = concentration of products at time t_1

ϵ_1 = extinction coefficient of bromine

ϵ_2 = extinction coefficient of 2-methylthiophen

d = cell path length

The disappearance of absorption due to tribromide was followed and consequently the apparent reaction between tribromide and 2-methylthiophen observed.

Specimen Experiment 8

$[Br_3^-]$ = 3.578×10^{-6}M [LiBr] = 0.10M

[2-methylthiophen] = 8.584×10^{-6}M $[LiClO_4]$ = 0.00M

25° 290nm.

Time mins.	D_t	$10^6(b - x)$ M	$10^6(a - x)$ M	$\log \frac{(b - x)}{(a - x)}$
0.0	0.764	8.584	3.758	0.380
1.0	0.543	7.026	2.020	0.541
2.0	0.420	6.155	1.149	0.729
3.0	0.362	5.744	0.738	0.891
4.0	0.322	5.461	0.455	1.079
5.0	0.299	5.298	0.292	1.259

ϵBr_3^- = 21,350 ϵproducts = 7,230

$k_2 = 8.00 \times 10^4$ l. mole^{-1} min.$^{-1}$

Figure 31

Figure 31 Bromination of 2-methylthiophen in 15% aqueous acetic acid under second order conditions.

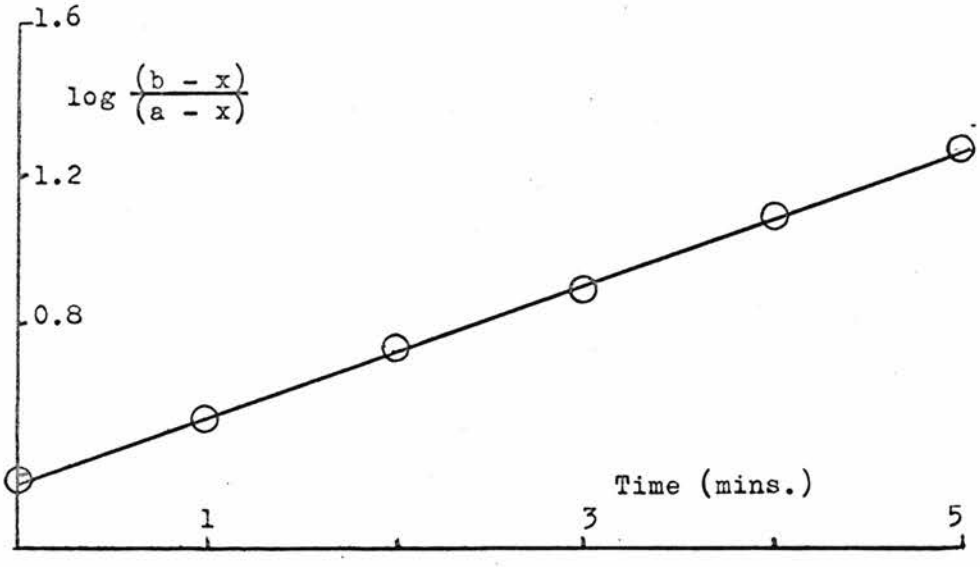
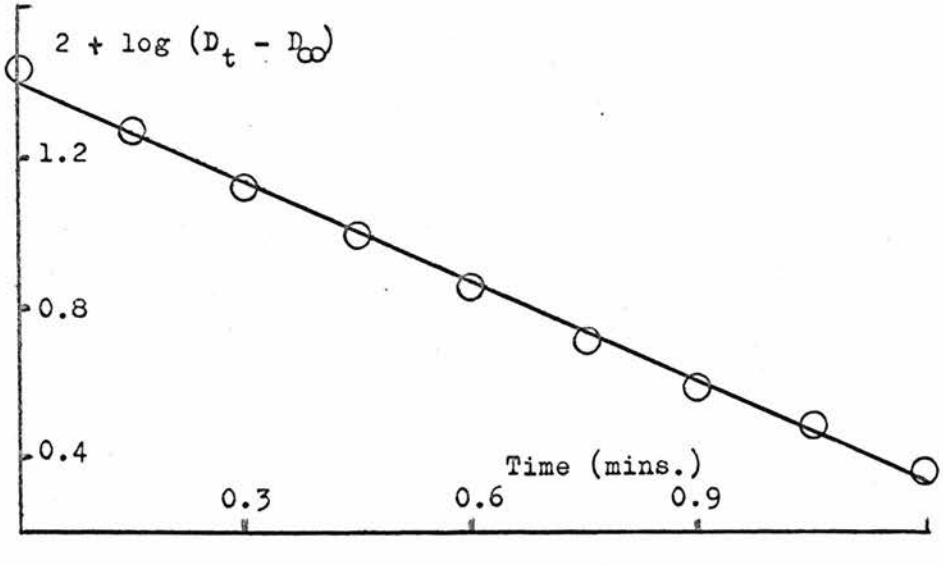


Figure 32 Bromination of 2-methylthiophen in 15% aqueous acetic acid under pseudo first-order conditions.



2) The runs were performed under pseudo first-order conditions. The experimental procedure being the same as in the above method, but with the 2-methylthiophen being in at least ten fold excess over bromine.

Specimen Experiment 9

$[Br_2]_{St}$ ca. 1.25×10^{-6} M [LiBr] = 0.10M

[2-methylthiophen] = 2.595×10^{-5} M $[LiClO_4]$ = 0.00M

25° 267nm.

Time mins.	D_t	$D_t - D_\infty$	$2 + \log (D_t - D_\infty)$
0.00	0.577	0.266	1.425
0.15	0.499	0.188	1.274
0.30	0.443	0.132	1.121
0.45	0.408	0.097	0.987
0.60	0.384	0.073	0.863
0.75	0.362	0.051	0.708
0.90	0.350	0.039	0.591
1.05	0.342	0.031	0.491
1.20	0.334	0.023	0.362

$k_2 = 79.45 \times 10^3$ l. mole^{-1} min.$^{-1}$

Figure 32

Bromination of 2-ethylthiophen at 25° in 15% aqueous acetic acid.

The runs were performed under pseudo first-order conditions by the same method as that used for 2-methylthiophen.

Specimen Experiment 10

$[Br_2]_{St}$ = 1.45×10^{-6}M [LiBr] = 0.10M

[2-ethylthiophen] = 2.558×10^{-5}M $[LiClO_4]$ = 0.00M

25° 267nm.

Time mins.	D_t	$D_t - D_\infty$	$2 + \log (D_t - D_\infty)$
0.00	0.648	0.320	1.505
0.15	0.560	0.232	1.366
0.30	0.501	0.173	1.238
0.45	0.450	0.122	1.086
0.60	0.413	0.085	0.929
0.75	0.387	0.059	0.771
0.90	0.370	0.042	0.623
1.05	0.359	0.031	0.491
1.20	0.351	0.023	0.362

k_2 = 87.13×10^3 l. mole^{-1} min.$^{-1}$

Figure 33

Figure 33 Bromination of 2-ethylthiophen in 15% aqueous acetic acid.

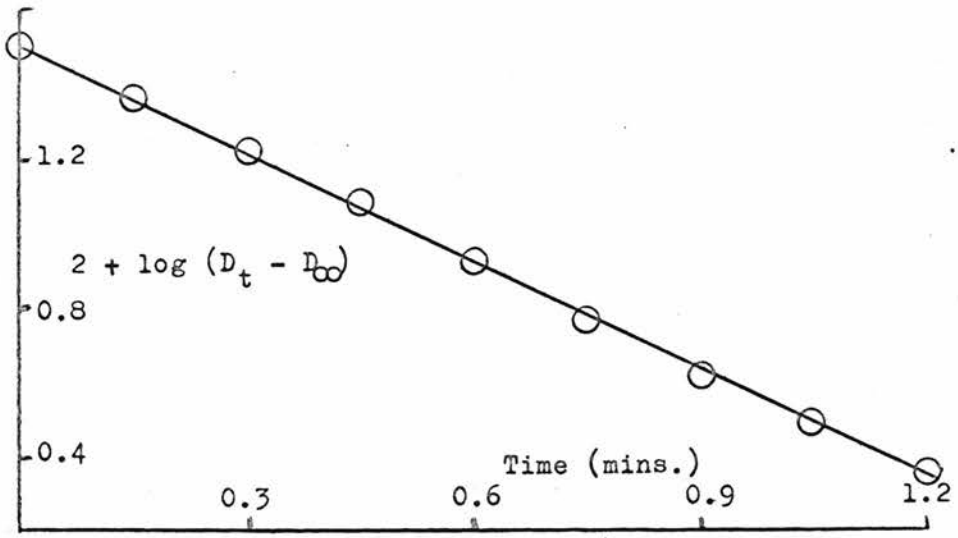
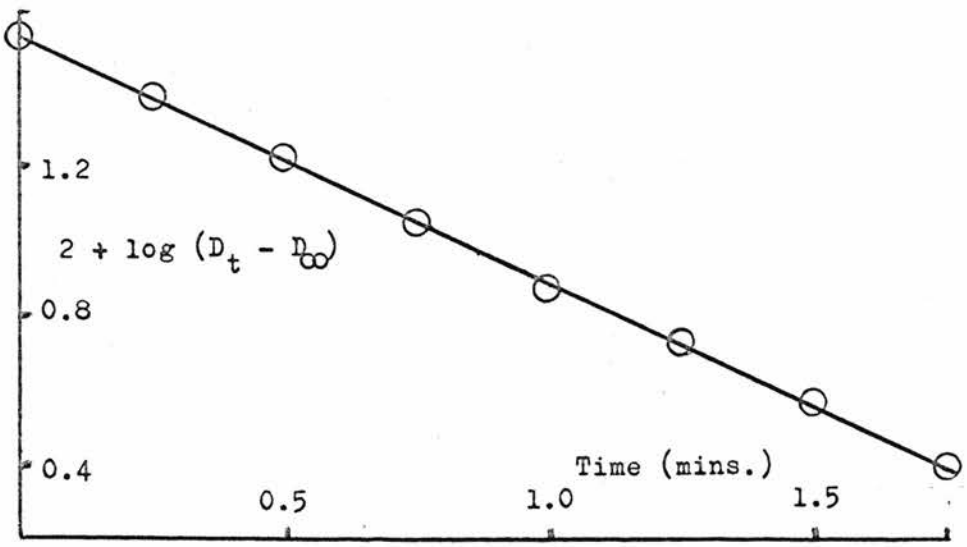


Figure 34 Bromination of 2-tert-butylthiophen in 15% aqueous acetic acid.



Bromination of 2-tert-butylthiophen at 25° in 15% aqueous acetic acid.

The runs were performed under both pseudo first-order and second order conditions by the same methods as used for 2-methylthiophen.

Specimen Experiment 11

$[Br_2]_{St}$ = 1 x 10^{-6}M [LiBr] = 0.08M

[2-tert-butylthiophen] = 2.328 x 10^{-5}M $[LiClO_4]$ = 0.02M

25° 267nm.

Time mins.	D_t	$D_t - D_\infty$	2 + log $(D_t - D_\infty)$
0.00	0.462	0.341	1.533
0.25	0.353	0.232	1.366
0.50	0.283	0.162	1.210
0.75	0.330	0.109	1.037
1.00	0.194	0.073	0.863
1.25	0.173	0.052	0.716
1.50	0.157	0.036	0.556
1.75	0.145	0.024	0.380

k_2 = 65.80 x 10^3 l. $mole^{-1}$ $min.^{-1}$

Figure 34

Bromination of 2-phenylthiophen in 15% aqueous acetic acid.

The runs were carried out under pseudo first-order conditions using 10mm. path length cells. 2-Phenylthiophen absorbs strongly in the same ultra violet region of the spectrum as the tribromide ion. It was therefore necessary to move to another region of the spectrum where the absorption of 2-phenylthiophen did not interfere. The absorption of the tribromide ion was also reduced making it necessary to work at higher concentrations. The subsequent increase in rate made it impossible to follow the reaction at 25° with the apparatus available. The reaction was followed at 8°, 11.8° and 16.5° and the value at 25° obtained by extrapolation.

Specimen Experiment 12

$[Br_2]_{St}$ ca. 5×10^{-5}M [LiBr] = 0.10M

[2-phenylthiophen] = 5.120×10^{-4}M $[LiClO_4]$ = 0.00M

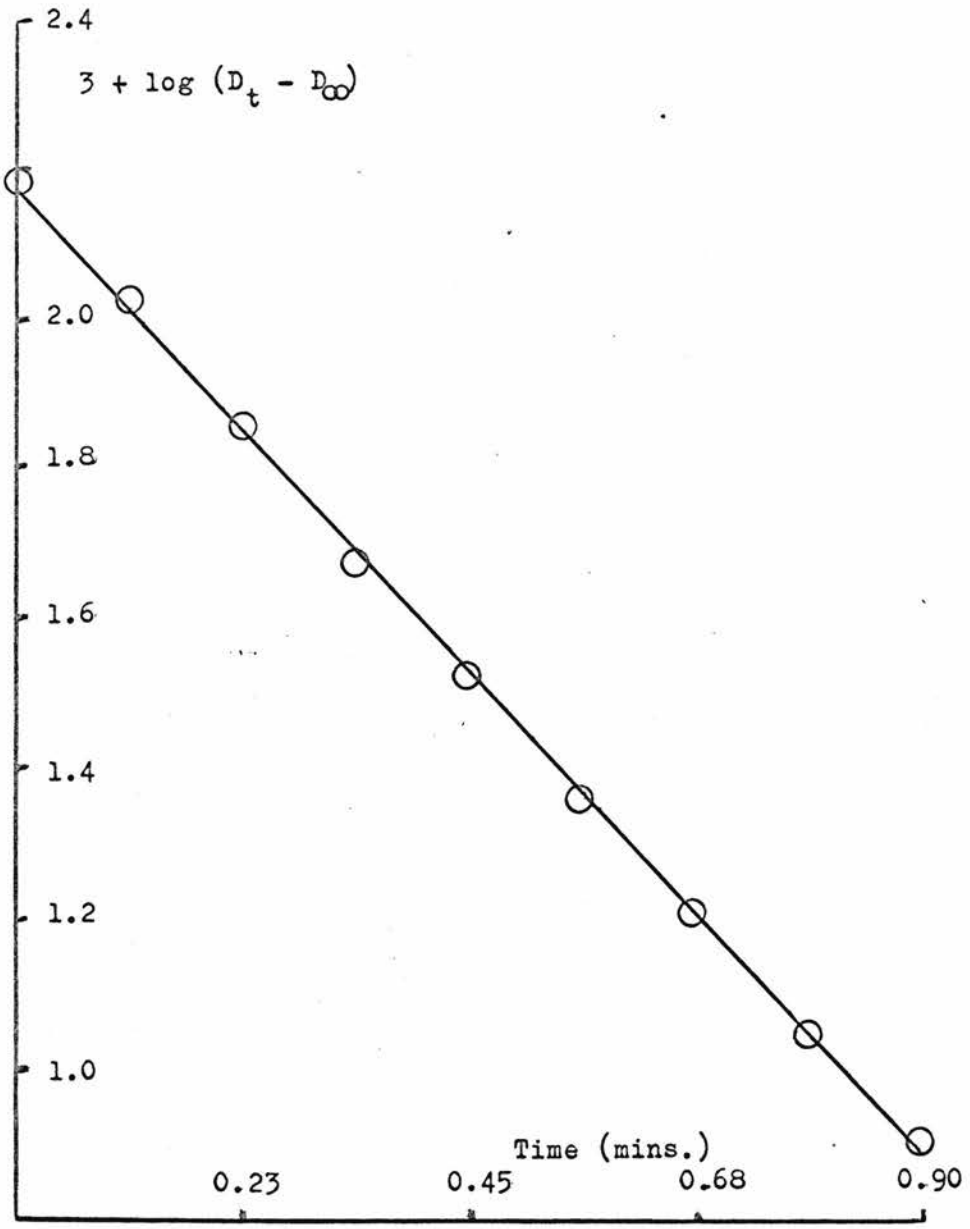
8^{o} 350nm.

Time mins.	D_t	$D_t - D_\infty$	$3 + \log (D_t - D_\infty)$
0.00	0.271	0.162	2.210
0.11	0.214	0.105	2.021
0.23	0.180	0.071	1.851
0.34	0.156	0.047	1.672
0.45	0.142	0.033	1.519
0.57	0.132	0.023	1.362
0.68	0.125	0.016	1.204
0.79	0.120	0.011	1.041
0.90	0.117	0.008	0.903

$k_2 = 65.72 \times 10^2$ l. mole^{-1} min.$^{-1}$

Figure 35

Figure 35 Bromination of 2-phenylthiophen in 15% aqueous acetic acid.



Bromination of thiophen-2-carboxylic acid and its ethyl ester in 15% aqueous acetic acid.

The reaction was followed by titration of the unreacted bromine with standard sodium thiosulphate. The thiophen was in excess giving pseudo first-order conditions but the results did not fit a first-order plot suggesting that third order terms are present in the kinetic equation. The data was analysed by the procedure given by Keefer and Andrews[92, 93]. The kinetic equation being:-

$$\text{rate} = \frac{k}{(1 + K[Br^-])}[ThX][Br_2]_{St} + \frac{k'}{(1 + K[Br^-])^2}[ThX][Br_2]^2_{St}$$

where [ThX] = concentration of the thiophen in moles/litre

and $[Br_2]_{St}$ = stoicheiometric concentration of bromine in moles/litre.

The rate of various values of $[Br_2]_{St}$ was taken as the slope of the tangent to the curve representing the variation of $[Br_2]_{St}$ with time. A plot of rate / $[ThX][Br_2]_{St}$ versus $[Br_2]_{St}$ has a slope of $k'/(1 + K[Br^-])^2$ and an intercept of $k/(1 + K[Br^-])$

Specimen Experiment 13

$[Br_2]_{St} = 2.99 \times 10^{-1}M$ $[LiBr] = 0.10M$

$[ThCOOH] = 9.97 \times 10^{-3}M$ $[LiClO_4] = 0.00M$

25°

$[Br_2]^a 10^3$	$10^6 \times$ Rate	$[Br_2][ThCOOH]10^3$	$\frac{10^3 \times \text{Rate}}{[Br_2][ThCOOH]}$
7.95	3.55	2.38	1.49
6.24	2.39	1.87	1.28
5.08	1.69	1.52	1.11
4.26	1.31	1.27	1.03
3.00	0.81	0.90	0.90

[a]Stoicheiometric concentration

Figures 36 and 37

Figure 36 Decrease in bromine concentration with time for the bromination of thiophen-2-carboxylic acid.

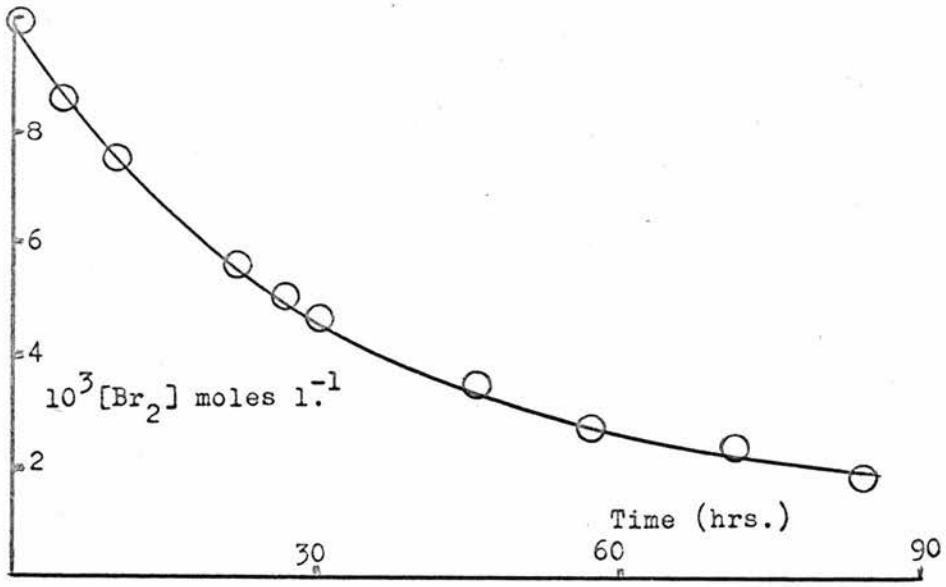
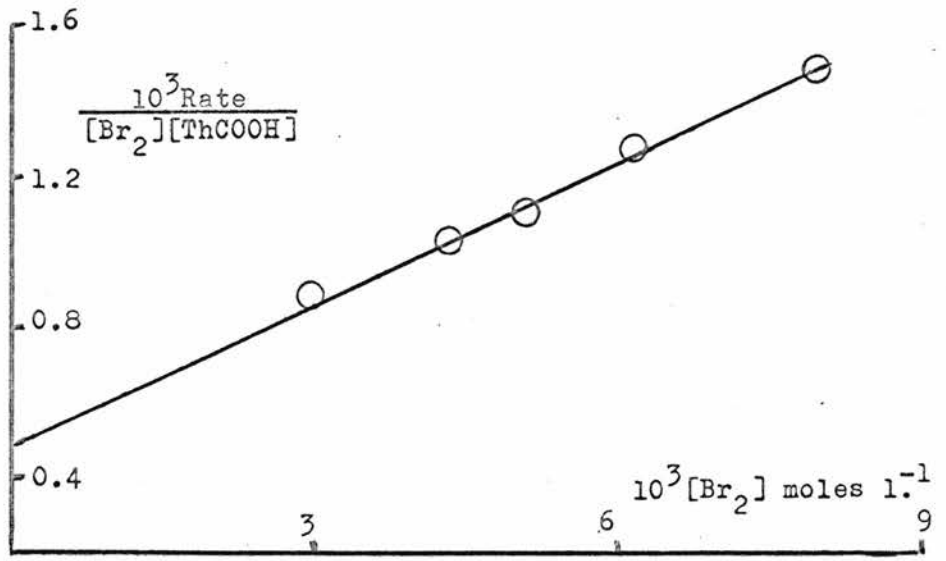


Figure 37 Bromination of thiophen-2-carboxylic acid in 15% aqueous acetic acid.



4. BROMINATION OF 2,3-BENZOTHIOPHEN AT 25° IN 15% AQUEOUS ACETIC ACID.

The bromination of 2,3-benzothiophen in 15% aqueous acetic acid was more complex than the bromination of other thiophens

On mixing solutions of 2,3-benzothiophen and tribromide ion in aqueous acetic acid and measuring the U.V. spectrum it was found that the resulting spectrum was not the sum of the two component spectra. There was an initial sharp fall off in absorption followed by a slower decrease in the tribromide region of the spectrum.

The rate of bromination was followed at 25° using 10mm. cells. The bromine / bromide solution (3ml.) was allowed to thermostat and the run commenced by addition of a small volume (0.1ml.) of benzothiophen solution by micropipette and shaking.

Specimen Experiment 14

$[Br_2]_{St}$ ca. 1×10^{-4}M [LiBr] = 0.10M

[BzTh] = 1.919×10^{-3}M $[LiClO_4]$ = 0.00M

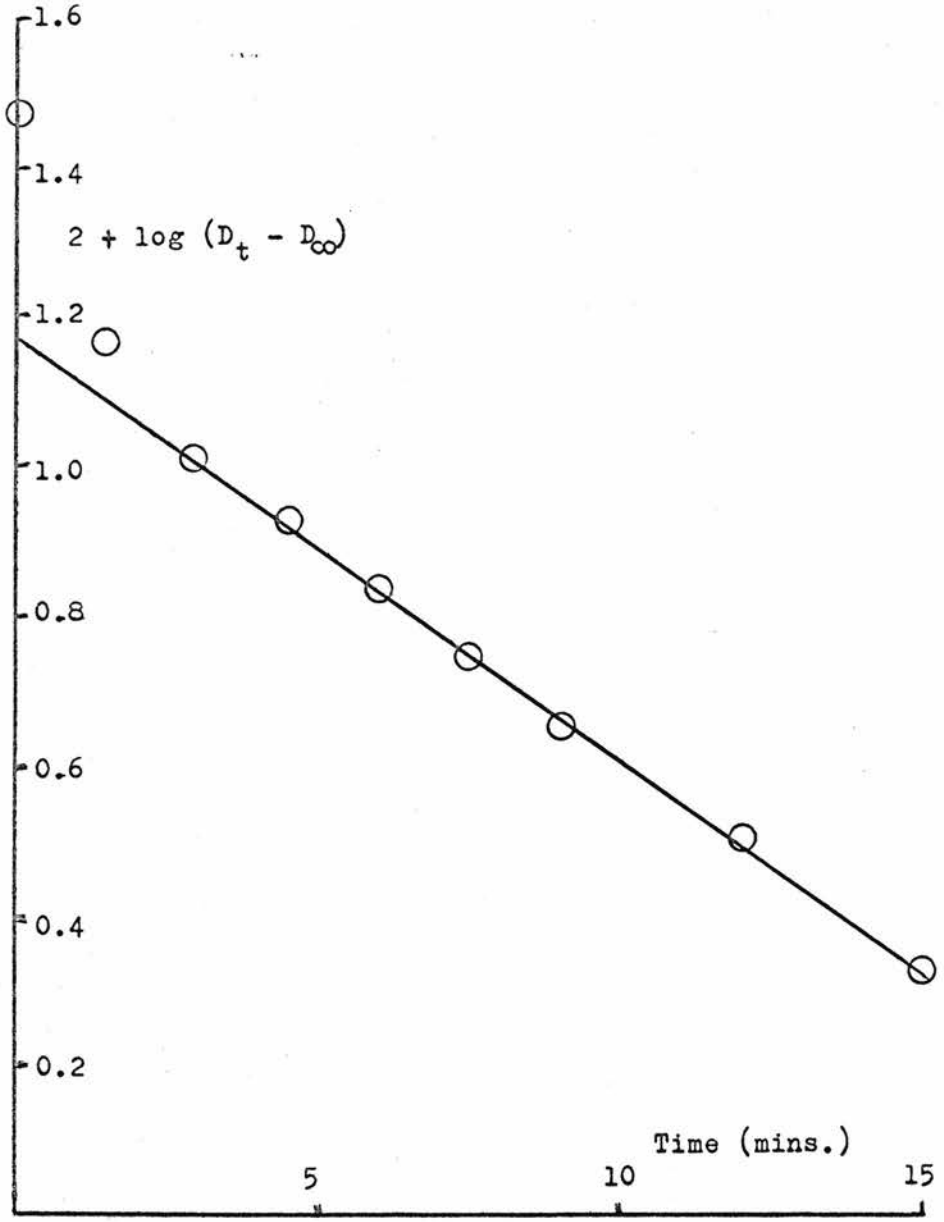
25° 325nm.

Time mins.	D_t	$D_t - D_\infty$	$2 + \log (D_t - D_\infty)$
0.0	0.299	0.297	1.473
1.5	0.147	0.145	1.162
3.0	0.106	0.104	1.017
4.5	0.087	0.085	0.929
6.0	0.071	0.069	0.839
7.5	0.058	0.056	0.748
9.0	0.047	0.045	0.653
12.0	0.034	0.032	0.505
15.0	0.023	0.021	0.322

Figure 38

The initial optical density of the first-order reaction was obtained by extrapolation of the first-order plot back to zero time.

Figure 38 Bromination of 2,3-benzothiophen in 15% aqueous acetic acid.



It was possible, knowing the value of K_1 the equilibrium constant for tribromide ion formation = 120 and the extinction coefficient of the tribromide ion = 3,580, to calculate an approximate value for K_2, the equilibrium constant for complex formation (assuming 1:1 formation)

e.g. initial absorption due to Br_3^- = 0.860

= 2.40×10^{-4} moles $l.^{-1}$

fall in absorption due to complex formation = 0.242

= 6.75×10^{-5} moles $l.^{-1}$

$$K_1 = \frac{[Br_3^-]}{[Br_2][Br^-]} = 120 = \frac{[Br_3^-]}{[Br_2][0.1]}$$

$$\therefore [Br_2] = [Br_3^-]/12$$

$$K_2 = \frac{[C]}{[Br_2][BzTh]} = \frac{[C] \times 12}{[Br_3^-][BzTh]}$$

$$= \frac{(6 \times 10^{-5}) \times 12}{(1.73 \times 10^{-4}) \times (1 \times 10^{-3})} = \frac{6 \times 10^{-4}}{1.73 \times 10^{-7}}$$

ca. 3×10^3 $mole^{-1}$ l.

5. CHLORINATION OF 2- SUBSTITUTED THIOPHENS

The rate of chlorination of a series of 2- substituted thiophens at 25° in anhydrous acetic acid was followed by measuring the decrease in the U.V. absorption of chlorine with time.

A solution of chlorine in anhydrous acetic acid was prepared by bubbling chlorine through the anhydrous acid. The concentration of chlorine being calculated by running an aliquot into a solution of excess potassium iodide and titrating the liberated iodine with standard sodium thiosulphate using starch as indicator.

A solution of the appropriate concentration of chlorine in acetic acid (30mls.) was placed in a 100mm. cell and allowed to thermostat. The run was commenced by adding a small volume of the thiophen (0.2ml.) in acetic acid to the cell, shaking and measuring the fall off in optical density at a particular wavelength (350 - 380nm. depending on the thiophen being chlorinated).

The volatile nature of chlorine meant that precautions had to be taken to prevent loss of chlorine from the acetic acid solutions. All flasks and cells containing solutions were kept tightly stoppered. The stoppers being removed for the minimum length of time when transferring solutions or commencing runs. The chlorine concentrations were checked

regularly by titration and immediately before commencing a run from a knowledge of the extinction coefficient[98] and by measuring the optical density of the solution.

Chlorination of thiophen in anhydrous acetic acid at 25°.

Specimen Experiment 15

$[Cl_2]$ = 5.880×10^{-4}M [Thiophen] = 8.130×10^{-4}M

25° 325nm.

Time secs.	D_t	$10^4(a - x)$ M	$10^4(b - x)$ M	$\log \frac{(b - x)}{(a - x)}$
0.00	0.441	5.880	8.130	0.141
11.25	0.374	4.706	6.956	0.170
22.50	0.312	3.880	6.130	0.199
33.75	0.266	3.266	5.516	0.228
45.00	0.231	2.800	5.050	0.256
56.25	0.198	2.360	4.610	0.291
67.50	0.173	2.026	4.276	0.325
78.75	0.149	1.706	3.956	0.365
90.00	0.136	1.533	3.783	0.392
101.25	0.120	1.320	3.570	0.432
112.50	0·110	1.186	3.436	0.462

$k = 1.76 \times 10^3$ l. mole^{-1} min.$^{-1}$

Figure 39

Figure 39 Chlorination of thiophen in anhydrous acetic acid.

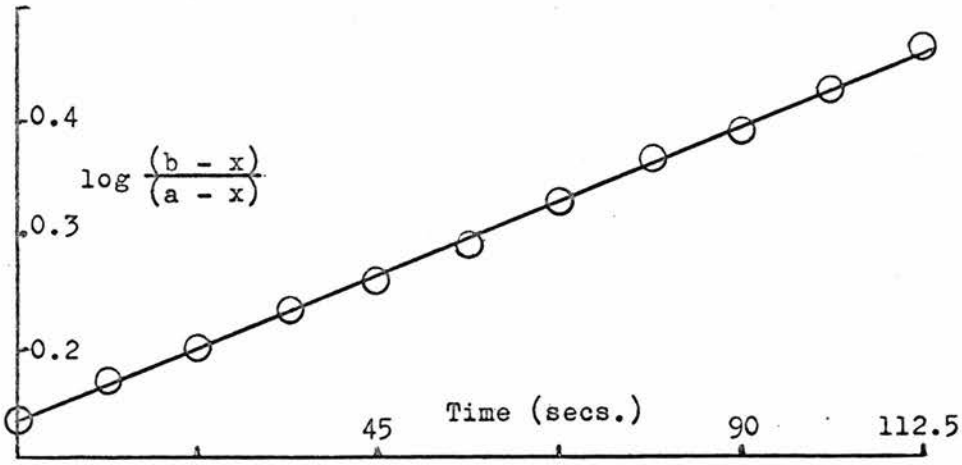
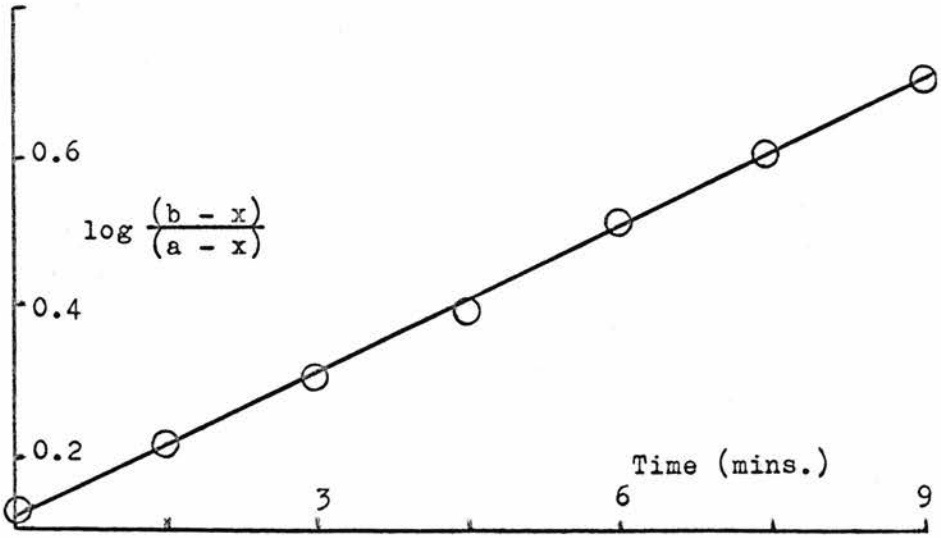


Figure 40 Chlorination of 2-bromothiophen in anhydrous acetic acid.



Chlorination of 2-bromothiophen in anhydrous acetic acid at 25°

Specimen Experiment 16

$[Cl_2]$ = 1.178×10^{-3}M [2-bromothiophen] = 1.558×10^{-3}M

25° 350nm.

Time mins.	D_t	$10^3(a - x)$ M	$10^3(b - x)$ M	$\log \frac{(b - x)}{(a - x)}$
0.00	0.595	1.178	1.558	0.122
0.75	0.417	0.796	1.176	0.169
1.50	0.319	0.601	0.981	0.213
2.25	0.255	0.475	0.855	0.255
3.00	0.204	0.374	0.754	0.305
3.75	0.165	0.297	0.677	0.358
4.50	0.143	0.253	0.633	0.398
5.25	0.119	0.205	0.585	0.455
6.00	0.099	0.166	0.546	0.517
6.75	0.088	0.144	0.524	0.561
7.50	0.079	0.126	0.506	0.604
8.25	0.069	0.106	0.486	0.661
9.00	0.062	0.093	0.473	0.706

$k = 3.95 \times 10^2$ l. mole^{-1} min.$^{-1}$

Figure 40

Chlorination of 2-chlorothiophen in anhydrous acetic acid at 25°.

Specimen Experiment 17

$[Cl_2]$ = 1.137×10^{-3}M [2-chlorothiophen] = 1.652×10^{-3}M

25° 350nm.

Time mins.	D_t	$10^3(a - x)$ M	$10^3(b - x)$ M	$\log \frac{(b - x)}{(a - x)}$
0.00	0.580	1.137	1.652	0.162
0.75	0.418	0.790	1.305	0.218
1.50	0.321	0.605	1.120	0.267
2.25	0.259	0.483	0.998	0.315
3.00	0.209	0.384	0.899	0.369
3.75	0.173	0.312	0.827	0.423
4.50	0.147	0.261	0.776	0.473
5.25	0.124	0.215	0.730	0.531
6.00	0.109	0.186	0.701	0.576
6.75	0.093	0.154	0.669	0.638
7.50	0.087	0.142	0.657	0.665

$k = 3.10 \times 10^2$ l. mole^{-1} min.$^{-1}$

Figure 41

Figure 41 Chlorination of 2-chlorothiophen in anhydrous acetic acid.

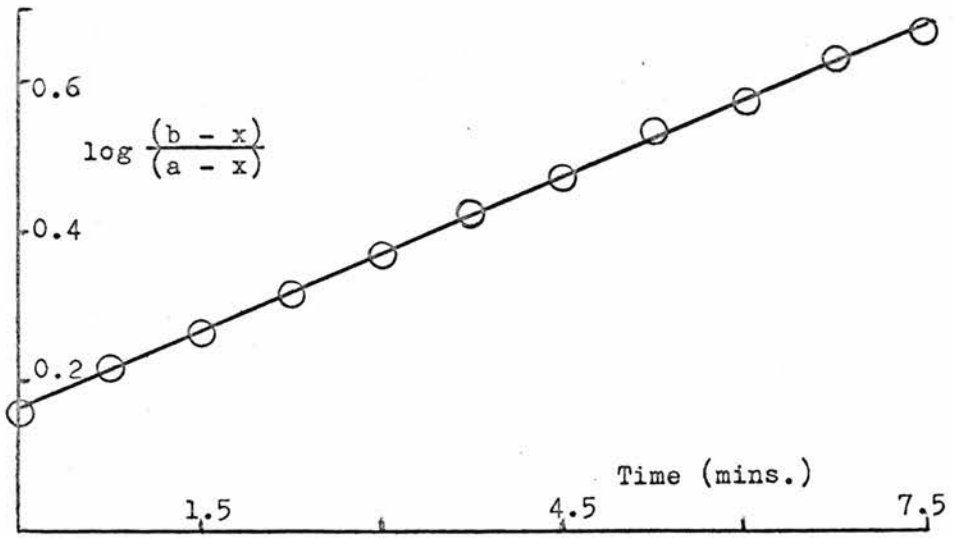
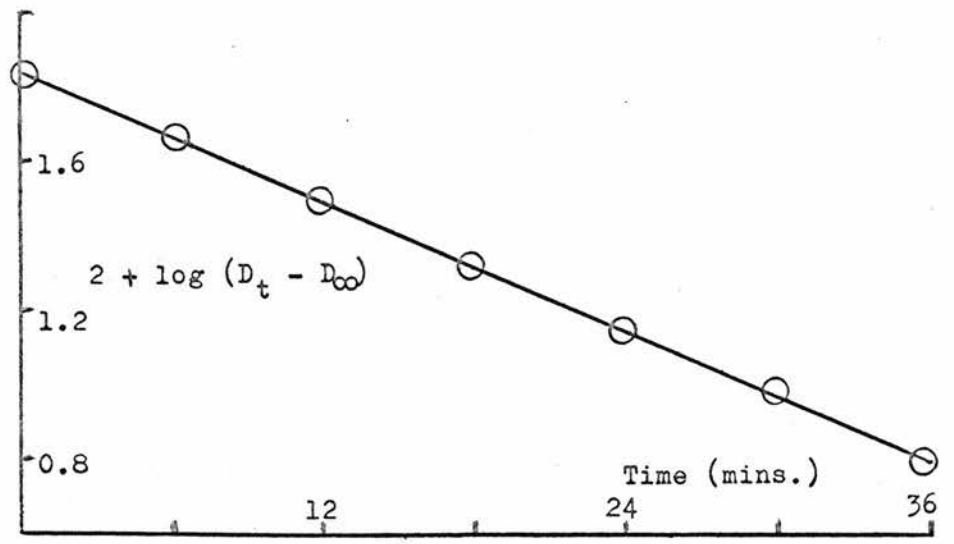


Figure 42 Chlorination of the ethyl ester of thiophen-2-carboxylic acid in anhydrous acetic acid.



Chlorination of the ethyl ester of thiophen-2-carboxylic acid in anhydrous acetic acid at 25°.

Specimen Experiment 18

The experiment was performed under pseudo first-order conditions with the thiophen present in ten fold excess using 10mm. cells.

$[Cl_2]$ = 5.271×10^{-2}M [ThCOOEt] = 5.700×10^{-1}M

25° 380nm.

Time mins.	D_t	$D_t - D_\infty$	$2 + \log (D_t - D_\infty)$
0	0.712	0.680	1.833
6	0.491	0.459	1.662
12	0.339	0.307	1.487
18	0.242	0.210	1.322
24	0.172	0.140	1.146
30	0.127	0.095	0.978
36	0.093	0.061	0.785

$k = 1.18 \times 10^{-1}$ l. mole^{-1} min.$^{-1}$

Figure 42

Chlorination of thiophen-2-carboxylic acid in anhydrous acetic acid at 25°.

Specimen Experiment 19

$[Cl_2]$ = 5.255×10^{-2}M $[ThCOOH]$ = 2.170×10^{-1}M

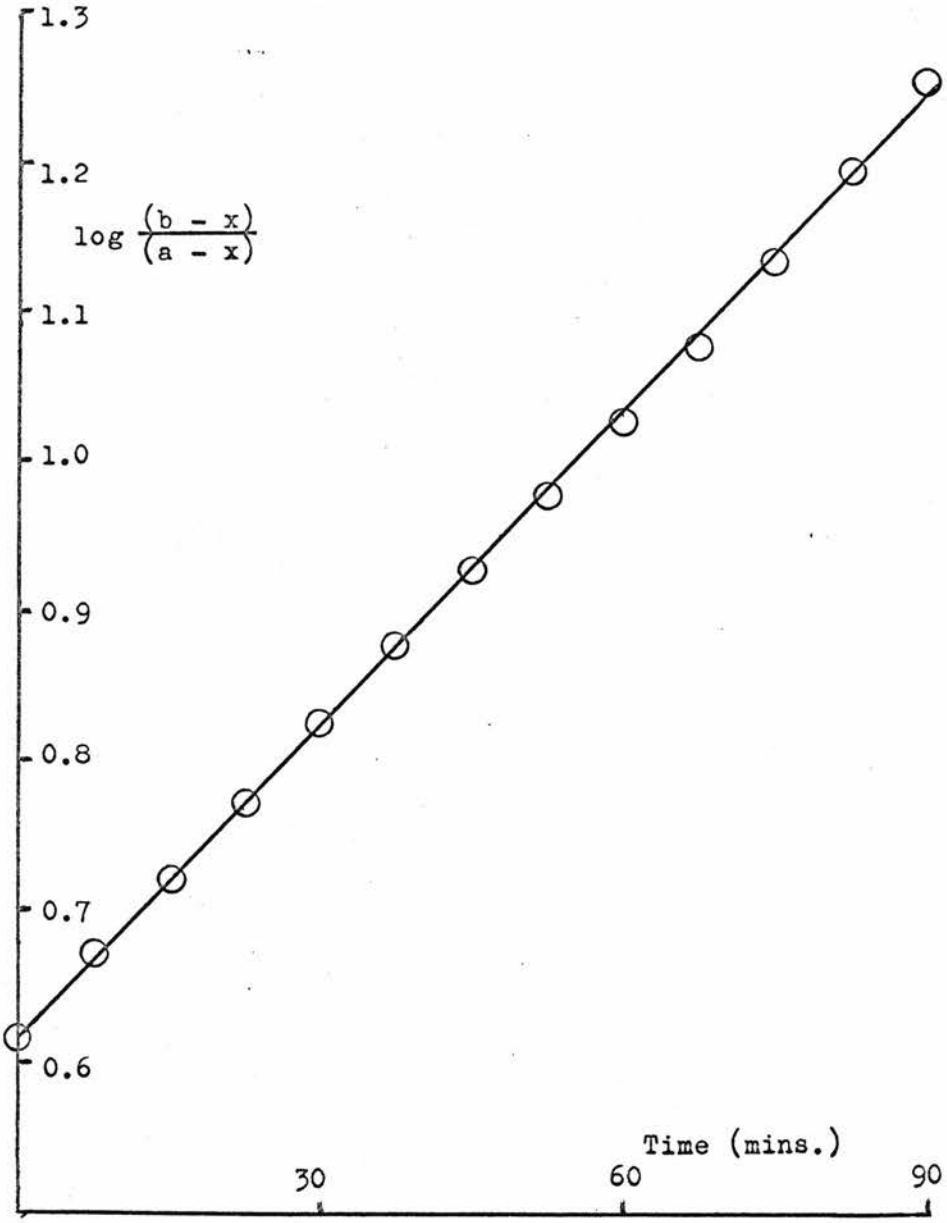
25° 380nm.

Time mins.	D_t	$10^2(a - x)$ M	$10^2(b - x)$ M	$\log \frac{(b - x)}{(a - x)}$
0.0	0.728	5.255	2.170	0.616
7.5	0.620	4.418	2.083	0.674
15.0	0.545	3.837	2.028	0.723
22.5	0.479	3.325	1.977	0.774
30.0	0.421	2.875	1.932	0.827
37.5	0.372	2.496	1.894	0.880
45.0	0.333	2.193	1.864	0.929
52.5	0.299	1.930	1.838	0.979
60.0	0.270	1.705	1.815	1.027
67.5	0.243	1.496	1.794	1.079
75.0	0.218	1.302	1.775	1.135
82.5	0.194	1.116	1.756	1.197
90.0	0.175	0.968	1.741	1.255

$k = 9.84 \times 10^{-2}$ l. mole^{-1} min.$^{-1}$

Figure 43

Figure 43 Chlorination of thiophen-2-carboxylic acid in anhydrous acetic acid.



6. PROTODETRITIATION OF THIOPHEN IN ACIDIC MEDIA.

The rate of protodetritiation at the 2- and 3- positions in thiophen was measured in sulphuric and perchloric acid at various temperatures.

A solution of the tritiated thiophen in water was prepared by stirring about 0.1ml. of thiophen in 75mls. of water for 30 minutes and filtering through a phase-separating filter paper (Whatman). The U.V. spectrum showed that this method gave a solution of reproducible concentration. An aliquot of this solution was diluted with the acid, with cooling, to the desired acid concentration. The acid concentration being determined by titration with standard sodium hydroxide before dilution. The solution was thermostatted for 30 mins. and 1ml. samples withdrawn by pipette and quenched by running into 50mls. of 2M sodium hydroxide and 10mls. of scintillator solution (Beckman Fluoralloy Cocktail in toluene) and shaking for two minutes. The organic layer was then separated and dried ($MgSO_4$). The activity of this solution was measured on a Beckman LS 100 Liquid Scintillation Counter. Protodetritiation was found to be first-order over at least four half lives. The activity of the sample falling to almost the background count at infinite time.

Protodetritiation of 2-tritiothiophen

Specimen Experiment 20

$[H_2SO_4]$ = 5.81M 25°

Time mins.	C_t	$C_t - C_\infty$	$\log (C_t - C_\infty)$
0.00	15,900	15,840	4.200
20.25	9,810	9,750	3.989
40.50	5,880	5,820	3.765
60.00	3,735	3,675	3.565
90.00	1,880	1,820	3.260
121.25	990	930	2.969

$k = 2.37 \times 10^{-2}$ min.$^{-1}$

C_t = counts per minute at time t.

C_∞ = counts per minute at infinite time.

Figure 44

Figure 44 Protodetritiation of 2-tritiothiophen in sulphuric acid.

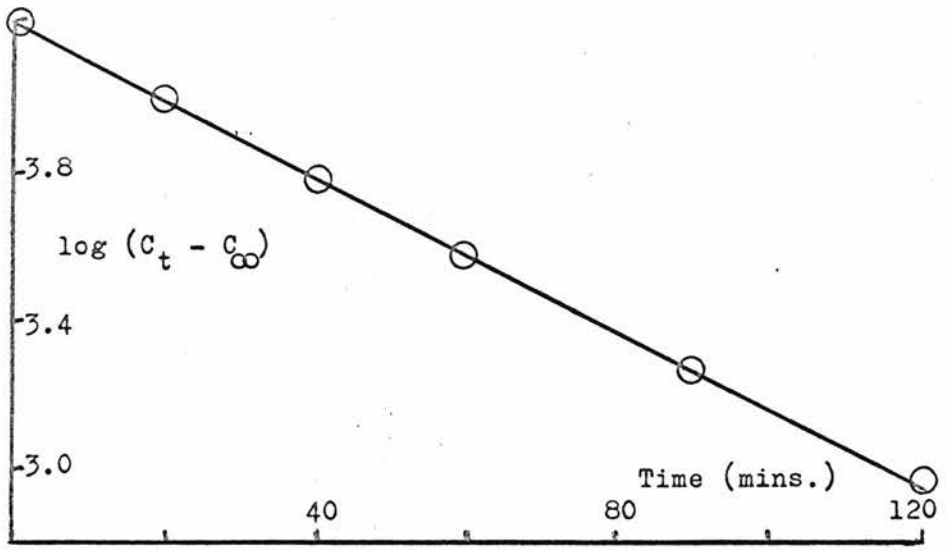
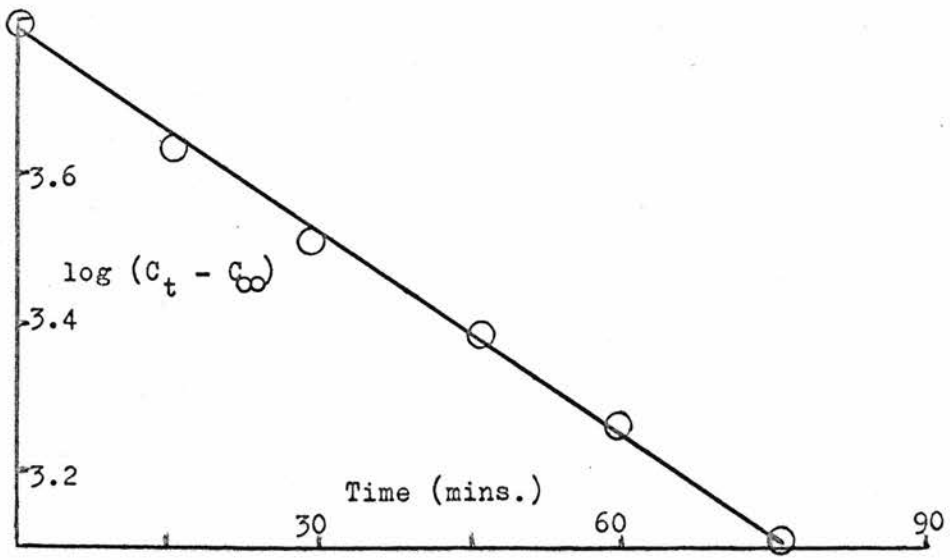


Figure 45 Protodetritiation of 3-tritiothiophen in sulphuric acid.



Protodetritiation of 3-tritiothiophen

Specimen Experiment 21

$[H_2SO_4]$ = 11.88M 1.9^{o}

Time mins.	C_t	$C_t - C_\infty$	$\log (C_t - C_\infty)$
0.00	6,290	6,220	3.794
15.75	4,360	4,290	3.633
29.50	3,320	3,250	3.512
46.25	2,440	2,370	3.375
60.00	1,870	1,800	3.255
76.00	1,365	1,295	3.112

$k = 2.03 \times 10^{-2}$ min.$^{-1}$

Figure 45

The rate of protodetritiation of 2-tritiothiophen and 3-tritiothiophen was measured at constant acidity at various temperatures, thus enabling activation parameters to be calculated (TABLE 43). The values of H_o were adjusted for variation in temperature according to the values of Tickle[117].

TABLE 43

Variation in the rate of protodetritiation of 2- and 3-tritiothiophen with temperature.

2- tritiothiophen[a]

Temp.	k $min.^{-1}$	4 + log k	$10^3 \frac{1}{T^\circ_A}$
1.9°	6.457×10^{-3}	1.81	3.635
9.7°	1.458×10^{-2}	2.16	3.535
17.9°	3.458×10^{-2}	2.54	3.435
25.0°	7.762×10^{-2}	2.89	3.354

[a] $[H_2SO_4]$ = 6.67M

3-tritiothiophen[b]

Temp.	k $min.^{-1}$	5 + log k	$10^3 \frac{1}{T^\circ_A}$
1.9°	2.951×10^{-4}	1.47	3.635
9.7°	6.918×10^{-4}	1.84	3.535
17.9°	1.726×10^{-3}	2.24	3.435
25.0°	4.571×10^{-3}	2.66	3.354

[b] $[H_2SO_4]$ = 9.34M

Figures 46 and 47

Figure 46 Arrhenius plot for the protodetritiation of 2-tritiothiophen in sulphuric acid.

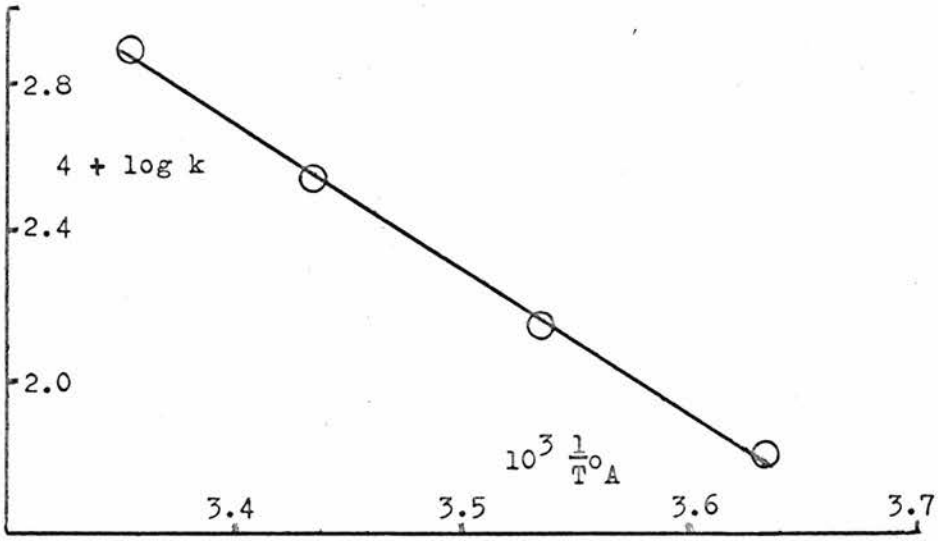
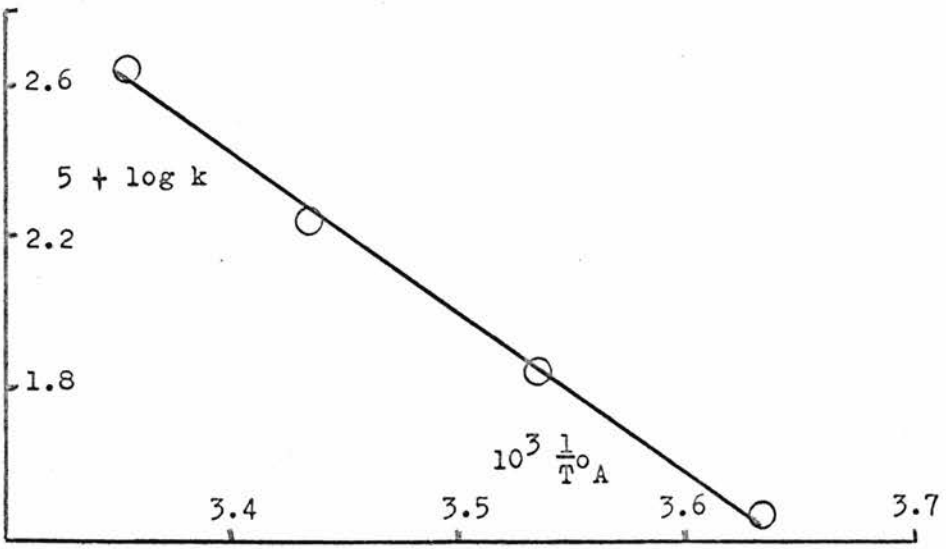


Figure 47 Arrhenius plot for the protodetritiation of 3-tritiothiophen in sulphuric acid.



Protodetritiation of 5-methoxy-2-tritiothiophen in acetate buffers at 25°.

An aqueous solution of 5-methoxy-2-tritiothiophen was prepared in a similar manner to that of 2-tritiothiophen. Higher residual counts were obtained in the protodetritiation experiments than with either 2- or 3-tritiothiophen. It was suspected that some tritium had been introduced into another position in the thiophen ring during the preparation of 5-methoxy-2-tritiothiophen. The preparation was repeated using deuterium oxide to hydrolise the lithiothiophen. Examination of the product by N.M.R. confirmed that about 5% of the product had deuterium in the 4- position.

The Guggenheim[179] method was used to calculate the first-order rate constants for protodetritiation in the acetate buffers. Good straight line plots were obtained and any loss of tritium from the 4- position did not interfere with the kinetics.

The buffer solutions were prepared by mixing sodium acetate and acetic acid solutions of known concentrations. The pH of the solutions was measured on a Beckman Research pH meter using glass and calomel electrodes. The ionic strength of the reaction mixtures was maintained at 0.5M by the addition of potassium chloride.

Specimen Experiment 22

[Buffer] = 1.00M [AcOH] = 0.50M

Time hrs.	Count
0.00	78,300
2.75	65,770
7.50	46,280
12.00	35,860
23.50	22,130
30.00	18,480
95.50	9,760

Guggenheim calculation

Time hrs.	λ	λ'	$\log (\lambda - \lambda')$
0	78,500	25,800	4.722
2	69,700	23,800	4.662
4	60,500	22,200	4.583
6	51,900	20,700	4.494
8	45,300	19,500	4.412
10	40,300	18,500	4.339
12	36,400	17,500	4.277

where λ = count at time t and λ' = count at time t + 20 hrs.

$k = 1.46 \times 10^{-3}$ min.$^{-1}$

Figures 48 and 49

Figure 48 Decrease in count with time for the protodetritiation of 5-methoxy-2-tritiothiophen in acetate buffer.

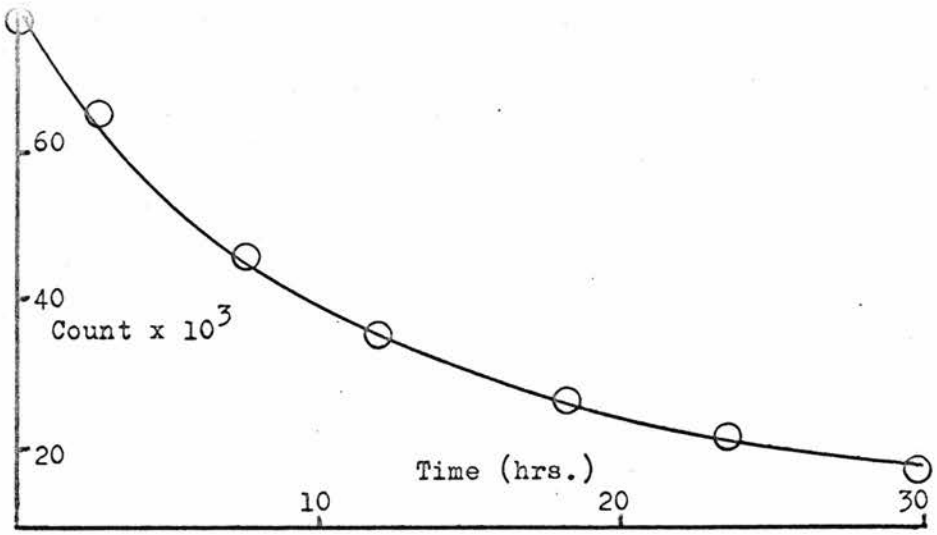
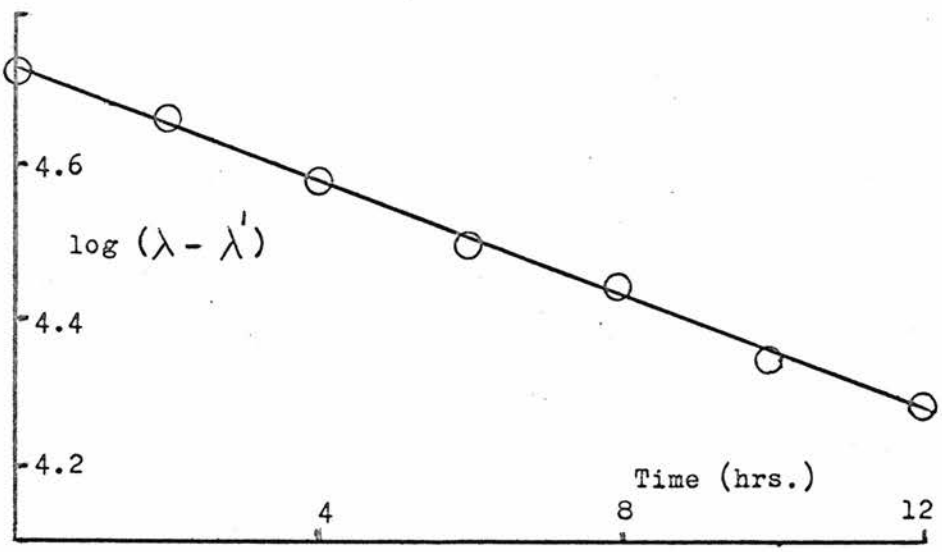


Figure 49 Guggenheim plot for the protodetritiation of 5-methoxy-2-tritiothiophen in acetate buffer.



7. NITRATION OF THIOPHENS IN ACIDIC MEDIA

The compositions of solutions of sulphuric acid and perchloric acid were determined by density measurements[180] (a 10ml. density bottle being used) with an allowance being made for the water added with the substrate during the kinetic runs. The stoicheiometric concentration of nitric acid was determined by titration with sodium hydroxide before diluting with sulphuric, perchloric or acetic acid.

Kinetic methods

a) Sulphuric and perchloric acid

A known volume (3ml.) of a solution of nitric acid in sulphuric or perchloric acid of known concentration was thermostatted in a 10mm. silica cell in a Unicam SP 500. A measured quantity (0.1ml.) of an aqueous solution of the thiophen was added by micropipette. The addition of this volume of an aqueous solution to acids of the concentration used did not produce any measurable rise in temperature. The increase in absorption at 300nm., due to formation of nitrothiophen, was measured as a function of time. The concentration of nitric acid was in at least a ten fold excess over the thiophen and the runs gave good pseudo first-order plots. A plot of log $(D_\infty - D_t)$ against time was linear, where D_∞ and D_t are the optical densities at infinite time

and time t respectively. The final spectrum of the solution corresponded to quantitative conversion of thiophen to 2-nitrothiophen. As nitrous acid is known to interfere with nitration reactions, a little urea (approx. 3×10^{-2} moles $l.^{-1}$) was added to remove any nitrous acid present. The addition of urea does not alter the rate of nitration.

b) Acetic acid

Nitric acid, at the concentrations used with acetic acid as solvent, absorbs strongly in the U.V. region and this prevented the use of method a) in following the rate of nitration in this solvent. However, certain runs were monitored at longer wavelengths (330 - 350nm.) where absorption due to nitric acid is less. In these runs a solution of thiophen in acetic acid was added to a mixture of nitric acid in acetic acid and thermostatted in the spectrophotometer for 30 mins. The thiophen concentration was higher than in method a) requiring the use of 1mm. cells in some runs.

An alternative procedure was used for some of the runs with acetic acid as solvent. An aliquot (1ml.) of the reaction mixture was removed by pipette at timed intervals and run into 10% sodium hydroxide solution (20mls.) and iso-octane (10mls.) and shaken for two minutes. The organic layer was separated and dried ($MgSO_4$) and its spectrum measured on a Unicam SP 800 (with dilution by more iso-octane

if required). Absorption due to 2-nitrothiophen increased with time. In the mesitylene runs the final spectrum corresponded to quantitative conversion to nitromesitylene.

Variation in the second order rate constant for the nitration of thiophen with acidity at 25°.

Specimen Experiment 23

[Thiophen] ca. 1×10^{-4}M $\quad [HNO_3]_{St} = 1.56 \times 10^{-3}$M

H_2SO_4 = 71.59% $\quad$ 300nm.

Time mins.	D_t	$(D_\infty - D_t)$	$1 + \log (D_\infty - D_t)$
0.00	0.261	0.809	0.908
0.25	0.401	0.669	0.825
0.50	0.519	0.551	0.741
0.75	0.613	0.457	0.660
1.00	0.692	0.378	0.578
1.25	0.749	0.321	0.507
1.50	0.800	0.270	0.431
1.75	0.844	0.226	0.354
2.00	0.889	0.181	0.258

k_2(obs.) = 4.69×10^2 l. mole^{-1} min.$^{-1}$

Figure 50

Figure 50 Nitration of thiophen in sulphuric acid.

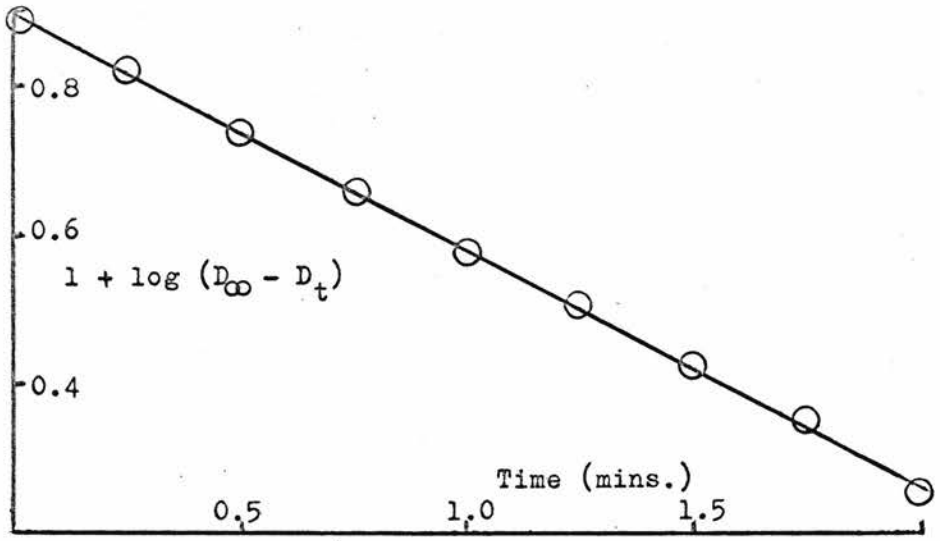
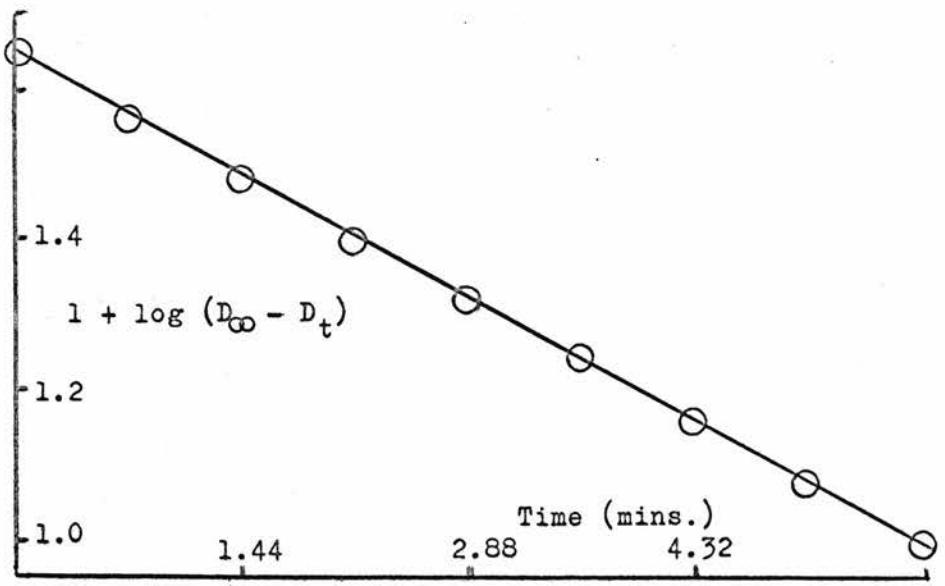


Figure 51 Nitration of 2-chlorothiophen in sulphuric acid.



Variation in the second order rate constant for the nitration of 2-chlorothiophen with acidity at 25°.

Specimen Experiment 24

[2-Chlorothiophen] ca. 1×10^{-4}M H_2SO_4 = 68.43%

$[HNO_3]_{St}$ = 1.56×10^{-2}M 325nm.

Time mins.	D_t	$(D_\infty - D_t)$	$2 + \log (D_\infty - D_t)$
0.00	0.137	0.445	1.648
0.72	0.219	0.363	1.560
1.44	0.279	0.303	1.481
2.16	0.334	0.248	1.395
2.88	0.375	0.207	1.316
3.60	0.408	0.174	1.241
4.32	0.439	0.143	1.155
5.04	0.465	0.117	1.068
5.76	0.485	0.097	0.987

k_2(obs.) = 1.70 x 10 l. mole^{-1} min.$^{-1}$

Figure 51

Variation in the second order rate constant for the nitration of 2-methylthiophen with acidity at 25°.

Specimen Experiment 25

[2-Methylthiophen] ca. 1×10^{-4}M H_2SO_4 = 66.45%

$[HNO_3]_{St}$ = 1.56×10^{-2}M 325nm.

Time mins.	D_t	$(D_\infty - D_t)$	$1 + \log (D_\infty - D_t)$
0.00	0.021	0.474	0.676
0.36	0.089	0.406	0.609
0.72	0.145	0.350	0.544
1.08	0.198	0.297	0.473
1.44	0.240	0.255	0.407
1.80	0.273	0.222	0.346
2.16	0.308	0.187	0.272
2.52	0.337	0.158	0.199
2.88	0.361	0.134	0.127
3.24	0.379	0.116	0.065
3.60	0.394	0.101	0.004

k_2(obs.) = 2.78 x 10 1. $mole^{-1}$ $min.^{-1}$

Figure 52

Figure 52 Nitration of 2-methylthiophen in sulphuric acid.

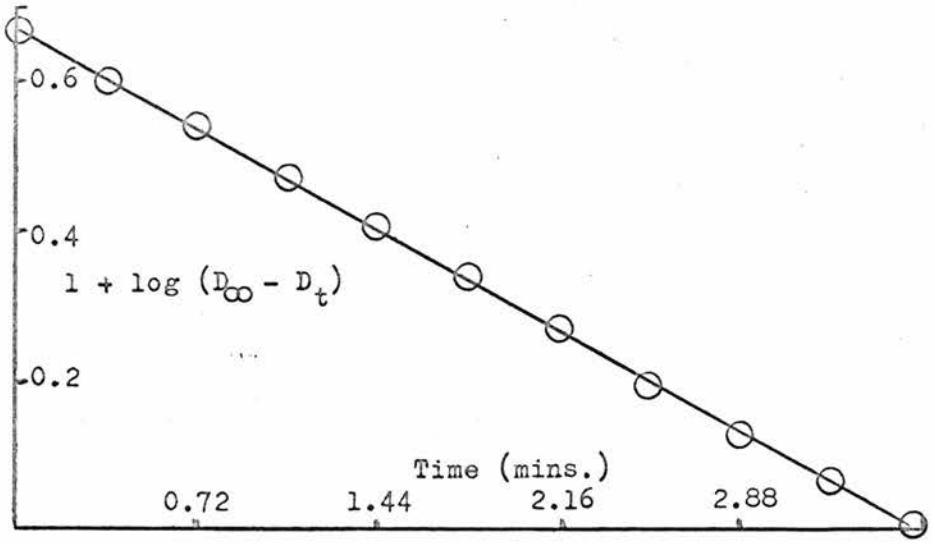
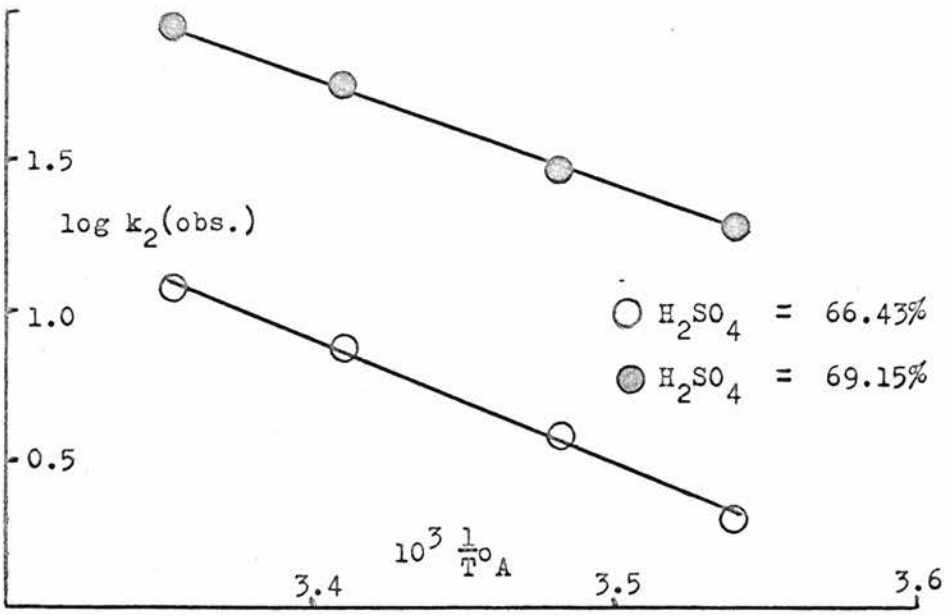


Figure 53 Arrhenius plots for the nitration of thiophen in sulphuric acid.



The rate of nitration of thiophen in sulphuric acid was measured at various temperatures, thus enabling activation parameters to be calculated (TABLE 44).

TABLE 44

Variation in the rate of nitration of thiophen with temperature.

H_2SO_4 = 66.43%

Temp.	k_2(obs.) l. mole^{-1} min.$^{-1}$	log k_2(obs.)	$10^3 \frac{1}{T^oA}$
9.2°	1.99	0.299	3.541
13.9°	3.76	0.575	3.483
19.9°	7.50	0.875	3.412
25.0°	11.1	1.045	3.354
H_2SO_4 = 69.15%			
9.2°	18.2	1.260	3.541
13.9°	28.3	1.452	3.483
19.9°	55.5	1.744	3.412
25.0°	85.2	1.930	3.354

Figure 53

Nitration of thiophen in acetic acid / nitric acid mixtures at 25°.

The product of the reaction was shown to be 2-nitrothiophen by comparison of the U.V. spectrum of the products in iso-octane with an authentic sample of 2-nitrothiophen.

Specimen Experiment 26

[Thiophen] = 2.117×10^{-2}M $[HNO_3]_{St}$ = 8.3M

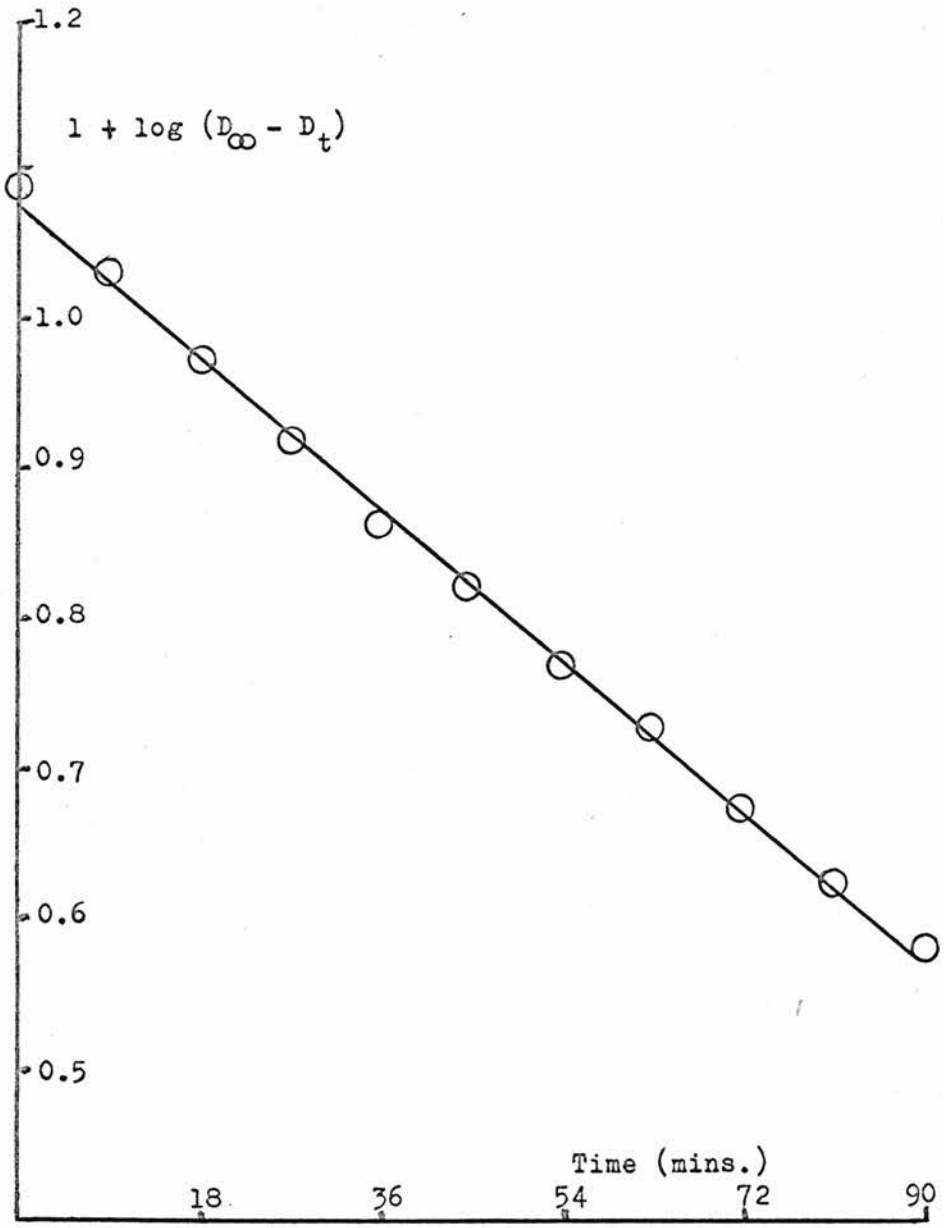
370nm.

Time mins.	D_t	$D_\infty - D_t$	$1 + \log (D_\infty - D_t)$
0	0.179	1.236	1.092
9	0.339	1.076	1.032
18	0.472	0.943	0.975
27	0.586	0.829	0.919
36	0.689	0.726	0.861
45	0.753	0.662	0.821
54	0.829	0.586	0.768
63	0.880	0.535	0.728
72	0.943	0.472	0.674
81	0.996	0.419	0.622
90	1.033	0.382	0.582

$k = 1.31 \times 10^{-2}$ min.$^{-1}$

Figure 54

Figure 54 Nitration of thiophen in acetic acid.



The nitration of thiophen in acetic acid / nitric acid mixtures was examined on a more preparative scale:-

e.g. To a stirred solution of 20mls. of acetic acid and 30mls. of nitric acid (Sp. Gr. = 1.42) plus 0.3g of urea was added 1ml. of thiophen in 15mls. of acetic acid during 45 mins. The mixture was stirred for two hours and turned dark brown with brown fumes being given off. After leaving for a further eight hours the mixture was poured on to 150g of ice. 1ml. of the filtered solution was extracted with iso-octane and the U.V. spectrum was taken showing the presence of some 2-nitrothiophen (about 20% of theoretical yield) and apparently no unreacted thiophen.

When the above experiment was repeated adding the thiophen solution much more slowly (over 36 hrs.) a yield of nitrothiophen of over 70% of the theoretical yield was obtained.

A solution of 0.5g of 2-nitrothiophen in 10mls. of acetic acid was added to 20mls. of acetic acid and 30mls. of nitric acid (Sp. Gr. = 1.42) plus 0.3g of urea and stirred for two hours. No reaction was observed.

The effect of urea on the yield of the nitro compound for thiophen and mesitylene at 25°.

The effect of the addition of urea (0.03 moles $l.^{-1}$) on the nitration of thiophen (1.032×10^{-2} moles $l.^{-1}$) in nitric acid (8.3M) in acetic acid and mesitylene (8.560×10^{-3} moles $l.^{-1}$) in the same nitrating medium was studied. The U.V. spectrum of the products in iso-octane was studied as previously. In the thiophen case the absorption due to 2-nitrothiophen was more than doubled by the addition of urea, whereas the production of nitromesitylene was unaffected.

Nitrosation of anisole

Two experiments were carried out.

a) 1ml. of N_2O_4 in acetic acid + 1ml. of anisole + 0.5ml of nitric acid was diluted to 10mls. with acetic acid.

b) 1ml. of N_2O_4 in acetic acid + 1ml. of anisole + 0.5ml. of nitric acid + 5mls. of acetic anhydride was diluted to 10mls. with acetic acid.

In experiment a) the purple colour due to formation of dianisyloxidoammonium ion developed. In experiment b) no purple colour was observed.

8. SPECTRA.

N.M.R. spectra of 2-methoxythiophen and deuteriated 2-methoxy--thiophen.

An analysis of the integrated spectrum of the deuteriated 2-methoxythiophen showed deuterium present in the 5- and 3-positions[181] in the ratio 10:1 approximately. The spectra were measured on a Varian HA 100.

N.M.R. spectra of thiophen and deuteriated thiophen.

A comparison of the N.M.R. spectrum of thiophen and the deuteriated thiophen showed the disappearance of peaks and splittings due to protons in the 2- and 5- positions[2]. The spectra were measured on a Perkin Elmer R10.

U.V. spectrum of 2,3-benzothiophen.

The purity of the 2,3-benzothiophen was checked by a comparison of the U.V. spectrum of the material with the literature spectrum[182]. The spectra were found to be identical.

U.V. spectrum of 2-nitrothiophen.

The U.V. spectra of the products of the reaction of thiophen and sulphuric acid / nitric acid or acetic acid / nitric acid were identical to the literature spectrum of 2-nitrothiophen[183]. The spectra were measured on a Unicam SP 800.

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