SOME ASPECTS OF THE HALOGENATION OF PHENOLS AROMATIC AMINES AND THEIR DERIVATIVES

being a

Thesis submitted for the Degree of Doctor of Philosophy

of the

University of London

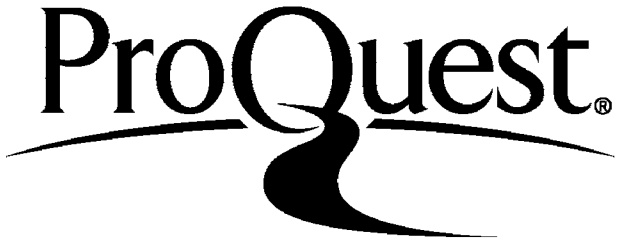
by

OSMAN MOHAMMED el HASSAN el DUSOUQUI, B.Sc.(Khartoum)

Department of Chemistry,

Bedford College, London.

June, 1966



ABSTRACT.

This thesis is divided into three main sections, as follows:

1. In "Section A" are outlined some of the features and broad concepts of the theory of electrophilic aromatic substitution with special reference to topics that are relevant to the present work.

2. In "Section B" are presented the results obtained for the rates of molecular chlorination in acetic acid at 25° of N-acetyldiphenylamine, N-acetylcarbazole, 2-chloro- and 3-chloro-N-acetylcarbazole. The isomer distribution has also been assessed, and partial rate factors have been calculated for the first two compounds. Results for competitive chlorination of carbazole and diphenylamine are also furnished. The reactivity of the various positions, as well as the overall relative reactivities of these systems are discussed in the context of the theory of aromatic substitution reactions, but with special reference to earlier work on these compounds.

3. In "Section C" the results are recorded for the bromination of phenol and of anisole at 25°, in presence of initially added bromide ion, with molecular bromine in either acetic acid or deuteroacetic acid as solvent. The ionic strength of the reaction medium has been kept constant

(0.2M) by adding lithium perchlorate whenever necessary. The rate ($k_{apparent}$; $k_{app.}$) of bromination of the two compounds in both solvents were obtained; and from these the rate constants for bromination by free bromine (k) were evaluated by graphical means. It has been necessary also to obtain the equilibrium constant for tribromide ion formation ($Br_2 + Br^- \rightleftharpoons Br_3^-$) in both solvents. The kinetics and mechanism of these reactions are discussed. Attempts are made to explain the observed isotope effects. The earlier suggestion by Robertson and de la Mare, that the greater reactivity of phenol as compared with anisole can in part be ascribed to OH hyperconjugation is revived.

CONTENTS

ACKNOWLEDGMENTS.

This thesis is dedicated to my supervisor, Professor P.B.D. de la Mare, in appreciation of his unfailing guidance, help and encouragement.

The author is greatly indebted to Dr. J. G. Tillett (Chemistry Department, University of Essex), Dr. E. A. Johnson (Medical Research Council, Hampstead, London), Dr. R. Bolton (Bedford College, London), and Dr. M. D. Johnson (University College, London), for their help, interest and co-operation.

The author also wishes to extend his sincere thanks to all members of the academic and technical staff, and to the students in the Chemistry Department, Bedford College, London who, in so many ways, made possible the realisation of this work. Special thanks are due to Mr. F. J. Robinson and Mr. C. Siggers for valuable technical assistance.

The generosity and understanding of the University of Khartoum, expressed in an extended scholarship to the author, is gratefully acknowledged.

SECTION (A)

GENERAL INTRODUCTION

I. An Outline. ------ .

The investigation contained in this thesis lies within the vast domain of "Electrophilic Aromatic Substitution". It seems appropriate, therefore, to summarise selectively the aspects of this subject that impinge most directly on the chosen problem; namely: electrophilic reagents, aromatic substrates, substituent effects, reaction medium, some features of the actual substitution process, relevant theoretical and empirical treatments, together with a brief review of earlier work on the compounds studied.

II. Aromaticity and Aromatic Compounds. ------ .

The criterion adopted for assigning "aromatic character" to the compounds to be discussed is that used earlier by de la Mare and Ridd[1]. An unsaturated ring-system can conveniently be considered to have "aromatic character" when it contains in its ring (or in each ring - in polynuclear compounds) at least six electrons extra to those constituting the single bonds of the ring.

The characteristic feature of these compounds, which is also of special importance here, is their greater tendency to undergo substitution rather than addition reactions. Some workers have considered that this property is directly

---

1. P.B.D. de la Mare and J.H. Ridd, "Aromatic Substitution - Nitration and Halogenation," Butterworths, London, 1959.

proportional to the degree of stability displayed by any aromatic compound[1]. However, the stability exhibited by an aromatic compound in the ground state could be further developed by introducing a suitable substituent in the system[1,2]. The substituent would then exert a stabilising influence on the system by virtue of its electronic effects (M and/or I effect), and also through the subsequent electron redistribution within the substituted molecule following the introduction of that substituent.

III. Transition States (T.S.). ------ .

Both the rate and the rate constant of a chemical reaction can be explained reasonably well in terms of either one of two theories - the "Transition State Theory" or the "Collision Theory". However, the former finds wider application because the parameters in which the theory expresses the reaction rates are, at least in principle, measurable. Another and stronger reason in favour of the transition state theory is the fact that very complex reactions can be simplified to comprehensible dimensions by the use of the concept of this theory.

---

1. L.F. Fieser, in "Organic Chemistry", ed. H. Gilman, John Wiley, New York, 1944, Vol. I, p. 117.
2. P.B.D. de la Mare and J.H. Ridd, "Aromatic Substitution -," Butterworths, London, 1959.

Though the transition state theory and the collision theory have two different approaches to the reaction rate problem, yet both can successfully be used to formulate a mathematical expression for the empirically defined Arrhenius equation,

$$- \log k = (\Delta E^{\ddagger}/RT) - \log A \quad .$$

This treatment holds best when the rate of the reaction obeys a simple rate law, e.g. in bimolecular reactions.

Given a simple bimolecular system on the threshold of a chemical reaction assigned a given energy value through which its molecular properties are fully described, it can conveniently be imagined, when reacting, to be moving along a reaction path involving a transition state through which reactants change into products. For such a system, activation energy ($\Delta E^{\ddagger}$) of a certain magnitude would be needed to bring that system to its transition state before a successful chemical change can occur. For complete visualization of free energy change with reaction progress a multi-dimensional contour map is necessary, but for a simplified description it often suffices to have a graph (Fig. I.) representing a cross-section along the reaction path, the ~~abscissa~~ ordinate of which represents free energy change, and the ~~ordinate~~ abscisa a "reaction co-ordinate". The transition state would then

correspond to a maximum in the curve, and a col in the contour map. The implication of this is that, the transition state represents a point of maximum energy along the reaction path (unstable displacement equilibrium) and of minimum energy in all other directions (stable displacement equilibrium). Consequently the only effective change the transition state can undergo is a one along the reaction path either irreversibly ultimately into products, or reversibly back into reactants. Combination of the expressions given by the thermodynamical treatment of the reversible step, and the statistical-mechanical treatment of the irreversible step would yield a mathematical expression for the overall rate. The rate-coefficient in this rate expression gives the Arrhenius equation in a form the terms of which are in principle directly measurable,

$$\text{Rate} = (kT/h)e^{-\Delta E^*/RT}\,[A]\,[B] \quad .....$$

Here changes in the entropy of activation are neglected as being unimportant, at least for comparative rate studies of reactions of similar nature. The overall reaction rate is, thus, determined by the changes its transition state undergo.

It is generally considered that reactions of molecularity higher than two are rare, and that complex reactions

can plausibly be imagined to involve a series of transition states of bimolecular collisions, decomposing to give reactive intermediates, prior to a transition state whose rate of formation is slowest, and, therefore, rate-determining. In that sense this transition state would embody and account for all the stages of the reaction preceding it.

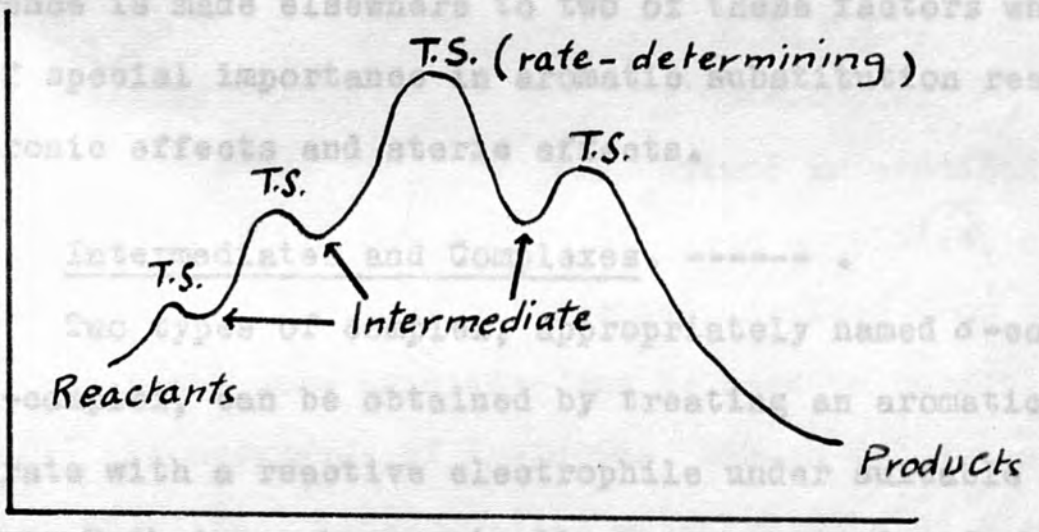


Fig.I. Energy-profile of an aromatic substitution reaction.

Since the observed overall rate of a reaction is a function of its rate-determining transition state only, then any change in the factors influencing the properties of this transition state (e.g. reaction medium, isotopic composition

of the system, etc.) would, as a result, manifest itself in the overall reaction rate. It is equally clear that factors of great and primary importance would be those that help to reduce the energy of the rate-determining transition state, making the transition state more stable and less demanding, and thereby offering an easier path for the reaction. Reference is made elsewhere to two of these factors which are of special importance in aromatic substitution reactions - electronic effects and steric effects.

IV. Intermediates and Complexes. ------ .

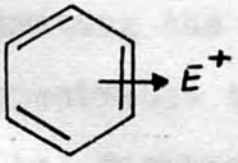
Two types of complex, appropriately named σ-complex and π-complex, can be obtained by treating an aromatic substrate with a reactive electrophile under suitable conditions. Both types have actually been prepared and characterized[1,2]. In some cases they have even been isolated, studied[3], and the products of further decomposition of some of them identified[4] (as products of normal substitution).

The extensive study of a large number of complexes from both types, culminating in the elucidation of their respective structures, was advanced by the use (among other

---

1. E.E. Ferguson, J. Chem. Phys., 1956, 25, 577; 1957, 26, 1357.
2. Brown and Pearsall, J. Amer. Chem. Soc., 1952, 74, 191.
3. de la Mare, O.M.H. el Dusouqui, J.G. Tillett and M. Zeltner,
4. G.A. Olah, L. Noszko and A. Pavlath, Nature, London, 1957, 179, 146.

physical and chemical methods) of u.v., i.r., n.m.r., and x-ray crystallography. The two types of complex are generally assigned the following structures (here with unsubstituted benzene as the substrate, and E^+ as the electrophile):



π-Complex

σ-Complex

(or Wheland intermediate)

The relative importance of these complexes, as far as aromatic substitution is concerned, derives from the fact that their mere existence can be used to corroborate the possible occurrence of analogous, though not necessarily exactly identical, intermediates often postulated when describing substitution processes, reaction rates, and relative reactivities.

The most widely accepted description of the substitution process advocates a two-staged process involving an intermediate, represented by an energy dip in the energy-profile diagram. This is flanked by two energy maxima corresponding to two transition states, the first being, in the majority of cases, the rate-determining step. It is not

a condition, however, that the intermediate be isolatable, or even long-lived for it to be formed in the course of a normal substitution process[1,2]. It has also been argued[3,4] that when a model for the transition state is to be constructed better results can often be obtained by approximating the structure of the model used to the structure of a conceivable intermediate, rather than to that of the reactants. Furthermore, the structure of such an intermediate, if it existed, would most probably be that of the Wheland intermediate (σ-complex). One piece of evidence in favour of using the Wheland intermediate as a model for the transition state comes from the correlation of the relative basicities of a number of aromatic compounds towards π-, and σ-complex-formation with their relative rates of substitution. Results from similar studies seem to indicate that π-complexes can occur only as loose associations of substrates and electrophiles near the beginning of the reaction path, and would, presumably, have very little effect on the transition

---

1. E. Berliner, in "Progress in Physical Organic Chemistry," eds. Cohen, Streitwieser, Jr., and Taft, Interscience, New York, 1964, Vol. II., p. 253.
2. de la Mare and Ridd, "Aromatic Substitution -," Butterworths, London, 1959, p. 17;
3. G.S. Hammond, J. Amer. Chem. Soc., 1955, 77, 334.
4. Bavin and Dewar, J. Chem. Soc., 1956, 164.

states following them[1]. However, cases have been reported[2,3] where strong argument can be presented explicitly in favour of representing the intermediate for the reactions then being discussed as a π-complex. A compromise is obtained by the plausible suggestion[2,4] of a mechanism for the substitution process in which reactants, π-complexes, and σ-complexes gradually merge and blend one into the other (probably in that order) to give finally the products of substitution.

In any case, as far as the kinetic form of reaction is concerned, the complex-formation is only important when it can actually be made rate-determining, or the forces responsible for its formation be deemed operative in the rate-determining transition state[1].

V. Kinetic Isotope Effects. ------ .

Mechanistic investigations are never considered complete without an adequate consideration of isotope effects, for which it often suffices to know whether such an effect

---

1. de la Mare and Ridd, "Aromatic Substitution -," Butterworths, London, 1959, pp. 45, 46.
2. G.A. Olah, in "Organic Reaction Mechanisms - an Internatial Symposium, Cork, Ireland, 1964 "The Chemical Society, London, 1965, p. 21.
3. H. Zollinger and his co-workers, Helv. Chim. Acta, 1962, 45, 2057 - 2090.
4. E. Berliner, in "Progress in Physical Organic Chemistry," eds. Cohen and others, Interscience, New York, 1964,Vol.II., p. 253.

is large, small, or absent. Here kinetic isotope effects are discussed with reference to hydrogen isotope effects only.

The strength of X-to-hydrogen bond (where X is, say, C,O, or N) increases on going from protium to deuterium to tritium, and consequently, the rate at which these bonds are ruptured would be expected to increase in the opposite direction. It follows, therefore, that if such a bond is broken in the rate-determining step of a reaction, that that reaction would be susceptible to isotope effects.

The occurance and magnitude of isotope effects seem to depend[1,2], among other factors, on the relative reactivities of substrates and substituting agents, changes in the nature of the medium, steric effects, acidifying effect of the electrophile on the departing hydrogen, and sometimes also on the amount of base used.

V.a. Primary Isotope effects.

Isotope effects are considered to be primary effects when they occur consequent to isotopic changes at the reaction site, and have, therefore, been used mainly to

---

1. E. Berliner, in "Progress in Physical Organic Chemistry," eds. Cohen and others, Interscience, New York, 1964, Vol. II., p. 253.
2. H. Zollinger, in "Advances in Physical Organic Chemistry," ed. V. Gold, Academic Press, London, 1964, Vol.II., p. 163.

determine whether, or not, a proton-loss is involved in the rate-determining step of a substitution reaction.

No generalized answer could be given[1,2] with certainty to this question except, perhaps, for nitration reactions where the proton-expulsion was proved to be kinetically unimportant. Consequently evidence for the presence or absence of such effects in any particular reaction should then be obtained from direct analysis, and not by analogy from other similar cases studied.

V.b. Secondary, and Solvent Isotope effects.

A secondary isotope effect is due to an isotopic change away from the bond being severed during the normal course of substitution. Qualitatively, the introduction of deuterium or tritium would then have the same effect as any other substituent[3]. Both would influence the electronic properties, and also the reactivity of the system in which they are introduced, by virtue of their inductive effects, hyperconjugative effects, and any accompanying steric effects.

---

1. E. Berliner, in "Progress in Physical Organic Chemistry," eds. Cohen and others, Interscience, New York, 1964, Vol. II., p. 253.
2. G.A. Olah, in "Organic Reaction Mechanisms - an International Symposium," The Chemical Society, London, 1965, p. 21.
3. E.A. Halevi, in "Progress in Physical Organic Chemistry," eds. Cohen and others, Interscience, New York, 1963, Vol. I., p. 109.

One interesting aspect of hydrogen isotope effects arises in connection with proton-transfer reactions in hydroxylic solvents. If the proton is transferred, or at least appreciably loosened in the rate-determining step, then an isotope effect would be expected if, say, deuterium is substituted in the base receiving the proton[1]. Of particular importance is the case when the base is also the solvent[2].

Long and Watson[2] studied the catalytic bromination of methylacetylacetone in both H_2O and D_2O. For the enolization of the ketone the ratio of the rates in the two solvents, i.e. k_H/k_D, was found to be 1.4. For the reverse reaction (the ketonization of the enolate ion) using acetic acid and acetic acid-d, again as solvent and catalyst, k_H/k_D was equal to 6. From these and corroborative investigations using the acetate ion as catalyst, the authors concluded that the observed isotope effects were "pure" solvent isotope effects.

However, in reactions where the proton concerned does not exchange to any appreciable extent with the solvent, the observed isotope effects were found to be considerably less than unity[2,3].

---

1. R.P. Bell, "The Proton in Chemistry," Methuen, London, 1959, Chap. XI.
2. F.A. Long and D. Watson, J. Chem. Soc., 1958, 2019.
3. Reity and Kopp, Z. phys. Chem.,1938, A, 182, 193.

VI. Electronic Effects. ------ .

Electronic effects can conveniently be grouped into permanent effects, time-variable effects, and hyper-conjugative effects.

VI.a. Permanent effects.

These are permanent polarisation effects, and are, therefore, reflected in the physical properties of molecules. They are either inductive in nature (inductive effects), or conjugative in origin (conjugative effects). These effects are usually described as being negative or positive effects, according to whether the groups responsible for them are, respectively, electron-attracting (e.g., halogens, nitro group), or electron-releasing (e.g., alkyl groups, hydroxyl group).

The nature, direction, and magnitude of an electronic effect (permanent) of a substituent can be determined by measuring a suitable physical property of the substituted molecule.

VI.b. Time-variable effects.

Time-variable effects are polarisability effects manifested in the transition state of a reaction, and also could be evoked at the instance of the attacking reagent. They are by nature temporary effects; and although they

are very difficult to distinguish from permanent effects, yet in many cases their relative contribution to molecular reactivity was clearly demonstrated.

Like permanent effects, time-variable effects are also conveyed by mechanisms that are either inductive or conjugative in nature - the former leads to the "inductomeric" effect, and the latter to the "electromeric effect".

Conjugative effects both in the ground and the transition states are subject to steric effects.

VI.c. Hyperconjugation.

The definition of this mode of electron release is best given with reference to the order of reactivity of alkyl substituents in unsaturated systems, where the established order (t-butyl> methyl) was found to have reversed (methyl> t-butyl). The discrepancy was explained in terms of a hyperconjugative effect[1,2]. Here, as the name implies, the electron pair constituting the C-H bond in the methyl group is considered to be conjugated with the unsaturated system. This was thought to be feasible because

---

1. E.D. Hughes, C.K. Ingold and N.A. Taher, J. Chem. Soc., 1940, 949.
2. J.W. Baker, "Hyperconjugation," O.W.P., London, 1952; M.J.S. Dewar, "Hyperconjugation," The Ronald Press Co., New York, 1962.

the carbon atom in the methyl group is directly attached to the unsaturated compound, and would have conjugated with the rest of the system, if it possessed a lone-pair of electrons. However, this is not true of the t-butyl group.

Emphasis has mostly been laid on C-H hyperconjugation, but N-H, O-H and C-C hyperconjugation have also been considered[1,2].

The importance of this concept derives from its ability to explain a diversity of physical and chemical phenomena, and a host of reactivity sequences which, otherwise, might have remained anomalous[3]. Quantum-mechanical calculations[4], empirical treatments[5], and substantial experimental data[1,3,6] have been amassed by many groups of workers to document this phenomenon.

---

1. de la Mare, Tetrahedron, 1959, 5, 107.
2. E. Berliner and F.J. Bondhus, J. Amer. Chem. Soc., 1948, 70, 854.
3. J.W. Baker, "Hyperconjugation," O.U.P., London, 1952; M.J.S. Dewar, "Hyperconjugation," The Ronald Press Co., New York, 1962.
4. C.A. Coulson and V.A. Crawford, J. Chem. Soc., 1953, 2052.
5. Ehrenson, J. Amer. Chem. Soc., 1961, 83, 4493.
6. E.D. Hughes, C.K. Ingold and N.A. Taher, J. Chem. Soc., 1940, 949.

VII. Steric Effects[1,2]. ------ .

VII.a. Primary steric effects and ortho, para-ratio[2].

Careful examination of the reaction products of suitably substituted compounds showed that the extent of ortho-substitution is partly influenced by the relative size of both the resident group and the attacking reagent. It was found[3,4] that an increase in the effective size of the directing group or the incoming reagent leads to a corresponding decrease in the percentage of ortho-substitution. In such cases the ortho, para-ratios would be expected to deviate from the statistical factor. Ortho, para-ratios could, therefore, be used to establish the relative importance of steric effects in reactions where these effects are expected to be operative. It is important, however, to give adequate consideration to any likely interference from structural, electrical or any other effects before an observed deviation in the ortho, para-ratio can be attributed, in whole or in part, to a primary steric effect.

Since resonance effects are negligible or absent in meta-substitution, some authors[3] advocate the use of the meta-

---

1. G.S. Hammond and M.F. Hawthorne, in "Steric Effects in Organic Chemistry," ed. M.S. Newman, John Wiley, New York, 1956, p. 164.
2. de la Mare and Ridd, "Aromatic Substitution -," Butterworths, London, 1959.
3. K.L. Nelson and H.C. Brown, J.Amer. Chem. Soc., 1951, 73,5605.
4. de la Mare, Harvey, Hassan, and Varma, J. Chem. Soc., 1958, 2756.

position for correlation of isomer distribution, and the assessment of the relative importance of steric factors. Unfortunately, meta-substitution is often absent, or too small in amount for accurate experimental analysis, and cannot, therefore, be used in such cases.

VII.b. Secondary steric effects[1].

This is also known as steric inhibition of mesomerism.

It is well known that for the operation of resonance, the substituent concerned and the aromatic nucleus to which it is attached must be effectively coplanar. Any departure from coplanarity would consequently be accompanied by diminution in conjugation, and, when activating groups are involved, also by reduction in the reactivity of the system as a whole. One way to impede conjugation is to place bulky substituents ortho to the group in question.

The importance of such steric effects in halogenation reactions was clearly demonstrated. The rates of bromination of anisole, and chlorination of acetanilide were shown[2,3] to

---

1. de la Mare and Ridd, "Aromatic Substitution -," Butterworths, London, 1959.
2. G. Baddeley, N.H.P. Smith and M.A. Vickars, J. Chem. Soc., 1956, 2455.
3. de la Mare and Hassan, J. Chem. Soc., 1958, 1519.

be greatly reduced on introducing methyl substituents ortho to the methoxyl and the acetamido groups.

VIII. Partial Rate Factors. ------ .

The partial rate factor at a given position in the ring in a benzene derivative is usually defined as the rate of substitution at that position, relative to the rate of substitution at one of the six equivalent positions in benzene. The partial rate factor is usually calculated from the percentage of substitution at the discussed position (as measured by the percentage of the corresponding isomer in the reaction products) and the overall rate of reaction of the derivative, relative to that of benzene. The symbol given to denote the partial rate factor is f. This symbol usually carries a superscript, which indicates the substituent concerned, and a subscript which specifies the nuclear position where the partial rate factor is being measured.

A limitation has been imposed[1] as regards the general usefulness of partial rate factors for correlating reactivity and orientation in aromatic substitution. It is considered that partial rate factors can be meaningful only for reactions

---

1. G.A. Olah, in "Organic Reaction Mechanisms - International Symposium, Cork, Ireland," The Chemical Society, London, 1965, p. 21.

where individual positions compete first for the electrophile, as is the case when the rate-determining transition state assumes the structure of a Wheland intermediate. If, however, the rate of formation of a π-complex becomes significantly important in the rate-determining process, then whole molecules would be expected to compete first (as π-donors) for the electrophile. It is argued[1] that, in such cases, treatments based on partial rate factors would be expected to break down.

IX. Reactivity and Orientation. ------ .

The study of "aromatic reactivity" demands[2,3] knowledge about the relative reactivity of substituents and substituting agents, the nature of the transition state of the reactions, and many other factors, e.g. steric effects.

Essentially, the following general, and rather qualitative statement is correct. All substituents which activate the aromatic nucleus are ortho, para-directing, and almost all those which deactivate it, cause substitution to

---

1. G.A. Olah, in "Organic Reaction Mechanisms - International Symposium, Cork, Ireland," The Chemical Society, London, 1965, p. 21.
2. de la Mare, J. Chem. Soc., 1949, 2871.
3. R.O.C. Norman and R. Taylor, "Electrophilic Substitution in Benzenoid Compounds", Elsevier, Amesterdam, 1965.

occur predomenantly in the meta-position. The most notable exceptions are the halogens, which deactivate the nucleus, and at the same time promote ortho, para-substitution, by virtue of their opposing -I and +M effects. Similar to the halogens are substituents of the type -CH=CH-X, where X is an electron-attracting group.

Reactivity and orientation are also determined in part by the reactivity of the electrophilic reagent. Electrophiles of comparatively low reactivity are usually more selective, in that they prefer nuclear positions of high electron density. Such electrophilic reagents would also be selective in their reaction with different aromatic molecules.

The above considerations could successfully be applied to mono- as well as to poly-substituted benzenes. For the latter systems it was found[1] useful to assume that the various substituents in a molecule affect additively its energy of activation.

X. Electrophilic Reagents. ------ .

X.a. Nitration.

For nitration with nitric acid in organic solvents

---

1. de la Mare, J. Chem. Soc., 1949. 2871.

(acetic acid, acetic anhydride, etc.), and in other media of widely varying nature and composition, the nitrating entity was proved[1,2] to be the nitronium ion, NO_2^+. Other species (e.g. N_2O_5), however, can also under certain conditions be effective nitrating agents. The relative importance of the latter species as nitrating agents would depend on the reactivity of the substrate, and the polarity of the medium[3]. In organic solvents, and for reactive aromatic substrates (e.g., toluene), the formation of the nitronium ion was proved to be rate-determining, in which case the overall reaction rate was found to be of zero-order with respect to the aromatic compound. However, kinetics which are of first-order in the aromatic substrate could be obtained[4], either by using compounds of comparatively low reactivity (e.g., p-dichlorobenzene), or by changing the nature of the reaction medium, say, by addition of large amounts of water.

Where second-order kinetics prevail, evidence is

---

1. G.A. Benford and Ingold, J. Chem. Soc., 1938, 929.
2. E.D. Hughes, Ingold and R.I. Reed, Nature, 1946, 158, 448; J. Chem. Soc., 1950, 2400.
3. de la Mare and Ridd, "Aromatic Substitution -," Butterworths, London, 1959.
4. Hughes, in "Theoratical Organic Chemistry - Kekule' Symposium, 1958", Butterworths, London, 1959, p. 209.

obtained in part from kinetic isotope effect measurements[1], to suggest that the loss of the aromatic hydrogen, which completes the process of substitution, does not occur in the rate-determining step.

Nitration reactions are subject to the general pattern of substituent effects described earlier in this chapter. In fact the framework of the "qualitative theory of aromatic substitution reactions" has been built considerably on results obtained from nitration reactions[2].

X.b. Halogenation.

X.b.1. Molecular halogenation.

It has been established[3,4] for both molecular bromination and chlorination in acetic acid as solvent, that the halogenating entity is the neutral halogen molecule, and not any other species derived from it.

The reaction of chlorine with a large number of aromatic substrates, over a wide range of reaction conditions was proved[4,5,6] to be bimolecular, of first-order

---

1. Lars Melander, "Isotope Effects on Reaction Rates," The Ronald Press Company, New York, 1960.
2. R.O.C. Norman and R. Taylor, "Electrophilic Substitution in Benzenoid Compounds," Elsevier, Amesterdam, 1965.
3. P.W. Robertson, J. Chem. Soc., 1954, 1276.
4. A.E. Bradfield and B. Jones, Trans. Faraday Soc., 1941, 37, 726; Bradfield Davies and Long, J. Chem. Soc., 1949, 1389.
5. de la Mare and Hassan, J. Chem. Soc., 1958, 1519.
6. E.R. Roberts and F.G. Soper, Proc. Roy. Soc., 1933,140 A,71.

in both chlorine and the aromatic compound;

$$-d\left[Cl_2\right]/dt = k_2\left[ArH\right]\left[Cl_2\right] .$$

However, second and third-order kinetics, with respect to bromine have been observed[1,2]. The overall kinetic form for these reactions could be given as:

$$-d\left[Br_2\right]/dt = k_2\left[ArH\right]\left[Br_2\right] + k_3\left[ArH\right]\left[Br_2\right]^2 + k_4\left[ArH\right]\left[Br_2\right]^3 .$$

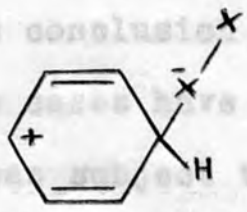
Under certain reaction conditions (e.g., in presence of an excess of bromide ion) strictly second-order kinetics were obtained[3],

$$-d\left[Br_2\right]/dt = k_2\left[ArH\right]\left[Br_2\right].$$

The structure of the transition state (shown below), adopted[1,4] for both molecular chlorination and bromination reactions resembles, and closely approximates the structure of a Wheland intermediate. It is also accepted that the transition state for these two reactions carries the whole molecule of the halogen (X_2).

---

1. P.W. Robertson, J. Chem. Soc., 1954, 1276.
2. Robertson, de la Mare and Johnston, J. Chem. Soc., 1943,276.
3. E. Berliner and M.C. Beckett, J. Amer. Chem. Soc., 1957, 74, 1425.
4. de la Mare, in "Theoratical Organic Chemistry - Kekule' Symposium, 1958," Butterworths, London, 1959, p. 219.



It is suggested[1] that the central halogen atom in the above intermediate had its octet expanded, thus closely resembling the state of affairs in the analogeus trihalide ion ($X-\bar{X}-X$). The $ArH-Cl_2$ complex is relatively unstable, and in acetic acid the fission of the chloride ion can easily be performed by the solvent, and in very polar solvents it can occur even without any participation from the solvent. However, the corresponding bromine complex is much more stable, and, therefore, additional bromine molecules are often required to rupture the Br-Br bond in the intermediate. This would undoubtedly account for the observed high orders in bromination reactions. Unassisted heterolysis of the Br-Br bond in the transition state can often be promoted[2] by increasing the polarity of the medium by the addition of water, salts, or acids.

In many halogenation reactions the final expulsion of the aromatic hydrogen from the reaction intermediate

---

1. de la Mare, in "Theoratical Organic Chemistry - Kekule' Symposium, 1958," Butterworths, London, 1959, p.219.
2. R.O.C. Norman and R. Taylor, "Electrophilic Substitution in Benzenoid Compounds," Elsevier, Amesterdam, 1965.

proved[1] to be of no kinetic importance. Care must be taken not to generalize this conclusion for all molecular halogenation reactions, since cases have been reported[2] in which the rate of reaction was subject to kinetic isotope effects, thus indicating partial involvement of the proton-loss in the rate-determining step of these particular examples.

Again, in molecular halogenation reactions the electronic effects of substituents provide the broad basis for the general discussion of positional, as well as substrate reactivity towards molecular halogens. However, it was often found necessary to call other factors (e.g., steric factors, unusual reaction paths, etc.) to help explain reactivity patterns, when electronic effects alone proved to be inadequate.

X.b.2. Tribromide ion.

It is known[1] that the tribromide ion, Br_3^-, is stable, and readily formed in media containing bromine. It could therefore be an effective brominating agent in such media.

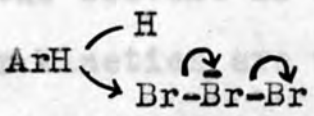
The tribromide ion has in fact been proved to be

---

1. de la Mare and Ridd, "Aromatic Substitution -," Butterworths, London, 1959.
2. E. Baciocchi, G. Illuminati and G. Sleiter, Tetrahedron Letters, 1960, 23, 30.

an important brominating entity, but considerably less significant than molecular bromine. Results have been published by many workers[1,2,3] from which the relative contribution of the tribromide ion to the overall rate of bromination by bromine in presence of bromide ion has been assessed, and found to be important only for very reactive aromatic compounds, e.g., phenols and amines.

A transition state, described as being "rather unusual" has, tentatively, been suggested[4] for the reaction between the tribromide ion and reactive aromatic substrates. It was assigned the following structure:



It was further stated that if such a transition state occured, it would mean that two Br-Br bonds would effectively be broken in the rate-determining step.

More important still is the fact that addition of bromide ion, and the consequent formation of Br_3^-, greatly reduces the overall rates of reactions of molecular bromine

---

1. E. Berliner and M.C. Beckett, J. Amer. Chem. Soc., 1957 74, 1425.
2. R.P. Bell and his co-workers, J. Chem. Soc., 1959, 1156; 1961, 63.
3. R.M. Keefer and L.J. Andrews, J. Amer. Chem. Soc., 1956, 3637.
4. de la Mare and Ridd, "Aromatic Substitution -," Butterworths, London, 1959.

with highly reactive aromatic compounds, and often simplifies the kinetic equations of these reactions[1].

X.c. Electrophilic removal of groups other than hydrogen.

Only two representative examples which are of particular relevance to the present investigation will be discussed here. The first is protodetritiation in which tritium is replaced by protium (hydrogen-exchange reaction), and the second is protodesilylation in which a trialkylsilyl group is being removed.

Since both reactions are usually conducted under conditions where the solvent is also the electrophilic reagent, pseudo first-order kinetics are usually obtained[2,3]. Though alternative mechanisms have been considered for protodetritiation, the accepted mechanism[4,5] for both reactions is the S_E2 mechanism, which was also shown to be common to many other electrophilic substitution reactions (halogenation, nitration, etc.).

Some of the salient features of these two reactions

---

1. E. Berliner and U.P. Zimmerman, J. Amer. Chem. Soc., 1962, 84, 3953.
2. G.M. Harris, Trans. Faraday Soc., 1951, 47, 716.
3. J.E. Bains and C. Eaborn, J. Chem. Soc., 1956, 1436.
4. A.J. Kresge and Y. Chiang, J. Amer. Chem. Soc., 1961, 83, 2877.
5. C. Eaborn and K.C. Pande, J. Chem. Soc., 1960, 1566.

are summarized below[1].

1. From the rates of reaction of isomeric compounds, the reactivity of the various nuclear positions of an aromatic system can be accurately assessed. This is particularly useful for estimating the reactivities of meta-positions, which are not otherwise accessible. The reactivities of the various positions are sometimes expressed[2] in terms of partial rate factors (rate factors, f), so that results from these reactions can be compared with results from other electrophilic substitution reactions (halogenation, nitration, etc.).

2. These reactions are also very useful in gauging the dependence of the activating (or deactivating) power of a substituent on the activity of the electrophilic reagent.

3. The steric requirements of these reactions are somewhat different from those of the other electrophilic reactions discussed earlier. In hydrogen-exchange reactions steric factors are small or negligible, and these reactions are, therefore, particularly useful for studying the effects of

---

1. R.O.C. Norman and R. Taylor, "Electrophilic Substitution in Benzenoid Compounds," Elsevier, Amesterdam, 1965.
2. R. Baker and Eaborn, J. Chem. Soc., 1961, 5077.

o-substituents. In protodesilylation[1], however, steric acceleration is much more important than steric hindrance.

4. In hydrogen-exchange reactions, as in molecular chlorination and bromination reactions, the demand for resonance-stabilization of the transition state is large, and, consequently, the activating powers of substituents are fully utilized, whereas in protodesilylation reactions there is less call on the mesomeric release from the aromatic system at the transition state.

XI. Reaction Medium. ------.

In acetic acid as solvent, bromination reactions often show[2] orders higher than one with respect to bromine. Berliner and Zimmerman[3] studied the bromination of fluorene by molecular bromine in aqueous and glacial acetic acid, in presence and absence of added bromide ion. They found that addition of water to the solvent increased the rate of the reaction, but at the same time reduced its order. When bromide ion was initially introduced into the medium the reaction actually became first-order in bromine.

---

1. Eaborn and J.A. Sperry, J. Chem. Soc., 1961, 4921.
2. de la Mare and Ridd, "Aromatic Substitution - ," Butterworths, London, 1959.
3. UN-JIN P. Zimmerman and E. Berliner, J. Amer. Chem. Soc., 1962, 84, 3953.

The above example serves to emphasize the importance of the nature of the medium to the study of the kinetics and mechanism of reactions. This is particularly relevant to reactions involving ionic or polar species in the reactants, the products, or the transition state.

It is difficult to determine quantitatively the effects of environment on reactivity and reaction rates, but a simple qualitative theory would often suffice, and has been developed[1] to explain and correlate observed or expected changes in rates of reactions with corresponding changes in the nature of the media in which the reactions are conducted. The theory postulates: that rates of reactions depend on the relative ionizing power of the medium, and the difference in charge-distribution in the initial and transition states of the reaction. A reaction involving development of charge, or of dipolar character in the transition state becomes more facile as the ionizing power of the medium is increased, e.g., by adding salts to the medium. Conversely, if going from initial to transition state involves a diminution or a dispersion of charge, the reaction will be slower in solvents of greater ionizing power.

---

1. E.D. Hughes, Trans. Faraday Soc., 1941, 37, 603.

Adequate control of the ionic strength must be exercised[1] on reactions in which salts are added to the medium, if reliable kinetic results are to be expected from the study of these reactions. A high but constant ionic strength is necessary for the study of any reaction whose order changes on changing the ionic strength.

---

1. A.A. Frost and R.G. Pearson, "Kinetics and Mechanism," John Wiley, New York, 2nd. edtn., 1961.

SECTION (B)

CHLORINATION REACTIONS

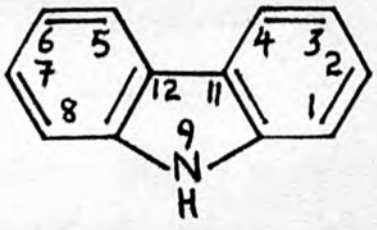
PART 1.

INTRODUCTION

1.1. Carbazole

Carbazole(dibenzopyrrole)occurs naturally, and is found in the anthracene fraction of coal tar. Carbazole and a large number of its' derivatives find extensive use in the dye and printing industries, cancer research, and polymer chemistry.

The system used by Chemical Abstracts for numbering carbazole is followed; carbazole would then have the following structure.



Earlier work on carbazole has been reviewed [1,2,3,4] and covered up to 1957. The work included nitration, chlorination, bromination, and iodination reactions of carbazole and some of its' derivatives. From all these reactions the 3-position emerged as the most reactive

---

1. N. Campbell and B.M. Barclay, Chem. Revs., 1947, 40, 359
2. W. Freudenberg, in "Heterocyclic Compounds", ed. R.C. Elderfield, John Wiley, New York, 1952, Vol. 111, p.291.
3. W.C. Sumpter and F.M. Miller, "The Chemistry of Heterocyclic Compounds; Heterocyclic Compounds with Indole and Carbazole Systems", Interscience, Wormerveer, 1954.
4. T.S. Stevens, in "Chemistry of Carbon Compounds", ed. E.H. Rodd, Elsevier, Amsterdam, 1957, Vol. IVa, p. 28.

centre in the system. This is followed by the 1-, 6-, and 8-positions, in that order. Controlled nitration[1,2] of carbazole gave 5-6% of 1-nitrocarbazole, and 70-75% of the 3-isomer. Exhaustive nitration yielded 1,3,6,8-tetranitrocarbazole[3,4]. A similar pattern of reactivity was also reported for the halogenation of carbazole. It was found[4,5] possible to obtain 3-bromo-, 3,6-dibromo-, 1,3,6-tribromo-, or 1,3,6,8-tetrabromocarbazole either by careful control of the amount of bromine used, or by choosing a suitable brominating agent. Similarly, carbazole can be chlorinated, and iodinated, to give the analogous chloro- and iodo-derivatives. The only earlier reference to the reactivity of the nuclear positions in carbazole, other than those discussed above, seems to be that of Murphy and his co-workers[3], who reported the occurrence of 1,2,6,8-tetranitrocarbazole (10%) in the products of nitration of carbazole.

---

1. H. Lindemann, Ber., 1924, 57, 555.
2. R.W.G. Preston, S. Tucker, and J.M.L. Cameron, J.Chem.Soc., 1942, 500.
3. D.B. Murphy, F.R. Schwartz, J.P. Picard, and J.V.R. Kaufman, J.Amer.Chem.Soc., 1953, 75, 4289.
4. Sumpter and Miller, "The Chemistry of Heterocyclic Compounds: Heterocyclic Compounds with Indole and Carbazole Systems", Interscience, Wormerveer, 1954.
5. von Schmid and P. Karrer, Helv.Chim.Acta, 1946, 29, 573.

It was also reported[1] that carbazole reacts instantaneously with both bromine and chlorine, and it seems that no attempt has so far been made to measure the rate of nitration of carbazole.

Both N-methyl- and N-ethylcarbazole give, on nitration, similar results to those found for carbazole[2].

More recently, quantitative studies have been made[3] on the nitration of carbazole and some other related compounds, under conditions where only mono-nitro derivatives are expected to result. The relative reactivities of the various positions of carbazole, gauged by their respective extents of substitution, were determined and found to be in the order 3> 1> 2. Competitive nitration of carbazole and diphenylamine showed the latter compound to be the more reactive. These conclusions are in good agreement with theoretical predictions[4] based upon molecular-orbital calculations.

The acid cleavage of the 3-trimethylsilyl derivative of N-ethylcarbazole, together with that of some other

---

1. R. Oda and K. Tamura, Sci.Papers Inst.Chem.Research (Tokyo), 1937, 33, No. 728, 129; from Chem.Abs., 1938, 32, 2516[6].
2. Sumpter and Miller, "The Chemistry of Heterocyclic Compounds; Heterocyclic Compounds with Indole and Carbazole Systems", Interscience, Wormerveer, 1954.
3. M.J.S. Dewar and D.S. Urch, J.Chem.Soc., 1958, 3079.
4. H.C. Longuet-Higgins and C.A. Coulsen, Trans.Faraday Soc., 1947, 43, 87; G. Berthier and B. Pullman, Compt. rend., 1948, 226, 1725.

trimethylsilyl derivatives of related heterocyclic compounds, has been studied by Eaborn and Sperry[1]. The partial rate factor (f) at the 3-position in N-ethylcarbazole was reported, and it was discussed with reference to the partial rate factor obtained for the same position in the nitration of carbazole.

1.2 N-Acetylcarbazole

Far less work has been published on N-acetylcarbazole compared with carbazole. Most of the studies reported on the electrophilic substitution reactions of N-acetylcarbazole have a semi-quantitative nature. In many of these reports only the percentage of the major isomer (obtained in its pure form) is reported. However, these results do not exclude the possible occurrence of other minor products, the presence of which was neither proved not disclaimed in these reports.

The bromination[2] and iodination[3] of N-acetylcarbazole gave predominantly the 3-isomer. Nitration of the same compound was reported[4] to have given no useful results, but no elaborate argument was presented to corroborate this statement. Chlorination of N-acetylcarbazole has not been

---

1. C. Eaborn and J.A. Sperry, J.Chem.Soc., 1961, 4921.
2. G.L. Ciamician and P. Silber, Gazzetta, 1882, 12, 276.
3. Tucker, J.Chem.Soc., 1926, 546.
4. Preston, Tucker, and Cameron, J.Chem.Soc., 1942, 500.

reported before, and as far as the author is aware, this investigation presents the first quantitative study of this reaction.

In all the electrophilic substitution reactions discussed so far, the order of reactivity in the carbazole system closely resembled that of its N-acetyl derivative. There is, however, one reaction, the Friedel-Crafts reaction, in which the two compounds exhibit[1] profoundly different reactivity patterns. For whereas the reaction of carbazole with acetyl chloride and chloro-acetyl chloride in the presence of aluminium chloride gave 3-acyl, and 3,6-diacyl-carbazoles, further acetylation of N-acetyl-carbazole, under the same conditions, yielded exclusively 2,9-diacetyl-carbazole. If these results are correct, then it could be concluded that in this reaction the phenyl group controls the course of the substitution in N-acetylcarbazole. However, N-alkylcarbazoles reacted in the same way as carbazole[2].

---

1. Plant, Rogers, and Williams, J.Chem.Soc., 1935, 741.
2. Freudenberg, in "Heterocyclic Compounds", ed. R.C. Elderfield, John Wiley, New York, 1952, Vol. III, p. 291.

1.3 The object of the present investigation

Dewar[1], Eaborn[2] and their co-workers studied the effect that ring-closure has on the reactivity of carbazole, and some other related non-alternant systems. They also discussed the importance of polarisability effects in the nitration and protodesilylation reactions of carbazole. Halogenation reactions, and in particular chlorination reactions are known[3] to be sensitive to polarisability effects, and structural changes. It seemed desirable, therefore, to investigate the importance of these factors in the chlorination of carbazole.

N-Acetylcarbazole was chosen for study because the reaction of carbazole itself with chlorine is very fast and cannot, therefore, be followed by conventional kinetic techniques. Furthermore, the study of the chlorination of N-acetylcarbazole presented many interesting features, which this compound shares with anilides, and diphenyls.

---

1. Dewar and Urch, J.Chem.Soc., 1958, 3079.
2. Eaborn and Sperry, J.Chem.Soc., 1961, 4921; R. Baker and Eaborn, ibid., 1961, 5077.
3. de la Mare, D.M. Hall, M.M. Harris, and Hassan, Chem. and Ind., 1958, 1086; de la Mare, in "Theoretical Organic Chemistry - Kekule Symposium", Butterworths, London, 1959, p. 219.

SECTION (B)

PART 2.

EXPERIMENTAL

2.1. Preparation and Purification of Materials. ------ .

Purification of Acetic acid:

A solution of bromine (0.5 ml.) in acetic acid (2 l.) was kept at room temperature for about 24 hrs. The solution was then vigourously shaken with small amounts of freshly prepared silver oxide until the resulting mixture became white. The acetic acid obtained from the distillation of this mixture was refluxed with potassium dichromate (200 g.), and water (100 ml.) for 8-10 hrs. On redistilling the acetic acid, the first 250 ml. were rejected. The rest of the distillate was fractionated from an efficient, helix-packed column to a constant freezing point (16.65°). The subsequent fractions, distilling at a constant boiling point (119°), were collected, and taken as the pure dry acid.

Purification of Bromoform:

Freshly distilled bromoform (M. & B.) was used. The distillations were carried out under reduced pressure (ca. 18 mm.).

Standard Solutions of Chlorine in Acetic acid:

Chlorine gas (I.C.I.) was passed in turn through water and concentrated sulphuric acid, to free it from

hydrogen chloride and water respectively, and then into acetic acid. The acetic acid solution was then standardised, iodometrically, against standard sodium thiosulphate, and subsequently diluted to the desired concentration.

$^{36}Cl_2$ gas was supplied in ampules by the Radiochemical Centre, Amersham. The ampules used had the following specifications; Volume at N.T.P., 11.2 ccs.; specific activity, 44.2 uc./mM.; total activity, 22.1 uc.

For a standard solution containing labelled chlorine, $^{36}Cl_2$ was separately dissolved in a small (but known) amount of acetic acid, and this was then added to another solution of non-labelled chlorine of known concentration. Restandardisation was, however, necessary.

Carbazole: m.p. 246° (lit.[1]; 245°).

It was a commercial specimen recrystallized from alcohol.

1-Chlorocarbazole: m.p. 106-107° (lit.[2]; 109-110°).

The method used for the preparation of 1-chlorocarbazole was essentially that of Barclay and Campbell[2]. o-Chlorophenylhydrazine, prepared from o-chloroaniline, was treated

---

1. S.H. Tucker, J. Chem. Soc., 1926, 546.
2. B.M. Barclay and N. Campbell, J. Chem. Soc., 1945, 530.

with cyclohexanone to give the corresponding phenylhydrazone, which, in turn, was cyclised to 8-chloro- 1,2,3,4- tetrahydrocarbazole using dilute sulphuric acid. The method adopted for the dehydrogenation of 8-chlorotetrahydrocarbazole to 1-chlorocarbazole was as follows. A mixture in benzene (35 ml.) of the tetrahydrocarbazole (1.23 g.) and chloranil (3 g.) sealed in a strong glass tube, was left for 3 days in a furnace at 120-130°. The contents of the tube were then chromatographed on alumina, and eluted with benzene. The benzene was then evaporated, and the residue was recrystallized first from a mixture of benzene and petroleum ether (60-80°), and then from ethanol. Analytical Results*: (Found: C, 71.4; H, 4.1; Cl, 17.8; N, 7.0. Calculated for $C_{12}H_8ClN$: C, 71.5; H, 4; Cl, 17.6; N, 7.0.)

2-Chlorocarbazole: m.p. 244° (lit.[1]; 244°).

This compound was prepared from 2-aminocarbazole (Light & Co.) by the Sandmeyer reaction. It was found necessary, however, to boil the reaction mixture for some time to affect complete and successful decomposition of the cuprous chloride complex into 2-chlorocarbazole. 2-Chlorocarbazole was

---

* All analysis was by Dr. A. Bernhardt, Mulheim, Germany.

1. F. Ullmann, Annalen, 1904, 332, pp. 96, 97.

recrystallized from methanol.

3-Chlorocarbazole: m.p. 200° (lit.[1]; 244°).

3-Chlorocarbazole was prepared from 3-aminocarbazole (Aldrich) as is described for 2-chlorocarbazole. The diazonium salt from 3-aminocarbazole was so stable, that it was possible to isolate it from the reaction mixture and purify it by washing it with dry acetone, before treating it with cuprous chloride. Recrystallization of 3-chlorocarbazole was from alcohol.

4-Chlorocarbazole: m.p. 95.5° (lit.[2]; 96°).

This compound and 4-chloro-N-acetylcarbazole were a very much appreciated gift from Dr. E.A. Johnson.

N-Acetylcarbazole: m.p. 76° (lit.[3]; 76°).

N-Acetylcarbazole, and all chloro-N-acetylcarbazoles (except 1-chloro-N-acetylcarbazole) were prepared by acetylating the corresponding carbazole by the route described below. Excess acetic anhydride, and a few drops of concentrated sulphuric acid were added to a solution in acetic acid of the

---

1. F. Ullmann, Annalen, 1904, 332, pp. 96,97.
2. R.C.G. Moggridge and S.G.P. Plant, J. Chem. Soc., 1937, 1125.
3. J. Boeseken, Rec. Trav. chim., 1912, 31, 364.

appropriate carbazole. The mixture was refluxed on a water-bath for about 1 hr. The contents were then poured into a large volume of ice-cold water, and the precipitate obtained was collected, and recrystallized from a suitable solvent.

N-Acetylcarbazole was recrystallized from ethanol.

2-Chloro-N-acetylcarbazole: m.p. 122-124°.

Recrystallized from methylated spirit.

Analytical Results: (Found: C, 69.0; H, 4.3; Cl, 14.5; N, 5.9. $C_{14}H_{10}ClNO$ requires: C, 69.0; H, 4.1; Cl, 14.6; N, 5.7.)

3-Chloro-N-acetylcarbazole: m.p. 124-125° (lit.[1]; 124°).

Recrystallization was from alcohol.

4-Chloro-N-acetylcarbazole: m.p. 101-107° (lit.[2]; 126°).

1-Chloro-N-acetylcarbazole:

The following standard techniques of acetylation were tried on 1-chlorocarbazole; boiling with acetic anhydride with (and without) added concentrated sulphuric acid; a mixture of acetic acid and acetic anhydride with a trace of sulphuric acid; acetyl chloride in presence of potassium

---

1. S.H. Tucker, J. Chem. Soc., 1924, 1145.
2. R.C.G. Moggridge and S.G.P. Plant, J. Chem. Soc., 1937, 1125.

hydroxide; and iso-propenylacetate with p-toluenesulphonic acid as a catalyst. The products of these reactions were analysed by both infrared spectroscopy, and thin-layer chromatography. From the results it could be inferred that 1-chloro-N-acetylcarbazole was present in all these reaction mixtures. All attempts to isolate 1-chloro-N-acetylcarbazole from the products of these reactions failed. Recrystallizations always gave fractions that contained either 1-chlorocarbazole by itself, or a mixture of it and its N-acetyl derivative; but it never gave pure 1-chloro-N-acetylcarbazole.

Diphenylamine: m.p. 53-54° (lit.; 54°).

Recrystallized from aqueous alcohol.

N-Acetyldiphenylamine: m.p. 101° (lit.[1]; 103°).

This compound was prepared by the acetylation of diphenylamine. Diphenylamine was refluxed for about 30 mins. in a mixture of acetic acid and acetic anhydride. N-Acetyldiphenylamine was also recrystallized from aqueous ethanol.

4-Chloro-N-acetyldiphenylamine*: m.p. 65°.

The method used for preparing this compound was that utilized by Wieland and Wecker[2] to obtain the corresponding

---

* The help of Mr. C. Siggers in preparing this compound is gratefully acknowledged.

1. A. Claus, Ber., 1881, 441, 2365.
2. I.H. Wieland and A. Wecker, Ber., 1922, 1804.

amine. The reaction was carried out under strictly anhydrous conditions; steam-distillation was replaced by distillation under reduced pressure. The final reaction products, containing the 4-chloro-N-acetyldiphenylamine, were purified by column chromatography using alumina. The products were eluted first with benzene, and then with pet. ether (40-60°). The residue obtained on evaporating the pet. ether was recrystallized first from alcohol and then from petroleum ether (80-100°). Analytical Results: (Found: C, 68.5; H, 4.9; Cl, 14.3; N, 5.6; $C_{14}H_{12}ClNO$ requires: C, 68.5; H, 4.9; Cl, 14.4; N, 5.7.)

2-Chloro-N-acetyldiphenylamine*: m.p. 84-86°.

This isomer was prepared by the same procedure described for the synthesis of 4-chloro-N-acetyldiphenylamine. Analytical Results: (Found: C, 68.3; H, 5.2; Cl, 14.2; N, 5.6.)

Standard Sodium thiosulphate Solutions:

The commercially available N/10 sodium thiosulphate solution (B.D.H.) was used. The stock solution was further diluted when necessary.

---

* The help of Mr. C. Siggers in preparing this compound is gratefully acknowledged.

2.2. Rate Measurement Technique. ------ .

Grade (B) volumetric flasks, pipettes, and burettes were used.

All chlorination reactions were carried out in blackened flasks immersed in a thermostat kept at 25° ± 0.05°. Solutions of reagents were left to attain the temperature of the thermostat before they were made to react with each other. Blanks were always run for an appropriate length of time before the reactions were started, to check upon any loss of chlorine due to volatility, and to provide zero titres for fast reactions. In the slow runs the intial concentrations of chlorine were calculated from the first experimental point recorded after the shortest lapse of time from actual zero time.

The rates of these reactions were determined by following the chlorine uptake during the course of the reaction. Using a fast pipette, aliquot parts (5 ml.) were sampled from the reaction flask at recorded regular intervals of time into aqueous solutions of iodine-free potassium iodide. The liberated iodine was then titrated against standard sodium thiosulphate solutions, using starch (and sometimes sodium starch glycollate) solution as indicator.

The concentrations of the reagents in all the kinetic runs to be described were in the region of M/80; the concentrations of the solutions of the aromatic substrates were always in excess to those of chlorine.

The rate coefficients for these chlorination reactions were calculated using the integrated rate equation derived for bimolecular reactions,

$$k_2 = \frac{2.303}{t(a-b)} \log \frac{b(a-x)}{a(b-x)} \quad ,$$

where (a) is the initial concentration of the aromatic compound, (b) is the initial concentration of chlorine, and (a-x) and (b-x) are, respectively, the concentrations of the aromatic substrate and chlorine at time (t).

2.3.a. Kinetic Data and Rate Constant for N-Acetylcarbazole. ------ .

I. First Run.

Intial concentrations:

N-Acetylcarbazole = 0.015 M

Chlorine = 0.01128 M

Time (mins.)	Titre (ml.of 0.01N $Na_2S_2O_3$)	k_2 ($l.mole^{-1}\ min.^{-1}$)
0.00	11.28 [b]	
0.83	10.7	4.2
2.93	9.75	4.4
5.4	8.4	4.0
9.37	7	4.1
14.4	5.7	4.1
17.75	4.7	4.5
42.25	2.2	4.5

b = Zero titre taken from a blank.

k_2 = 4.3 $l.mole^{-1}\ min.^{-1}$ ($\pm$ 0.2).

II. Second Run.

Initial concentrations:

N-Acetylcarbazole = 0.015 M

Chlorine = 0.0128 M

Time (mins.)	Titre (ml.of 0.01N $Na_2S_2O_3$)	k_2 ($l.mole^{-1}min.^{-1}$)
0.00	12.8 [b]	
3.2	10.65	4.1
11.5	7.3	4.1
18.35	5.67	4.2
26.65	4.4	4.2
33.4	3.4	4.6
43.75	2.8	4.4
58	2.1	4.4
69.25	1.8	4.4

k_2 = 4.3 $l.mole^{-1}$ $min.^{-1}$ (± 0.2).

III. Third Run.

Initial concentrations:

N-Acetylcarbazole = 0.01616 M

Chlorine = 0.01373 M

Time (mins.)	Titre (ml.of 0.01N $Na_2S_2O_3$)	k_2 ($l.mole^{-1}$ $min.^{-1}$)
0.00	13.73 [b]	
2.45	11.23	4.1
11.5	7.47	4.3
18.33	5.68	4.3
26.75	4.3	4.4
33.4	3.7	4.2

$k_2 = \underline{\underline{4.3}}$ $l.mole^{-1}$ $min.^{-1}$ ($\pm$ 0.1).

IV. Fourth Run.

Intial concentrations:

N-Acetylcarbazole = 0.015 M

Chlorine = 0.0117 M

Time (mins.)	Titre (ml.of 0.01N $Na_2S_2O_3$)	k_2 ($l.mole^{-1}$ $min.^{-1}$)
0.00	11.7 [b]	
2.45	10.1	4.2
9.4	7	4.4
16.83	5.15	4.4
31.2	3.3	4.3
51.25	1.9	4.4
72.15	1.15	4.6
87.3	0.85	4.6

$k_2 = \underline{\underline{4.4}}$ $l.mole^{-1}$ $min.^{-1}$ ($\pm$ 0.2).

2.3.b. Kinetic Data and Rate Constant for 2-Chloro-N-acetylcarbazole. ------ .

Intial concentrations:

2-Chloro-N-acetylcarbazole = 0.0125 M

Chlorine = 0.01008 M

Time (mins.)	Titre (ml.of 0.024N $Na_2S_2O_3$)	k_2 ($l.mole^{-1}$ $min.^{-1}$)
0.00	4.2 [e]	
29.85	3.21	0.80
46.35	2.82	0.80
59.95	2.56	0.81
75.15	2.3	0.81
90	2.08	0.82
110	1.85	0.82
130	1.56	0.83

e = Zero titre from first experimental point.

k_2 = 0.81 $l.mole^{-1}$ $min.^{-1}$ ($\pm$ 0.01).

2.3.c. Kinetic Data and Rate Constant for 3-Chloro-N-acetylcarbazole. ------ .

Intial concentrations:

3-Chloro-N-acetylcarbazole = 0.0125 M

Chlorine = 0.01044 M

Time (mins.)	Titre (ml.of 0.024N $Na_2S_2O_3$)	k_2 ($l.mole^{-1}\ min.^{-1}$)
0.00	4.35 [e]	
5.3	4.2	0.57
7.75	4.12	0.58
15.66	3.9	0.58
18.65	3.84	0.56
42.7	3.32	0.56
66.95	2.9	0.57
93.4	2.58	0.56

k_2 = 0.57 $l.mole^{-1}\ min.^{-1}$ ($\pm$ 0,01).

2.3.d. Kinetic Data and Rate Constant for N-Acetyl-diphenylamine. ------ .

I. First Run.

Intial concentrations:

N-Acetyldiphenylamine = 0.01 M

Chlorine = 0.006616 M

Time (mins.)	Titre (ml.of 0.008N $Na_2S_2O_3$)	k_2 ($l.mole^{-1}$ $min.^{-1}$)
0.00	8.27 [e]	
6.6	7.7	1.10
14.65	7.1	1.10
36	5.87	1.8
60.1	4.79	1.8
89.75	3.83	1.9
122	3.04	1.11

e = Zero titre taken from first experimental point.

k_2 = 1.09 $l.mole^{-1}$ $min.^{-1}$ ($\pm$ 0.01).

II. Second Run.

Intial concentrations:

N-Acetyldiphenylamine = 0.01 M

Chlorine = 0.00834 M

Time (mins.)	Titre (ml. of 0.008N $Na_2S_2O_3$)	k_2 ($l.mole^{-1}\ min.^{-1}$)
0.00	10.425 [e]	
5.5	9.54	1.1
17.1	8	1.11
27.15	7	1.09
43.7	5.69	1.08
55.25	4.93	1.09
72.25	4.06	1.1
94.2	3.18	1.11
124	2.42	1.09

$k_2 = \underline{1.1}\ l.mole^{-1}\ min.^{-1}\ (\pm 0.01)$.

2.4. Methods of Product Analysis. ------ .

Infrared spectroscopy, isotopic dilution, vapour-phase chromatography, and thin-layer chromatography techniques were used to analyse the products of chlorination of N-acetylcarbazole. The products from the reaction of chlorine with N-acetyldiphenylamine were studied by vapour-phase chromatography.

2.4.a. Infrared spectroscopy method:

It was found that 2-chloro-N-acetylcarbazole absorbs strongly at 915 cm^{-1}. This band was, however, absent from the spectra of both N-acetylcarbazole and 3-chloro-N-acetylcarbazole. It was, therefore, used to detect the presence of the 2-chloro-isomer, and to give a rough estimate of the extent to which it is formed in the reaction products.

Pure bromoform was found to be an ideal solvent, because it does not absorb[1] seriously in the 9-13 u region, except for a very weak band at 870 cm^{-1}.

To begin with a series of mixtures of N-acetylcarbazole, 2-chloro-, and 3-chloro-N-acetylcarbazole in pure bromoform were prepared so that the concentration of N-acetylcarbazole in any one mixture was always 50 % of the total concentration

---

1. J.R. Knowles and R.O.C. Norman, J. Chem. Soc., 1961, 2938.

of the mixture, and that the concentration of chloro-N-acetylcarbazole (whether only 2-chloro- or 3-chloro-, or both) was approximately 0.025 g. per ml. of solution. In these solutions the percentage of the 2-chloro- isomer varied from 2.5 % to 50 %. The spectra of these solutions were then determined.

Known amounts of N-acetylcarbazole were treated with chlorine solutions of known concentrations, so that about 50 % mono-chloro-N-acetylcarbazole were produced. These reactions were conducted in acetic acid as solvent. Two methods were used for isolating the reaction products from the acid.

I) Acetic acid was distilled under reduced pressure. The residue was washed twice with ether, dried, and dissolved in pure bromoform to give about 0.025 g. of chloro-N-acetylcarbazole per ml. of solution.

II) A solution of the reaction mixture in ether was washed several times with water to remove acetic acid. The ether extract was evaporated to dryness, and the residue was dissolved in an appropriate amount of bromoform.

The spectra of these bromoform solutions were obtained, and compared with those of the synthetic mixtures.

All the spectroscopic measurements were done on a Grubb Parsons i.r. recording spectrophotometer, Type G.S.2_A, using sodium chloride cells of 0.8 mm. thickness. Blanks of pure bromoform were used. Base lines were drawn for each separate set of determinations.

2.4.b. Isotopic dilution method:

This technique was used to determine the percentage of 3-chloro-N-acetylcarbazole in the chlorination products.

The whole procedure consisted of dissolving a known weight of this isomer, in its inactive form, in a measured sample taken from a reaction mixture (of known concentration) in which all the isomers were obtained in their radioactive form; by using labelled chlorine. The isomer was then precipitated by pouring the diluted mixture into a large volume of cold water. The diluted isomer was then filtered off, and fractionally recrystallized from alcohol. The isomer was deemed pure when neither its melting point, nor its activity showed any significant change over a range of three consecutive recrystallizations.

The specific activity of the starting material was then indirectly determined as follows. Part of the labelled chlorine was treated with a solution of sulphur dioxide in

water to convert free chlorine into hydrochloric acid, which was then neutralized with lithium hydroxide. The neutralized mixture was evaporated to dryness, and the residue was washed with pure acetone to selectively abstract lithium chloride. The specific activity of this lithium chloride solution was then determined, and was taken as the specific activity of the undiluted isomer.

The specific activity of the diluted isomer was calculated from the activity of a solution, of known molarity, of this isomer dissolved in pure acetone.

The relation of the specific activity (A_o) of the starting material (x g.) to the specific activity (A_1) of the diluted isomer (x + d; where d is the weight of the inactive isomer added) is given[1] by,

$$A_1(x + d) = A_o x$$

$$A_o/A_1 = 1 + d/x$$

A_o/A_1 is designated dilution ratio (D.R.).

Hence,

$$x = d/(D.R. - 1)$$

---

1. C.J. Collins, "Advances in Physical Organic Chemistry," es. V. Gold, Academic Press, London, 1964, Vol.II, p.4.

2.4.c. Vapour-phase chromatography method:

Products of chlorination of N-acetylcarbazole were prepared, and isolated by the same technique that was described for preparing similar mixtures for infrared analysis. Gas-chromatography analysis on samples from these reaction products was carried out by Dr. E.A. Johnson[1].

2.4.d. Thin-layer chromatography method:

This method was used to analyse the products of chlorination of N-acetylcarbazole. It was also used to study the results of chlorination of carbazole, and of competitive chlorination of carbazole and diphenylamine.

Thin-layer chromatograph (T.L.C.) plates were prepared by spreading, evenly, aqueous slurries (2 g./5 ml. of water) of silicagel G. (E. Merck, Germany) on thin, clean, dry glass plates. 2 g. of silicagel were used for every 8 x 10 cm^2. The adsorbent was reactivated by allowing the plates to dry first at room temperature for about 20 minutes, and then in an oven at 95° for a period of approximately 3 hours. The reactivated plates were stored in a desiccator over silicagel.

Micro-pipettes were used for spotting the various solutions on the plates. Spots on the same plate intended

---

1. Dr. E.A. Johnson, Medical Research Council, Holly Hill, London, N.W.2.

for quantitative comparisons were delivered by the same pipette.

The ideal solvent for developing the chromatograms was found to be a mixture of benzene (40 %) and petroleum ether (40-60°; 60 %). It was found necessary, however, to use pure benzene for eluting the disubstitution products. After the solvent was removed from them, the developed plates were exposed to ultra violet radiations from a U.V.S. 500 lamp (Hanovia) until all the spots on the plates were adequately visible to the naked eye. For analytical comparisons, spots from the reaction mixtures were matched in size and density with suitable reference spots.

The following chlorination reactions were carried on N-acetylcarbazole:

I) Chlorination of 50 % of the N-acetylcarbazole.

II) Chlorination using equimolar concentrations of reagents.

III) Chlorination in presence of excess of chlorine.

The products of these reactions were isolated, and then hydrolysed by boiling under reflux and for 30 minutes a solution of the products in alcohol to which concentrated hydrochloric acid was previously added. The mixture was cooled, made alkaline with sodium hydroxide, and then carefully

extracted with ether. After it was washed several times with water, the ether extract was evaporated to dryness, and the residue was finally dissolved, quantitatively, in benzene.

The products of the 50 % chlorination reaction were tested in both the hydrolysed, and the unhydrolysed form.

2.5. Data and Results of Product Analysis. ------ .

2.5.a. N-Acetylcarbazole.

2.5.a.I. Analysis by the infrared spectroscopy method.

Data:

The following is a typical reaction mixture that was prepared, and submitted for analysis.

Reactants,

N-Acetylcarbazole	=	0.5231 g.
Chlorine	=	0.1808 g.

Products,

N-Acetylcarbazole (unreacted)	=	0.2563 g.
Chloro-N-acetylcarbazole	=	0.3107 g.
Added N-acetylcarbazole	=	0.0544 g.
Total amount of products		0.6214 g.

These 0.6214 g. were dissolved in 12.4 ml. of pure bromoform.

Results:

Comparison of the spectra of the above reaction mixture with those of suitable synthetic mixtures lead to the following conclusions.

1. 2-Chloro-N-acetylcarbazole is one of the products of chlorination of N-acetylcarbazole.

2. The percentage of this isomer is 5 % approximately.

2.5.a.II. Analysis by the isotopic dilution method.

Data:

I) 250 ml. of reaction mixture were prepared to contain,

N-acetylcarbazole = 1.046 g.

chlorine (0.1847 N)= 25 ml.

II) A sample (100 ml.) of this reaction mixture was removed, and was analysed for 3-chloro-N-acetylcarbazole. Assuming that all the chlorine went into monosubstitution, then this sample would contain 0.225 g. of mixed chloro-N-acetylcarbazoles.

III) Weight of inactive 3-chloro-N-acetylcarbazole added (diluent) = 2 g.

IV) Activity of the starting material (0.00164 M solution) = 9510 counts/ 15 mins.

V) Activity of the diluted isomer (0.02052 M solution) = 9100 counts/ 15 mins.

Results:

D.R. = 9510/0.00164 x 0.02052/9100 = 13.08

Weight of radioactive 3-chloro-N-acetylcarbazole

(in 100 ml. sample)

= 2/12.08 = 0.1656 g.

∴ Percentage of 3-chloro-N-acetylcarbazole

= 100 x 0.1656/0.225 = 74 %.

But this percentage had to be corrected for the chlorine that was removed as dichloro-N-acetylcarbazole. It was found reasonable to assume that the loss due to this amounts to about 5 % of the total chlorine concentration.

∴ The percentage of 3-chloro-N-acetylcarbazole = 83 %.

2.5.a.III. Analysis by the v.p.c. method.

Data:

Two reaction mixtures were prepared in which N-acetylcarbazole and chlorine were present in the following concentrations.

1. N-Acetylcarbazole = 0.5292 g.
   Chlorine (0.472 N) = 5 ml.
2. N-Acetylcarbazole = 0.5235 g.
   Chlorine (0.5036 N) = 5 ml.

Results:

In each case the reaction products were recovered, quantitatively, and analysed by v.p.c.

The ratio of 2-chloro- to 3-chloro- to 4-chloro-N-acetylcarbazole was found to be in the order of 3:44:3, respectively.

2.5.a.IV. Analysis by the t.l.c. method.

Data:

1. 50 % Chlorination reaction.

Reactants,

N-acetylcarbazole = 0.8276 g.

chlorine (0.8 N) = 5 ml.

Products,

chloro-N-acetylcarbazole = 0.46 g.

chlorocarbazole = 0.38 g.

2. Chlorination reaction using equimolecular quantities of reagents.

Reactants,

N-acetylcarbazole = 0.8276 g.

chlorine (0.8 N) = 10 ml.

Products,

chloro-N-acetylcarbazole = 0.92 g.

chlorocarbazole = 0.76 g.

3. Chlorination reaction using excess of chlorine.

Reactants,

N-acetylcarbazole = 0.41 g.

chlorine (0.36 N) = 15 ml.

Results and Conclusions:

Analysis, by thin-layer chromatography, of the above reaction mixtures (before and after they were hydrolysed)

enabled the following conclusions to be drawn.

I) Carbazoles travelled faster than their N-acetyl derivatives. (Fig.I) The following oder for the rate of elution was also given for the compounds described: 1-chlorocarbazole> 2-> 3-~4-~carbazole> N-acetyl- ~ chloro-N-acetylcarbazoles.

II) Hydrolysis of the N-acetylcarbazoles was complete under the reaction conditions used. (Plate I.)

III) Analysis of the products of 100 % chlorination of N-acetylcarbazole, in which all the isomers were present in their hydrolysed form, established the presence of all the four monochlorocarbazoles in the products of chlorination. (Plate II.)

IV) The separation of the chloro-N-acetylcarbazoles was very poor. Consequently, no attempt was made to analyse these isomers quantitatively. The separation of carbazole, 3-chloro-, and 4-chlorocarbazole was equally poor. However, 1-chloro-, and 2-chlorocarbazole separated neatly from one another, and from all the other isomers. (Fig. I) It was, therefore, possible to obtain a reasonable estimate of the percentages of these two isomers.

V) The percentages of 1-chloro-N-acetylcarbazole, and 2-chlorocarbazole were estimated to be 3 % and 6 %, respect-

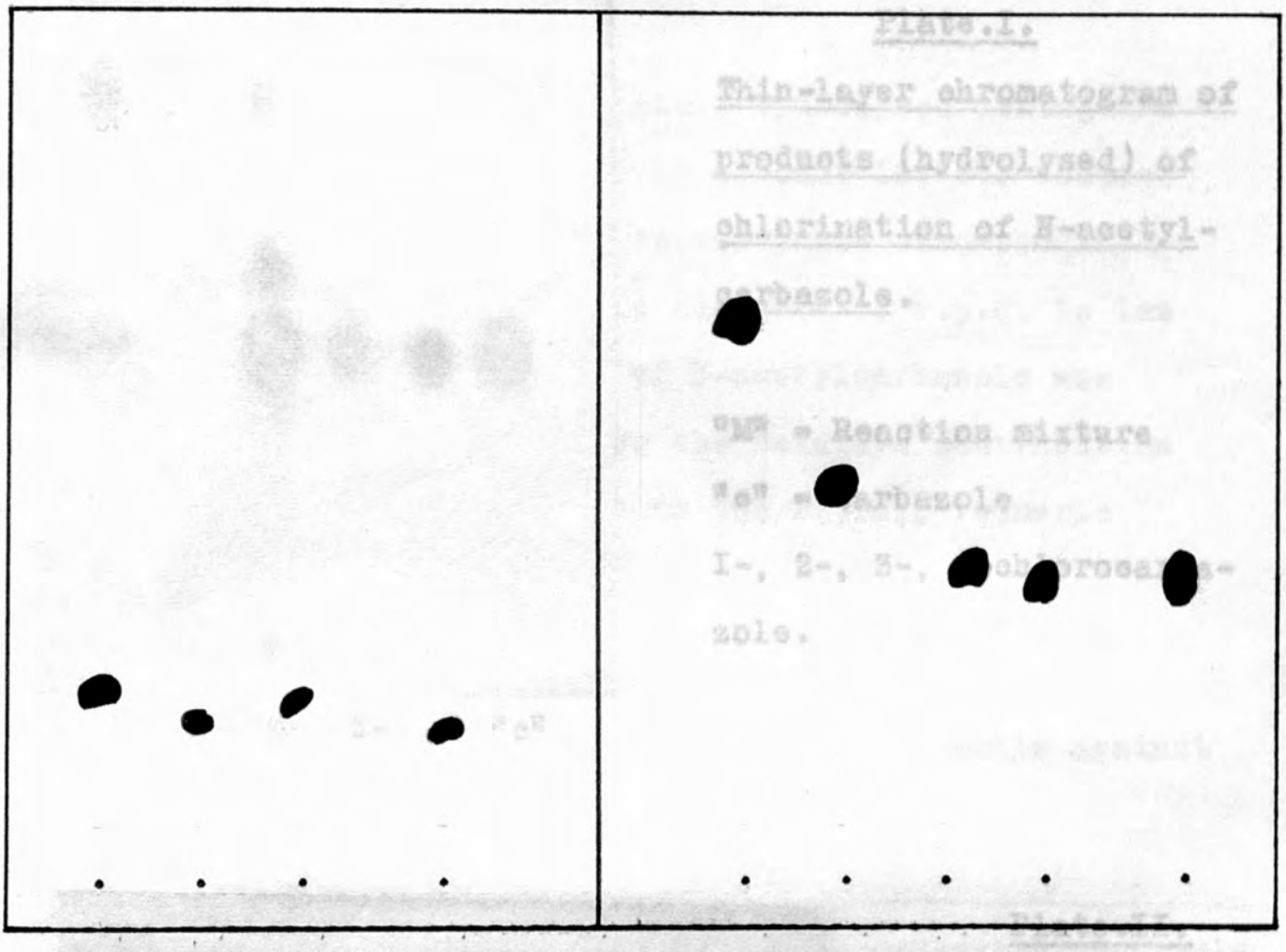
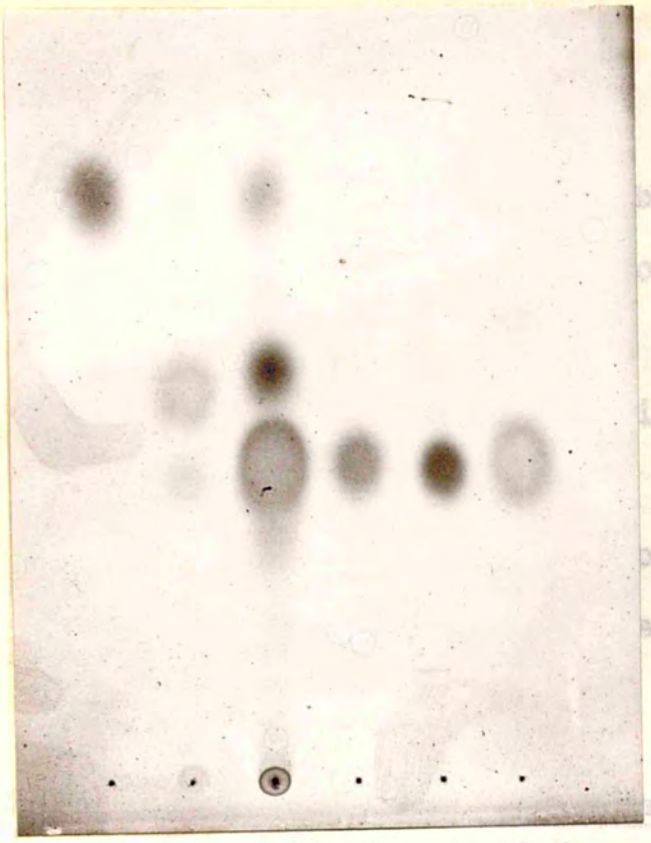


Fig.I. Order of elution of carbazole, chlorocarbazole, and their N-acetyl derivatives, using benzene-light petroleum (2:4) as solvent.



I- 2- "M" 3- 4- "c"

Plate.I.

Thin-layer chromatogram of products (hydrolysed) of chlorination of N-acetyl-carbazole.

"M" = Reaction mixture

"c" = carbazole

I-, 2-, 3-, 4-chlorocarbazole.

Reaction mixture

4-,3-,2-,I-chlorocarbazole

Plate.II.

Two-dimensional development of products (hydrolysed) of 100 %-chlorination of N-acetylcarbazole.

ively. (Plate III. and IV.)

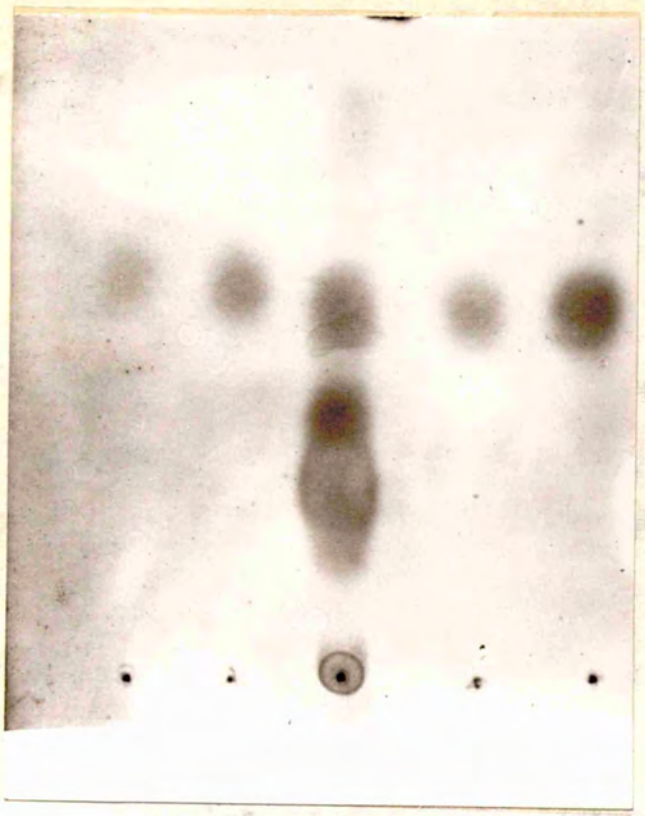
VI) 1-Chloro-N-acetylcarbazole hydrolysed during the process of isolation; this would account for its absence from the results obtained by vapour-phase chromatography. Consequently, the isomer ratio assigned by v.p.c. to the products of monochlorination of N-acetylcarbazole was recalculated to accomodate for the relative contribution by 1-chloro-N-acetylcarbazole to the overall isomeric distribution.

2.5.a.V. Summary of methods and results.

The following table lists the isomer ratio against the methods by which it was obtained.

Analytical Method	Percentage of Chloro-N-acetylcarbazole			
	1-	2-	3-	4-
Infrared spectroscopy		5		
Isotopic dilution *			83	
V.P.C.*		6	85	6
T.L.C.	3	6		
Representative ratio	3	6	85	6

* The corrected values are quoted here.



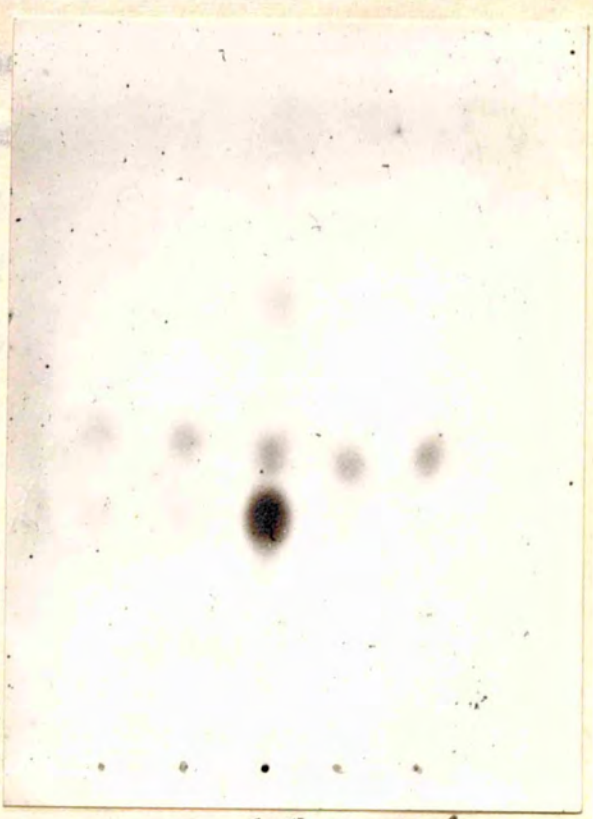
2 3 "M" 4 5 %

Plate.III.

Absolute percentage of the I-chloro-isomer in the products of chlorination of N-acetylcarbazole.

Plate.IV.

Absolute percentage of the 2-chloro-isomer in the products of chlorination of N-acetylcarbazole.



4 6 "M" 6 8 %

2.5.b. N-Acetyldiphenylamine.

2.5.b.I. Analysis by the v.p.c. method.

Data:

N-Acetyldiphenylamine and chlorine were made to react in pure acetic acid as solvent. The two compounds were present in the following concentrations.

1. N-Acetyldiphenylamine = 0.532 g.
   Chlorine = 5 ml.
2. N-Acetyldiphenylamine = 0.5285 g.
   Chlorine = 5 ml.

The products of these reactions were isolated by the standard method described earlier.

Results:

2-Chloro-N-acetyldiphenylamine = 34 %.
4-Chloro-N-acetyldiphenylamine = 66 %.

2.6. Competitive Chlorination of Carbazole and Diphenylamine. ------ .

2.6.a. Method of analysis.

To begin with carbazole and diphenylamine were chlorinated separately using pure acetic acid as solvent. In both cases the ratio of the aromatic substrate to that of chlorine was 3:1. The products of the reactions were isolated by the method described before. Solutions of the isolated material in acetone (A.R.) were analysed by thin-layer chromatography. From this analysis it was possible to estimate the relative percentage of all the mono-chloro-carbazoles.

Carbazole was then chlorinated in presence of diphenyl-amine. The ratio of the mixed substrate to that of chlorine was also 3:1. The chlorination products were analysed for 1-chlorocarbazole. By comparing the amount of 1-chloro-carbazole obtained in the products of chlorination of carbazole in presence, and in absence of diphenylamine it was possible to establish an order of reactivity for carbazole relative to diphenylamine.

2.6.b. Chlorination of carbazole.

Data:

Reactants,

chlorine (0.0912 N) = 5 ml.

carbazole = 0.114 g.

Products,

chlorocarbazoles (expected) = 0.046 g.

1-chlorocarbazole = 0.00414 g.

Results:

1-Chlorocarbazole = 9 %.

3-Chlorocarbazole = 91 %.

2-Chlorocarbazole was found to be absent from the chlorination products, and it seems reasonable, therefore, to assume that the 4-chloro isomer was also absent.

2.6.c. Chlorination of diphenylamine.

Data:

Diphenylamine = 0.1164 g.

Chlorine (0.0912 N) = 5 ml.

Results:

The products of chlorination of diphenylamine were analysed qualitatively, with particular emphasis on the pattern of separation of a mixture of the products and 1-chlorocarbazole.

2.6.d. Chlorination of carbazole in presence of diphenylamine.

Data:

Reactants,

chlorine (0.0912 N) = 5 ml.

carbazole = 0.114 g.

diphenylamine = 0.1161 g.

Products,

1-chlorocarbazole = 0.00069 g.

chlorocarbazole = 0.007667 g.

Results:

When analysing the results of the competitive chlorination reaction, it was assumed that the presence of diphenylamine did not alter the isomer ratio in the products of chlorination of carbazole.

Calculations based on data from chlorination of carbazole (2.6.b.), and those from competitive chlorination (2.6.d.) gave the following results:

Carbazole (unreacted) = 0.108 g.

Diphenylamine (unreacted) = 0.084 g.

The relative reactivities of carbazole and diphenylamine were then evaluated using the equation derived by Ingold[1]

---

1. C.K. Ingold and E.H. Ingold, J. Chem. Soc., 1931, 2354.

for the calculation of the relative rates of any two reactive substrates in a competitive reaction,

$$k_y/k_x = (\log y_o - \log y)/(\log x_o - \log x),$$

where y_o and x_o are the intial concentrations of the two competing substrates, and y and x are their respective concentrations after time t.

Hence,

$$k_{carbazole}/k_{diphenylamine} = \frac{\log 0.114 - \log 0.108}{\log 0.1161 - \log 0.084}$$

$$= 1/6.$$

2.7. Compilation of Infrared Spectra of Carbazole and Some of its Derivatives. ------ .

The infrared spectra of carbazole, 1-, 2-, 3-, and 4-chlorocarbazole together with their N-acetyl derivatives, are reported in Table 1. and Table 2. The spectral measurements were made on samples of these compounds in nujol, and using sodium chloride plates. The spectra were recorded with a Unicam S.P. 200 spectrophotometer.

Table 1.

Infrared absorption bands ($cm.^{-1}$) of carbazole, and its four monochloro derivatives.

Carbazole	Chlorocarbazole			
	1-	2-	3-	4-
	680 w		670 w	665 m
722 s		725 s	725 s	718 s
750 s	740 s	750 s	745 s	750 s
	785 w		780 w	782 s
	810 w	812 s	818 s	815 w
860 m	865 w	855 m	850 w	850 w
			885 m	895 w

(s = strong; m = medium; w = weak.)

Table 1. (continued)

Carbazole	Chlorocarbazole			
	1-	2-	3-	4-
		905 w		
930 s	935 m	935 m	935 m	950 s
1011 m	1030 m	1000 w		1000 w
	1068 w	1065 m	1065 m	1022 w
1100 w			1110 w	
1133 m	1135 m	1150 w	1160 w	1140 m
1197 m	1182 w			1175 s
1218 w	1210 w	1200 w	1200 w	
1230 w	1228 w	1230 m	1240 w	1230 w
1280 w	1268 w		1270 m	1280 m
				1295 w
	1317 w			
1332 s	1332 m	1323 s	1335 w	1330 w
	1495 m			
1593 m	1560 m	1593 m		1570 m
	1602 w			1610 w
1615 m	1620 w	1695 w		1625 w
1765 w				
1880 w				
3380 s	3390 m	3360 s	3420 m	3470 s

Table 2.

Infrared absorption bands ($cm.^{-1}$) of N-acetylcarbazole, and its monochloro derivatives.

N-Acetylcarbazole	Chloro-N-acetylcarbazole			Products of acetylation of 1-chlorocarbazole
	2-	3-	4-	
665 w	665 w		668 w	668 w
				682 w
720 s	720 s	720 m	710 s	
750 s	740 s	750 s	740 s	745 s
	763 m	770 m		
	780 w		784 s	788 m
	815 m	815 s		810 m
865 m	865 m	880 m		870 m
	915 m			
940 m	935 m	935 w		940 w
980 w			960 w	952 w
1015 m	1015 w	1010 w	1000 w	
		1020 w		
1030 m	1030 w	1035 m	1228 s	1035 s
	1065 w	1070 m	1065 w	1070 w
1120 w		1120 w	1125 m	
				1135 s

Table 2. (continues)

N-Acetylcarbazole	Chloro-N-acetylcarbazole			Products of acetylation of 1-chloro-carbazole
	2-	3-	4-	
1150 w			1155 s	
1188 m	1178 w	1185 w	1170 s	1185 s
1205 m	1200 m	1205 m	1205 m	
	1215 w			
1235 m		1230 w	1225 w	1225 m
	1265 w	1270 w	1263 m	1265 s
1295 s	1295 m	1295 s	1290 s	
1325 s	1320 m	1325 w		1332 s
				1412 m
	1410 m			1425 s
				1490 s
1595 w	1585 w	1575 w	1585 m	1555 s
		1605 w	1600 w	1600 m
	1660 m	1678 s	1683 s	
				1620 w
1695 s	1695 w			1695 m
1785 w				1765 w
				1880 w
1900 w				
				3340 s

SECTION (B)

PART 3.

DISCUSSION

3.1 Kinetics and Mechanism

3.1a Kinetics.

The rate coefficients for molecular chlorination in pure acetic acid at 25° of N-acetyldiphenylamine, N-acetylcarbazole, 2-chloro- and 3-chloro-N-acetylcarbazole were calculated using the integrated rate equation for bimolecular reactions,

$$k_2 = \frac{2.303}{t(a-b)} \log \frac{b(a-x)}{a(b-x)}$$

Consistent values were obtained for the rate constants of all these reactions. The maximum error observed for these values was about 4%, the reactions usually being followed for over 60% of the reaction range. From this finding it could be reasonably concluded that these reactions are of the second order, overall, first-order in both chlorine and the aromatic compound. The plausibility of this conclusion is strengthened by the fact that molecular chlorination reactions of other anilides were also found to be of second order[1]. The following kinetic equation has been adopted[2] for these reactions,

$$-d[Cl_2]/dt = k_2[ArH][Cl_2].$$

---

1. O.M.H. el Dusouqui and M. Hassan, J.Chem.Soc., 1966, B, 374; and references therein.
2. P.W. Robertson, J.Chem.Soc., 1954, 1276.

It has also been proved[1] that the chlorinating entity in these chlorination reactions is molecular chlorine, rather than positive chlorine or chlorine acetate.

The rate constants obtained for the chlorination of the compounds enumerated above are summarised in the following table:

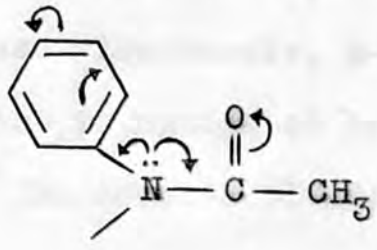
Compound	k_2* (l.mole^{-1}min^{-1})
N-Acetyldiphenylamine	1.1
N-Acetylcarbazole	4.3
2-Chloro-N-acetylcarbazole	0.81
3-Chloro-N-acetylcarbazole	0.57

*Mean of values is given.

No rate constant has as yet been furnished for the chlorination of carbazole, but the reaction is known to be very fast, so much so that its rate could not be followed by conventional kinetic methods[2]. Acetylation of carbazole to N-acetylcarbazole, however, greatly reduced the reactivity of the latter compound towards molecular chlorine. The high reactivity of carbazole derives from the lone-pair of electrons which reside on the nitrogen atom being available for conjugation with the various appropriate positions in the benzene rings. Introduction of the acetyl group results

1. P.W. Robertson, J.Chem.Soc., 1954, 1276.
2. R. Oda and K. Tamura, Sci.Papers Ind.Chem.Research (Tokyo), 1937, No. 728, 129; from Chem.Abs., 1938, 32, 2517^7.

in marked reduction of the electron-releasing power of the lone-pair of electrons, through the abtraction of part of the electrons available for conjugation by the carbonyl centre of the substituted acetamido-group in N-acetylcarbazole:



The further reduction in the rate of reaction of N-acetylcarbazole on introducing chlorine atoms (at the 2- or 3-position) in this system, accords with the general observation relating to the deactivating influence of the halogens by virtue of their -I effect.

3.1b. Mechanism

The mechanism of chlorination reactions has been discussed earlier (Section "A", X.b), and the accepted[1] form of it is herein adopted for correlating the results of the chlorination reactions conducted in this work.

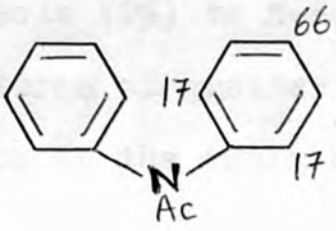
3.2 Isomer Distribution in Reaction Products

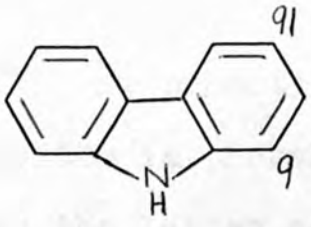
The products of molecular chlorination in acetic acid of N-acetylcarbazole were analysed by infrared spectroscopy, isotopic dilution, vapour-phase chromatography, and thin -

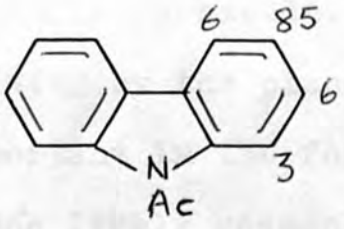
---

1. P.W. Robertson, J.Chem.Soc., 1954, 1276.

layer chromatography technique. The results obtained by one method of analysis served to supplement, and where possible also to confirm the results furnished by the other methods described. The products of chlorination under similar conditions of N-acetylcarbazole, N-acetyldiphenylamine, and carbazole were also investigated by thin-layer chromatography and by v.p.c.. The results of these analyses (%) are given below:







The absence of the 2-isomer from the products of chlorination of carbazole has been proved by analysis, and the reasonable assumption that the 4-isomer would consequently be absent has then been made.

The above results clearly demonstrate the greater reactivity in these systems of the 1- and 3-positions as compared with the 2- and 4-positions, in accordance with

what has previously been reported for the reaction of these compounds with other electrophilic reagents[1,2]. These results are also in essential agreement with theoretical predictions[3]. The superiority of the amino and the acetamido group in controlling orientation, even when in competition with an aryl group held in a planar configuration, has been considered before.[4]

The decrease in the percentage of the 1-isomer on going from carbazole (9%) to N-acetylcarbazole (3%) could be explained in terms of greater steric (and may be also polar) retardation to the entry of the electrophile ortho to the bulky acetyl group in N-acetylcarbazole.

The 2-position and the 4-position are shown to be more reactive in N-acetylcarbazole than in carbazole. This would suggest that promotion of reactivity by the planar biphenyl-like system is probably more important in the former compound than in the latter compound. One likely reason could be that the introduction of the acetyl group in the 9-position in N-acetylcarbazole sufficiently reduces the effectiveness of the electron-releasing power of the lone-pair of electrons,

---

1. Sumpter and Miller, "The Chemistry of Heterocyclic Compounds; Heterocyclic Compounds with Indole and Carbazole Systems", Interscience, Wormerveer, 1954.
2. Dewar and Urch, J.Chem.Soc., 1958, 3079.
3. H.C. Longuet-Higgins and C.A. Coulsen, Trans.Faraday Soc., 1947, 43, 87; G. Bertheir and B. Pullman, Compt.rend. 1948, 226, 1725.
4. de la Mare and Ridd, "Aromatic Substitution", Butterworths, London, 1959.

to give the phenyl group partial control of orientation in this system. Nitration of carbazole was reported[1] to have given about 2% of 2-nitrocarbazole, whereas in the Friedel-Crafts acylation of N-acetylcarbazole apparently the phenyl group takes over complete control of the position of substitution in this compound, hence the isolation of a single isomer, the 2,9-diacetylcarbazole, from the products of this reaction[2].

It is known that the mesomeric electron-release by both the amino and the acetamido groups to the residues they activate normally leads to higher electron densities at the *para* than at the *ortho* positions. With selective electrophilic reagents, such as molecular chlorine, greater *p*-substitution would be expected for such molecules[3]. The $\frac{1}{2}o/p$ ratio for the chlorination of acetanilide was reported[4] to be 0.24. The results obtained here give a value of 0.26 for the same ratio for N-acetyldiphenylamine, approximating that of acetanilide. However, the *o*/*p*-ratio for both carbazole and N-acetylcarbazole are significantly low, being only 0.1 and 0.035 respectively. This marked decrease in

---

1. Dewar and Urch, J.Chem.Soc., 1958, 3079.
2. Plant, Rogers and Williams, J.Chem.Soc., 1935, 741.
3. de la Mare, in "Progress in Stereochemistry", eds. W. Klyne and de la Mare, Butterworths, London, 1958, Vol. II, p. 65.
4. de la Mare and Hassan, J.Chem.Soc., 1958, 1519.

the o/p-ratio, on going from acetanilide and N-acetyldiphenylamine to N-acetylcarbazole, is accompanied by an important structural change, i.e. ring closure in N-acetylcarbazole. A similar trend has also been observed for the chlorination of diphenyl ($\frac{1}{2}$o/p-ratio = 0.31) and fluorene[1] (0.13); the nitration of diphenyl[2] (1.6), diphenylmethane (0.31) and fluorene[3] (0.27); and the nitration[3] of diphenylamine (1.22) and carbazole (0.4).

If one takes into account the fact that ring-closure might conceivably make the "closed" systems more planar than the corresponding "open" systems, one is left with the desire to suggest that in systems containing powerfully activating substituents, further enhancement of substitution para to these groups could be affected through such structural changes. Evidently, further research on this subject is necessary if this statement is to be qualified. The lowest values recorded so far for the o/p-ratio, and which could, at least in part, be attributed to the structural factors discussed above, are those obtained for chlorination reactions. Hence one wonders whether the electrophilic reagent plays any part in augmenting these effects, provided, of course, it is assumed in the first place that these effects are important

---

1. Beaven, de la Mare, Johnson, and Hassan, J.Chem.Soc., 1962, 989.
2. Dewar, T. Mole, Urch and E.W.T. Warford, J.Chem.Soc., 1956, 3573.
3. Dewar and Urch, J.Chem.Soc., 1958, 3079.

3.3. Effect of Ring-Closure on Reactivity in the Carbazole System.

The fact that diphenyl sulphide, diphenyl ether, and diphenylamine were found to be more reactive in nitration[1], protodesilylation[2] and protodetritiation[3] reactions than, respectively, dibensothiphen, dibenzofuran, and carbazole, led to the suggestion that ring-closure reduces reactivity in these systems. The conclusion drawn from the results of competitive nitration in acetic anhydride of diphenylamine and carbazole was that the former compound was about twenty times more reactive than the latter.

From the results of competitive chlorination of carbazole and diphenylamine(Section "B", 2.6)it was possible to estimate the relative reactivities of these two compounds in this reaction; and diphenylamine was found to be more reactive than carbazole by a factor of about 6. This result was qualitatively similar to that obtained by Dewar and Urch[1] for the nitration reaction, but numerically significantly different. It is to be noted, however, that these authors gave their results a wide marginal error.

---

1. Dewar and Urch, J. Chem. Soc., 1958, 3079.
2. Eaborn and Sperry, J. Chem. Soc., 1961, 4921.
3. Eaborn and Baker, J. Chem. Soc., 1961, 5077.

A reason has been suggested by Eaborn[1] and his co-workers to explain the relation between the lowering of reactivity and closure of the five-membered ring in the systems considered above. It is thought that the lone-pair of electrons on the hetero atoms are actively engaged in giving, through resonance, aromatic character to the five-membered ring, and that the availability of these electrons to the appropriate peripheral positions in the benzene rings of these systems, can only occur at the expense of this special aromatic character.

On the other hand, molecular chlorination of N-acetyl-diphenylamine (k_2 = 1.1) and N-acetylcarbazole (k_2 = 4.3) showed that the latter compound was the more reactive of the two, thereby giving an order of reactivity which is directly opposite to what has been observed for other related systems. The reversal in the order of reactivity in the case of N-acetyl-diphenylamine and N-acetyl-carbazole could be attributed to the behaviour of these compounds as substituted anilides.

One special feature of substituted anilides, and which is of special importance to the present discussion, is the susceptibility of their molecular chlorination reactions to steric inhibition of mesomerism[2].

---

1. Eaborn and Sperry, J.Chem.Soc., 1961, 4921.
2. de la Mare and Hassan, J.Chem.Soc., 1958, 1519.

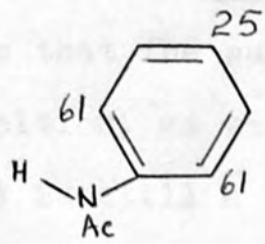
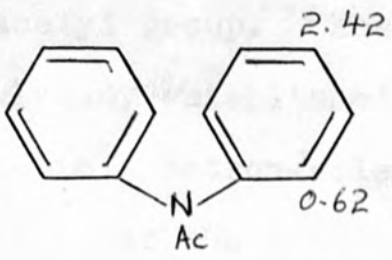
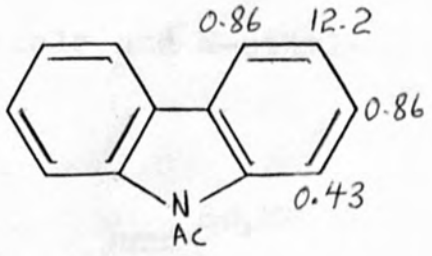
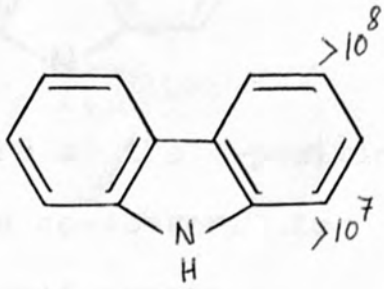
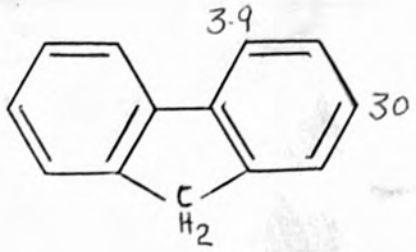
Impedance of coplanarity between the substituted acetamido group and the benzene ring in N-acetyldiphenylamine resulting from steric repulsion between the bulky acetyl group and the hydrogen atom ortho to it is expected to influence conjugation in the system, and to reduce the mesomeric effect of the acetamido group. However, by analogy with the similar situation in biphenyl and fluorene, ring-closure would effectively restore coplanarity in N-acetylcarbazole, and would lead to greater conjugative electron release from the acetamido group. This alone would make N-acetylcarbazole more reactive than N-acetyldiphenylamine.

3.4 Partial Rate Factors.

The rate constants (Section "B", 3.1) and isomer distribution (Section "B", 3.2) of controlled molecular chlorination of N-acetyldiphenylamine and N-acetylcarbazole allow the following partial rate factors listed in the next page to be calculated for the various positions in these two compounds. The relative rates (also given below) are based on the value obtained by de la Mare and Hassan[1] for the chlorination of benzene under comparable conditions. The accuracy of these values is, of course, a function of the precision of the analytical methods used for determining the rates and isomer distribution in these reactions. This has been discussed before. The partial rate factors for acetanilide[1] and fluorene[2] are included for comparison. Because of the uncertainty in the measurement of the rate of chlorination of carbazole, due to the speed of the reaction, only the lower limits of the partial rate factors for this reaction are given[3]; the actual magnitude of the rates are expected to be considerably higher than the quoted figures.

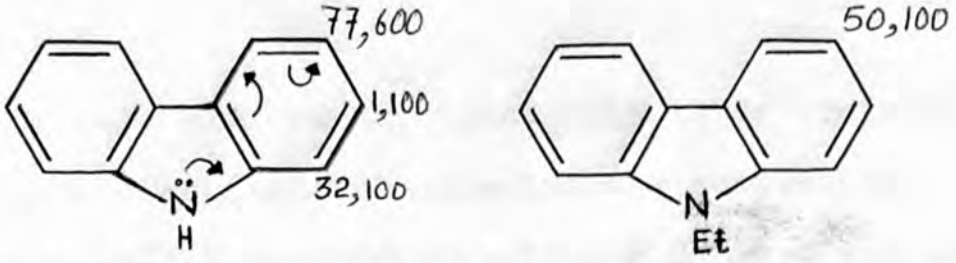
---

1. de la Mare and Hassan, J.Chem.Soc., 1958, 1519.
2. de la Mare, Johnson, and J.S. Lomas, J.Chem.Soc., 1964, 5317.
3. de la Mare and co-workers, J.Chem.Soc., in the press.

Compound	10^{-4} x Relative Rate (Benzene = 1)	10^{-4} x Partial Rate Factor
Acetanilide	62	
N-Acetyldiphenylamine	1.2	
N-Acetylcarbazole	4.8	
Carbazole	> 4000	
Fluorene	11.3	

The results demonstrate the striking reactivity of carbazole towards molecular chlorine. Comparison of the partial rate factor <u>para</u> to the acetamido group in N-acetylcarbazole (12.2×10^4) with the partial rate factor <u>para</u> to the -NH group in carbazole ($>10^8$) shows that the substituted acetamido group in this structural position, as well as in N-acetyldiphenylamine ($f^{NAc} = 2.4 \times 10^4$) is still a powerful conjugative electron-releasing substituent, in spite of the great deactivating effect of the acetyl group. These results also confirm the effectiveness (already established) of molecular chlorine in evoking electromeric electron-release.

Partial rate factors are now available for the nitration[1] and protodesilylation of carbazole and N-ethylcarbazole respectively:



The similarity of the partial rate factors at the 3-position in these two compounds led Eaborn and his co-workers[2] to conclude that polarisability factors (curved arrows in carbazole) might be of little importance in carbazole as

---

1. Dewar and Urch, J.Chem.Soc., 1958, 3079.
2. Eaborn and Sperry, J.Chem.Soc., 1961, 4921.

compared with dibenzothiphen and dibenzofuran. However, the partial rate factors now established for molecular chlorination of carbazole and N-acetylcarbazole give greater spread of rates than is so far observed for these systems. In this connection it has been pointed out by de la Mare and Ridd[1] that electromeric electron-release is usually evoked much more effectively by neutral reagents (e.g. molecular halogens) than by positive entities. It could, therefore, be concluded that polarisability effects are of great importance in the carbazole system, at least insofar as molecular chlorination reactions are concerned.

The following argument refers, unless otherwise stated, to the partial rate factors given above for the positions para to the acetamido group in acetanilide, and para to the substituted acetamido group in N-acetyldiphenylamine and N-acetylcarbazole.

Steric effects play an important role in determining the reactivity of N-acetyldiphenylamine and substituted anilides generally[1]; N-acetyldiphenylamine is less reactive than acetanilide (by a factor of about 100), and than N-acetylcarbazole (by a factor of about 8, allowance being made for deactivation by a meta phenyl group in N-acetyl-

---

1. de la Mare and Ridd, "Aromatic Substitution", Butterworths, London, 1959.

carbazole).

If we assume that the enforced coplanarity in N-acetylcarbazole has restored to this system much of the reactivity that has been lost through steric inhibition of mesomerism, it would then be possible to determine the factors, other than this steric effect, which determine the relative reactivity of N-acetylcarbazole.

N-Acetylcarbazole is 21 times less reactive than acetanilide. The reactivity in N-acetylcarbazole is partly reduced by the meta phenyl substituent. Indirect estimates[1] (through the use of the additivity principle) showed that a phenyl substituent reduces the rate of substitution meta to it by a factor of about 1.5. If the assumption is made that the rate of substitution of N-acetylcarbazole is reduced by this same factor, there will still remain a discrepancy of about 14 to be accounted for. This might partly be due to the replacement of hydrogen by a phenyl group in N-acetylcarbazole, and partly to the "special aromatic character" of the five-membered ring in this compound. The latter factor has been proposed by Eaborn and his coworkers[2] to explain the reactivities of some other similar heterocyclic compounds, namely dibenzofuran and dibenzothiophen. They argued that

---

1. de la Mare and Hassan, J.Chem.Soc., 1958, 1519.
2. Eaborn and Sperry, J.Chem.Soc., 1961, 4921; Baker and Eaborn, ibid., 5077.

the engagement of the lone-pair of electrons on the hetero-atoms in giving aromatic character to the five-membered rings in these systems, reduces the availability of the lone-pair for conjugation with the various positions (mainly the 1-, and 3-positions) in the benzene rings, and consequently lowers the rate of substitution at the ring positions in question.

However, by considering the rate by which reactivity is ebing reduced on going from acetanilide to N-acetyldiphenyl-amine (105), and the factor by which an ortho methyl group lowers the rate (through steric inhibition of mesomerism) in acetanilide[1] (about 20), it is possible to assign, strictly from these considerations, a factor of roughly 5, to the inductive effect of the aryl group in N-acetyldiphenylamine, and probably also in N-acetylcarbazole. An essentially qualitative prediction would then be that the above "special aromatic character", though probably of a small magnitude, could nevertheless be an important factor in determining the reactivity of N-acetylcarbazole.

No partial rate factors are available for the chlorination of diphenylamine, but the enormous reactivity of carbazole ($f_p^{-NH-} = > 10^8$) could be taken as an indication that the special resonance factor described earlier is not of great importance in carbazole either. However, the

---

1. de la Mare and Hassan, J.Chem.Soc., 1958, 1519.

magnitude of this factor in the carbazole system cannot as yet be decided upon.

The 2-position in fluorene ($f_m^{-CH_2-} = 30 \times 10^4$) is roughly 35 times more reactive than the same position in N-acetylcarbazole ($f_m^{-NAc-} = 0.86 \times 10^4$). The <u>meta</u> acetamido group might be responsible for part of this factor. The effect of this group on the rate of substitution <u>meta</u> to it has been considered by de la Mare and Hassan with reference to some methyl derivatives of acetanilide. Using their values for the appropriate partial rate factors, a change from a <u>meta</u> methyl substituent ($f_m^{Me} = 5$) to a <u>meta</u> acetamido group ($f_m^{-NHAc} = 0.38$) involves a 13-fold reduction in the rate of substitution at this position. On this basis it could be assumed that factors other than the effect of a <u>meta</u> acetamido group might have contributed to the observed low reactivity of the 2-position in N-acetylcarbazole. One of these factors could be identified with the special resonance effect, which has been mentioned earlier in connection with the reactivity of the 3-position in this system.

---

1. de la Mare and Hassan, J.Chem.Soc., 1958, 1519.

SECTION (C)

BROMINATION REACTIONS

PART 1.

INTRODUCTION

1.1 Introductory Note

Most of the material and ideas that are presented in the following pages can be found in the paper by de la Mare, D usouqui, Tillett and Zeltner[1].

1.2 Kinetics and Mechanism of Bromination of Phenol and Anisole.

Bromination of anisole in acetic acid usually gave[2] reaction orders that were higher than one with respect to bromine, following the pattern observed for bromination reactions in general.[3] However, it was observed that in concentration regions (M/640) where the bromination of phenol proceeded essentially by second-order kinetics, that of anisole was accompanied by a significant contribution from a third order term.

---

1. de la Mare, Dusouqui, Tillett and Zeltner, J.Chem.Soc., 1964, 5306.
2. de la Mare, Robertson, and Swedlund, J.Chem.Soc., 1953, 782.
3. de la Mare and Ridd, "Aromatic Substitution - ", Butterworths, London, 1959.

The brominating entity for molecular bromination reactions was proved[1] to be molecular bromine, and the transition state was identified as a complex containing both the aromatic molecule and the bromine molecule as a whole. A similar mechanism has been suggested[2] for the bromination reaction of phenol. The same was also considered[3] to apply to the reaction of anisole.

Moreover, experiment proved the absence (or near absence) of primary isotope effects in the bromination of both phenol[4] and anisole[5].

In the light of the above findings, the following mechanism has been proposed for the bromination reaction of phenol and anisole (R = either H or Me):

$$C_6H_5OR + Br_2 \rightleftharpoons Br_2, C_6H_5OR \qquad \text{fast}$$

$$Br_2, C_6H_5OR \rightleftharpoons C_6H_5ORBr^+ + Br^- \qquad \text{slow}$$

$$C_6H_5ORBr^+ \longrightarrow BrC_6H_4OR + H^+ \qquad \text{fast}$$

---

1. de la Mare and Ridd, "Aromatic Substitution-", Butterworths, London, 1959.
2. L.M. Yeddanapalli and N.S. Gnanapragasam, J. Chem. Soc., 1956, 4934.
3. Berliner, Chem. & Ind. (London), 1960, 177
4. Vainshtein, Shilov and Grishin, Zhur. Vsesoyuz. Khim. obshchestva im. D.I. Mendeleva, 1960, 5, 119; from Chem. Abs., 54, 24492e.
5. Berliner. Chem & Ind. (London), 1960, 177.

By considering what is known now about the speed of the process of complex-formation, and the absence of primary isotope effects in these reactions, the first and the last steps in the above scheme can be considered to be fast, and, therefore, of no consequence inasfar as the overall rate of reaction is concerned. The second step is then the rate-determining stage. Detailed analysis of this step in the bromination reaction of anisole and phenol is reserved for the discussion.

1.3. Relative Reactivity of Phenol and Anisole ---

Results of a number of electrophilic substitution reactions seem to indicate that phenol is much more reactive than anisole[1]. The possibility that this difference might be due to the presence in the reaction medium of a small amount of the very reactive phenoxide ion has been excluded by the conditions of the experiments.

Anisole, however, is expected to be if anything more reactive than phenol, since the inductive order of the alkyl groups has been shown[2] to obtain for anisole, and some other related aromatic ethers.

---

1. de la Mare, Tetrahedron, 1959, 5, 107.
2. Bradfield and Jones, Trans., Faraday, Soc., 1941, 37, 726.

Steric inhibition of mesomerism in anisole, and OH- hyperconjugation in phenol were considered[1] to be the most important and likely reasons to account for the greater reactivity of phenol as compared to anisole. Other factors, e.g. hydrogen bonding between phenol and the solvent, have been suggested[2].

1.4. Solvent Isotope Effects in Bromination Reactions.

As far as the author is aware, the only reference to solvent isotope effects in bromination reactions in acetic acid appears to be that of Keefer and Andrews[3]. These authors brominated mesitylene in dry, and 90% aqueous acetic acid, and in their deuterated analogues (i.e. Ch_3COOD and 90% aqueous Ch_3COOD; using D_2O), and then calculated the second and the third-order rate constants for these reactions. They reported that the change in the third-order rate constant accompanying the change of the medium from acetic acid to deutero-acetic acid was insignificant, whereas the corresponding change in k_2 was appreciable. Their results indicate a normal isotope effect (k_H/k_D) of magnitude of about 1.2 - 2.5 for acetic acid, and 1.3 for 90% aqueous acetic acid.

---

1. de la Mare, Tetrahedron, 1959, 5, 107.
2. Eaborn, J. Chem. Soc. 1956. 4858
3. Keefer and Andrews, J. Amer. Chem Soc. 1956.78. 3637.

The authors further compared these results with the rate constants for the bromination of mesitylene in chlorobenzene, inwhich k_2 was found to be virtually absent, and k_3 considerably lower than in acetic acid.

In an attempt to explain the large increase in the rate of bromination of mesitylene on going from dry to 90% aqueous acetic acid, Keefer and Andrews concluded, by referring to the results of the experiments discussed above, that the observed rate increase could be attributed in part to an increase in the dielectric constant of the medium, and in part to the hydroxylic nature of the solvent. It is to be noted, however, that the same authors failed to observe any appreciable isotope effect for the bromination of mesitylene in carbon tetrachloride containing light and heavy water.

1.5 Purpose of This Work

The greater reactivity of phenol than of anisole is attributed[1] in part to the presence in phenol and absence in anisole of a hyperconjugative effect, namely O-H hyperconjugation. The hydrogen of the hydroxyl group (i.e. as in phenol) is known[2] to exchange rapidly with hydroxylic solvents. If hydrogen exchange follows hyperconjugation, and if the loosening, or an actual fission of the O-H bond in phenol occurs in the rate-determining step of the reaction, then the bromination of phenol in a hydroxylic solvent such as acetic acid would be expected to be susceptible to solvent isotope effects. One aim of the present investigation is to test the truth of this argument.

Keefer and Andrews[3] tentatively suggested that in bromination reactions by molecular bromine in the presence of initially added bromide ion, tribromide ion might be an effective brominating agent if pure acetic acid was used as solvent. The experimental evidence needed to confirm this proposal has been sought for in this study.

---

1. de la Mare, Tetrahedron, 1959, 5, 107.
2. Bell, Quart.Revs., 1959, 13, 169.
3. Keefer and Andrews, J.Amer.Chem.Soc., 1956, 78, 3637.

SECTION (C)

PART 2.

EXPERIMENTAL

2.1. Preparation and Purification of Materials. ------ .

Deuteroacetic acid: f.p. 15.35° ± 0.5°.

Treatment of deuterium oxide with a slight excess of acetic anhydride in presence of a trace of concentrated sulphuric acid has been reported[1] by many authors to give pure deuteroacetic acid (acetic acid-d) in good yields. Unfortunately, analysis by n.m.r.* of a sample of the acid prepared by this method showed that it, in fact, contained about 50 - 60 % acetic acid. That this should happen is explained by the fact that acetic acid-d was found[2] to exchange rapidly, and extensively with the hydrogen of the methyl group in acetic anhydride, even in absence of catalysts.

A more successful method of synthesis was provided[3] by the reaction of pure acetyl chloride with deuterium oxide under strictly anhydrous conditions. This method is described in greater detail below.

For this preparation only highly clean, and dry equipment was used. The reaction vessel and attachments were well flushed with nitrogen before the reagents were introduced.

---

1. A.Murry, III, and D.L. Williams, "Organic Synthesis with Isotopes," Interscience Publishers, London 1958, Part II., p.1261.

* All n.m.r. analysis were by Dr. M.D. Johnson, U.C., London.

2. G.P. Miklukhin and A.F. Rekashera, Doklady Akad. Nauk S.S.S.R., 1955, 101, 881; from Chem. Abs., 49, 12090 e (1955).

3. R. Renaud and L.C. Leitch, Canad. J. Chem., 1956, 34, 98.

Research grade acetyl chloride (M. & B.) was further purified, by first distilling it over dimethylaniline (10 %, v/v), and then fractionating it, again over dimethylaniline (5 %). The pure, hydrogen-chloride-free fraction (b.p. 51°) was collected, and kept in a very dry atmosphere.

Pure acetyl chloride (300 ml.) was very quickly measured into a 3-necked, round-bottomed flask (500 ml.). The acetyl chloride was stirred, magnetically, and a stream of nitrogen was passed through it for some time before the reaction was started, and throughout the reaction duration. Deuterium oxide (75 g.) was added slowly, and in small amounts, allowing each portion to react, most of the deuterium chloride to escape, and the reaction mixture to cool, before the next fraction of deuterium oxide was introduced. After all the heavy water was added, the reaction mixture was gently boiled under reflux until deuterium chloride was no longer evolved. The deuteroacetic acid was distilled, and then fractionated by the method described for acetic acid. (Section 'B'; 2.1.)

The pure acid had the following physical constants: b.p. 119°; f.p. 15.35°; 99-99.5 % CH_3COOD (analysis by n.m.r.).

Yield of the pure acid = 60 - 75 %.

Preparation of Standard solutions of Bromine in Acetic acid (and acid-d):

Bromine (A.R.) was used without further purification. Stock solutions of bromine in the acid were prepared, and standardised, iodometrically, against a standard sodium thiosulphate solution.

Lithium bromide:

Lithium bromide (B.D.H.) was dried by heating for 6 hrs. under a constant stream of nitrogen. A stock solution of dry lithium bromide in pure acetic acid (or acid-d) was prepared, and standardised against standard silver nitrate solution.

Lithium perchlorate:

Pure, dry lithium perchlorate was prepared by the method described[1] by Pullin and Pollock. Stock solutions of lithium perchlorate in acetic acid, of desired concentrations, were prepared by weighing quickly known amounts of pure lithium perchlorate in standard volumes of solution.

Phenol: m.p. 41-40° (lit.; 43°).

Phenol was redistilled under reduced pressure. The middle fraction was used.

---

1. A.D.E. Pullin and F.McC. Pollock, Trans. Faraday Soc., 1958, 54, 11.

Anisole: b.p. 151° (lit.[1]; 153-154°).

Dry anisole ($CaCl_2$) was fractionated and the middle cut, distilling at constant temperature (151°), was used.

---

1. "Organic Synthesis," ed. A.H. Blatt, Chapman and Hall, London, 1941, Col. Vol. I., p.58.

2.2. Determination of the Equilibrium constant for Tribromide ion Formation. ------ .

2.2.a. Procedure:

The equilibrium constants for the formation of the tribromide ion in acetic acid, and in acetic acid-d were determined by the same general method.

Reaction mixtures of varying compositions, but constant ionic strength (0.2 M) were prepared in acetic acid (or acid-d) as solvent. These solutions contained bromine (the same total concentration in all solutions of the same solvent), lithium bromide (concentration range, 0.00 - 0.04 M), and lithium perchlorate (concentration, M = 0.2 - concentration of lithium bromide in the same mixture). Blanks were also prepared. The composition of each blank was that of the corresponding reaction mixture, except for the absence of bromine in the former.

The optical densities of these solutions were then measured at selected wave-lengths in the range 3400 - 3800 Å. The measurements were made in 1 cm. cells, and using a Unicam S.P. 500 spectrophotometer.

From the recorded optical densities (D), and the total bromine concentration, the corresponding molecular extinction coefficients (E) were calculated using the

Beer-Lambert law:

$$E = D/cl,$$

where l is the length of the cell used (1 cm.), and c is bromine concentration (g-mol./titre).

The equilibrium constant for the tribromide ion formation was then evaluated, graphically, for each wavelength from the concentration of lithium bromide in the various solutions, and the extinction coefficients of these solutions at that wavelength. The calculations were based on the equation derived by Ketelaar[1] for analysing the equilibrium constant of the dioxan-I_2 complex in pure carbon tetrachloride, and in n-hexane. When it is translated into the terms of the reaction investigated here, the above equation assumes the following form[2]:

$$1/E_{app.} - E_{Br_2} = K/[Br^-] \cdot (E_{Br_3^-} - E_{Br_2}) + 1/(E_{Br_3^-} - E_{Br_2}) ,$$

where,

$E_{app.}$ = the apparent extinction coefficient, measured

---

1. S.A.A. Ketelaar, C. van de Stolpe, A. Goudsmit and W. Dzcubas, Rec. Trav. chim., 1952, 71, 1104.
2. R.M. Keefer and L.J. Andrews, J. Amer. Chem. Soc., 1956, 78, 3637.

experimentally, of both free and complexed bromine,

E_{Br_2} = the extinction coefficient of free bromine, i.e. in the absence of bromide ion,

$E_{Br_3^-}$ = the extinction coefficient of the tribromide ion,

$[Br^-]$ = bromide ion concentration, and

K = the equilibrium constant for the reaction,

$$Br_3^- \rightleftharpoons Br_2 + [Br^-] \quad .$$

Implicit in the above equation are the following assumptions:

1. The equilibrium concentration of the bromide ion is essentially equal to its stoichiometric concentration.

2. Since the optical density measurements were made in a region of wavelengths where the tribromide ion absorbs very strongly and bromine only very weakly, then E_{Br_2}, at equilibrium, could, conveniently, be represented by the extinction coefficient of a mixture in which only the bromide ion is absent.

3. The optical density of any mixture is additively made up of the optical densities of all the contributing species in that mixture.

The above equation is that of a straight line, whose

$$\text{intercept} = 1/E_{Br_3^-} - E_{Br_2},$$

and

$$\text{slope} = K/E_{Br_3^-} - E_{Br_2}.$$

Hence,

$$K = \text{Slope/Intercept}.$$

For each wavelength, $1/E_{app.} - E_{Br_2}$ was plotted against $1/[Br^-]$, the slope and intercept of the curve measured, and the equilibrium constant then calculated.

2.2.b. Data and Results in Acetic acid.

Data:

The optical densities of a number of solutions of varying lithium bromide concentrations, measured at a number of different wavelengths, are summarised in Table 1. The molecular extinction coefficients calculated from these data are listed in Table 2.

Table 1.

Recorded optical densities (D.), of the solutions described, listed against the corresponding wavelengths (λ) at which they were measured.

Bromine = 5.31×10^{-4} M

$LiClO_4$, M	0.2	0.1984	0.196	0.192	0.184	0.16
LiBr, M	0.00	0.0016	0.004	0.008	0.016	0.04
λ (Å)	D.*	D.	D.	D.	D.	D.
3450	0.025	0.219	0.382	0.563	0.728	0.860
3500	0.036	0.183	0.316	0.449	0.578	0.672
3550	0.044	0.156	0.262	0.372	0.490	0.543
3600	0.052	0.143	0.230	0.320	0.410	0.467
3700	0.070	0.143	0.212	0.280	0.348	0.397

* Mean of values obtained before and after the other measurements.

Table 2.

The calculated molecular extinction coefficients (E.) tabulated against the corresponding wavelengths (λ) at which the measurements were made.

LiBr, M	0.000	0.0016	0.004	0.008	0.016	0.040
λ (Å)	E.	E.	E.	E.	E.	E.
3450	47.08	412.4	719.4	1060	1371	1619
3500	66.86	344.6	595.1	845.5	1088	1266
3550	98	293.8	493.4	700.4	922.8	1023
3600	131.8	269.3	433.1	602.6	772.1	879.4
3700	163.8	269.3	399.2	527.3	655.1	747.6

Results:

For each reported wavelength a graph was constructed in which $1/(E_{app.} - E_{Br_2})$ was plotted against $1/[Br^-]$, when $[Br^-]$ is the bromide ion concentration, E_{Br_2} is the extinction coefficient taken from the values given in the first column in Table 2., and $E_{app.}$ is the extinction coefficient of any of the other solutions in the table. A representative example of such a plot is given in Fig.I; the wavelength chosen is 3500 Å.

The equilibrium constant was then calculated from the values obtained in the graph for the slope and the intercept, and using the relation:

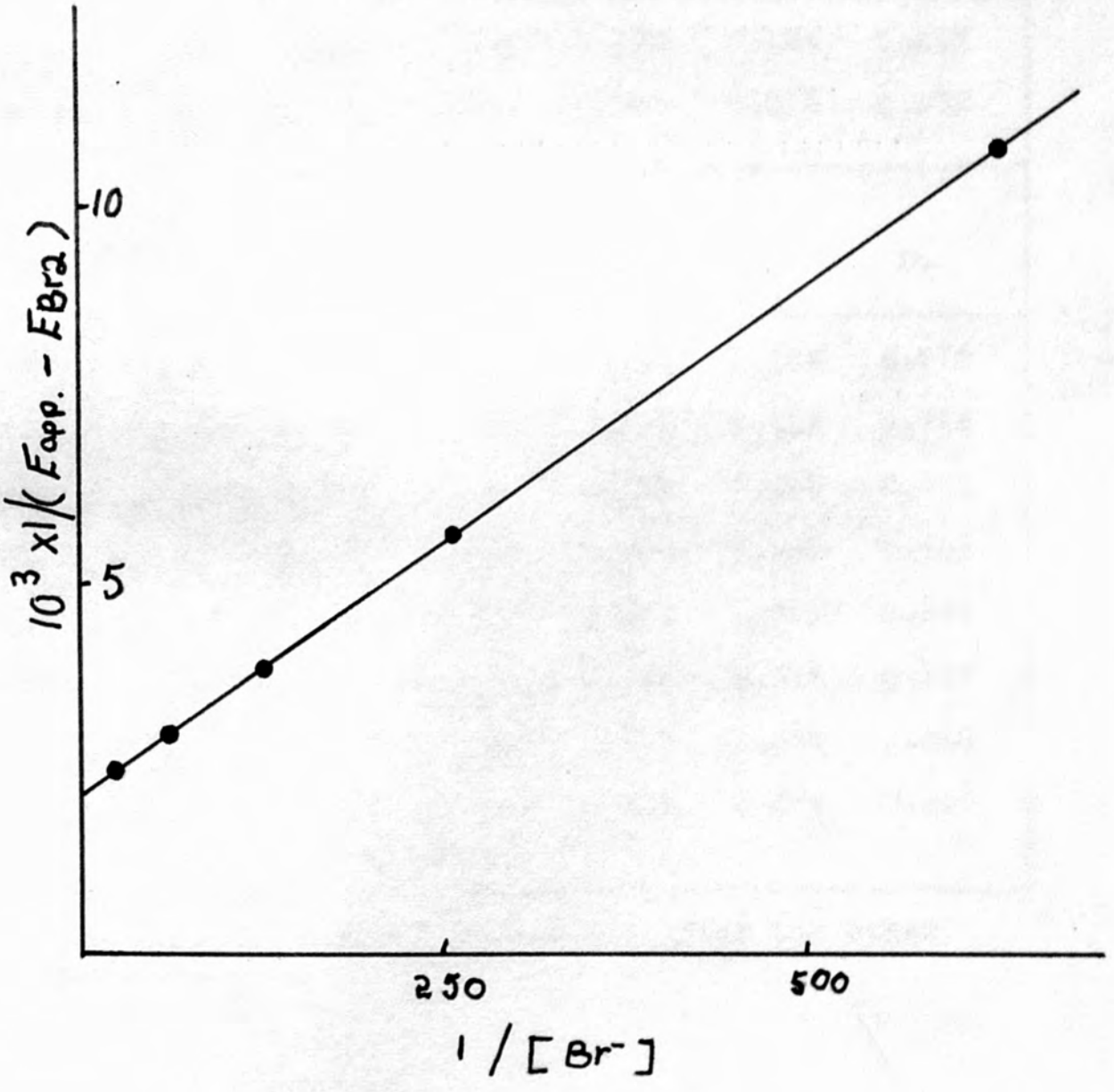
$$K = \text{Slope/Intercept.}$$

The equilibrium constants evaluated in this way are summarised in Table 3.

Table 3.

λ(Å)	3450	3500	3550	3600	3700
K (mole litre^{-1})	0.0065	0.0066	0.0065	0.0067	0.0066

Fig.I. Plot of the reciprocal of the extinction coefficient, at λ = 3500 Å, of complexed bromine ($E_{app.} - E_{Br.}$) in acetic acid, against the reciprocal of the concentration of bromide ion.



2.2.c. Data and Results in Acetic acid-d.

Data of the recorded optical densities (D.), and the calculated extinction coefficients (E.) of the solutions studied in acetic acid-d as solvent are given in Table 4. and Table 5. respectively.

Table 4.

Recorded optical densities (D.), of the solutions described, listed against the corresponding wavelengths (λ) at which they were measured.

Bromine = 4.256×10^{-4} M

$LiClO_4$, M	0,20	0.198	0.196	0.192	0.184	0.168
LiBr, M	0.00	0.002	0.004	0.008	0.016	0.032
λ (Å)	D.*	D.	D.	D.	D.	D.
3400	0.041	0.316	0.448	0.620	0.774	0.912
3450	0.042	0.254	0.361	0.498	0.618	0.714
3500	0.044	0.211	0.299	0.404	0.495	0.571
3550	0.052	0.181	0.253	0.334	0.408	0.464
3600	0.055	0.164	0.224	0.292	0.350	0.394
3650	0.063	0.154	0.212	0.269	0.314	0.358
3700	0.068	0.151	0.203	0.252	0.293	0.330
3800	0.079	0.150	0.190	0.237	0.274	0.303

* Mean of values obtained before and after the other measurements.

Table 5.

The calculated molecular extinction coefficients (E.) listed against the corresponding wavelengths (λ).

LiBr, M	0.000	0.002	0.004	0.008	0.016	0.032
λ (Å)	E.	E.	E.	E.	E.	E.
3400	96	742	1053	1456	1819	2143
3450	99	597	849	1170	1452	1678
3500	103	496	702	949	1162	1342
3550	122	425	594	785	959	1090
3600	129	385	526	686	822	926
3650	148	362	498	632	738	841
3700	160	355	477	592	689	776
3800	186	353	446	557	644	712

Results:

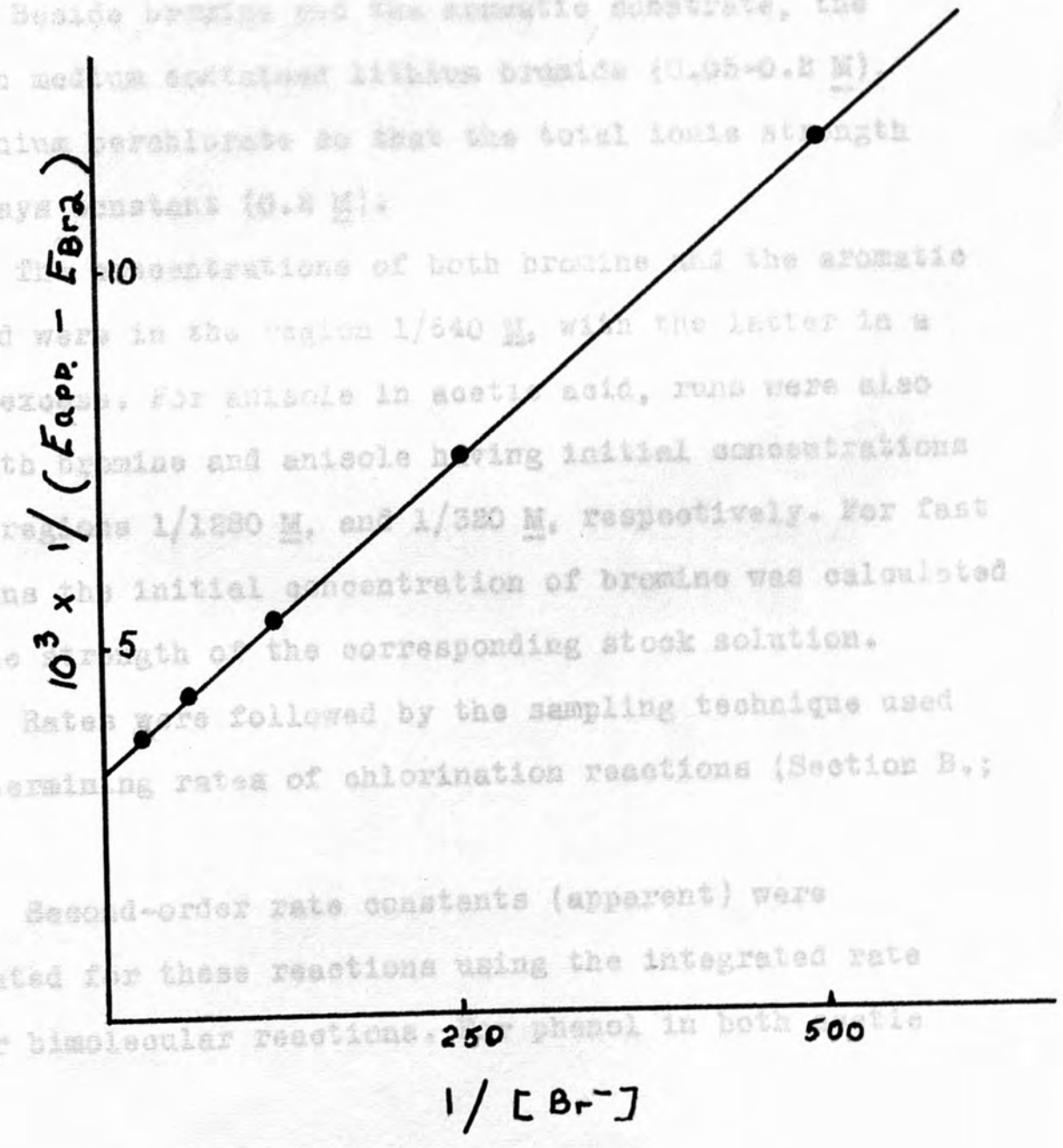
The equilibrium constants of the tribromide ion formation in this medium were similarly analysed by the graphical method described above; the representative plot (Fig. II.) is for results obtained at λ = 3600 Å. A summary of the equilibrium constants is given in Table 6.

Table 6.

λ (Å)	3400	3450	3500	3550	3600
K (mole litre^{-1})	0.0054	0.0053	0.0052	0.0054	0.0053

3650	3700	3800
0.0054	0.0054	0.0052

Fig.II. Plot of the reciprocal of the extinction coefficient, at λ = 3600 Å, of complexed bromine($E_{app.} - E_{Br2}$)in deuteroacetic acid, against the reciprocal of the concentration of bromide ion.



2.3. Technique of Rate Measurement. ------ .

Phenol and anisole were brominated at 25° in both acetic acid and deuteroacetic acid as solvents; molecular bromine was used. The kinetic conditions under which the bromination reactions were conducted were essentially those described earlier for chlorination reactions.

Beside bromine and the aromatic substrate, the reaction medium contained lithium bromide (0.05-0.2 M), and lithium perchlorate so that the total ionic strength was always constant (0.2 M).

The concentrations of both bromine and the aromatic compound were in the region 1/640 M, with the latter in a slight excess. For anisole in acetic acid, runs were also made with bromine and anisole having initial concentrations in the regions 1/1280 M, and 1/320 M, respectively. For fast reactions the initial concentration of bromine was calculated from the strength of the corresponding stock solution.

Rates were followed by the sampling technique used for determining rates of chlorination reactions (Section B.; 2.2.).

Second-order rate constants (apparent) were calculated for these reactions using the integrated rate law for bimolecular reactions. For phenol in both acetic

and deuteroacetic acid, the second-order rate constants were also obtained for values taken from graphs of percentage reaction (x) against time (t), and using the relation:

$$k = x/ta(a-x) \quad ,$$

where (a) is the initial concentration of bromine (and of the aromatic substrate), and (x) is the amount of bromine consumed after time (t).

2.4. Kinetic Data and Rate Coefficients. ------ .

2.4.a.1. Phenol in Acetic acid.

I.

Initial concentrations:

Phenol = 0.0015 M

Bromine = 0.001478 M

Lithium bromide = 0.20 M

Volume of each sample titrated = 5 ml.

Time (mins.)	Titre (ml.of 0.004N $Na_2S_2O_3$)	$k_{app.}$ ($l.mole^{-1}$ $min.^{-1}$)	x (%)	$k_{app.}$
0.00	3.695 [b]			
2.06	3.42	30	10	30
9.41	2.60	30	20	28
11.95	2.38	31	30	30
18.93	1.97	31	40	31
28.05	1.58	32	50	32
39.01	1.28	32	60	32
45.85	1.14	32	70	33

b = Based on the concentration of the stock solution used.

$k_{app.}$ = 32 $l.mole^{-1}$ $min.^{-1}$ ($\pm$ 1).

II.

Initial concentrations:

Phenol = 0.0015 M

Bromine = 0.001475 M

Lithium bromide = 0.15 M

Lithium perchlorate = 0.05

Volume of each sample titrated = 5 ml.

Time (mins.)	Titre (ml.of 0.004N $Na_2S_2O_3$)	$k_{app.}$ ($l.mole^{-1}$ $min.^{-1}$)	x (%)	$k_{app.}$
0.00	3.69 [b]			
2.04	3.23	43	10	49
9.40	2.35	41	20	42
15.70	1.86	41	30	41
18.32	1.73	41	40	40
24.68	1.43	42	50	42
34.04	1.14	43	60	43
42.73	0.95	44	70	44
57.65	0.76	43		

$k_{app.}$ = 45 $l.mole^{-1}$ $min.^{-1}$ (± 4).

III.

Initial concentrations:

Phenol = 0.0015 M

Bromine = 0.001442 M

Lithium bromide = 0.10 M

Lithium perchlorate = 0.10 M

Volume of each sample titrated = 5 ml.

Time (mins.)	Titre (ml.of 0.004N $Na_2S_2O_3$)	$k_{app.}$ ($l.mole^{-1}$ $min.^{-1}$)	x (%)	$k_{app.}$
0.00	3.605 [b]			
1.56	3.125	63	10	74
3.02	2.77	68	20	69
4.25	2.56	63	30	67
5.58	2.3	66	40	66
9.17	1.9	64	50	66
10.24	1.78	66	60	67
12.05	1.64	65	70	71
17.44	1.31	65		
18.86	1.22	67		

$k_{app.}$ = 66 $l.mole^{-1}$ $min.^{-1}$ (± 3).

IV.

Initial concentrations:

Phenol = 0.0015 M

Bromine = 0.00144 M

Lithium bromide = 0.05 M

Lithium perchlorate = 0.15 M

Volume of each sample titrated = 5 ml.

Time (mins.)	Titre (ml.of 0.004N $Na_2S_2O_3$)	$k_{app.}$ ($l.mole^{-1}$ $min.^{-1}$)	x (%)	$k_{app.}$
0.00	3.6 [b]			
1.07	3.0	126	10	106
2.3	2.53	124	20	119
3.39	2.23	125	30	124
4.84	1.91	120	40	127
6.06	1.66	126	50	126
8.17	1.41	123	60	127
9.65	1.26	124	70	130
10.68	1.18	123		

$k_{app.}$ = 122 $l.mole^{-1}$ $min.^{-1}$ (± 3).

2.4.a.2. Phenol in Deuteroacetic acid.

I.

Initial concentrations:

Phenol = 0.0012 M

Bromine = 0.001173 M

Lithium bromide = 0.20 M

Volume of each sample titrated = 5 ml.

Time (mins.)	Titre (ml.of 0.004N $Na_2S_2O_3$)	$k_{app.}$ ($l.mole^{-1} min.^{-1}$)	x (%)	$k_{app.}$
0.00	2.93 [b]			
1.8	2.8	19	10	19
5.55	2.62	20	20	18
12.70	2.28	19	30	19
21.35	2.	18	40	20
35.8	1.54	21	50	22
55.7	1.04	21	60	26
			70	27

b = Based on the concentration of the corresponding stock solution.

$k_{app.}$ = 19 $l.mole^{-1} min.^{-1}$ (± 1).

II.

Initial concentrations:

Phenol = 0.0012 M

Bromine = 0.00104 M

Lithium bromide = 0.15 M

Lithium perchlorate = 0.05 M

Volume of each sample titrated = 5 ml.

Time (mins.)	Titre (ml.of 0.004N $Na_2S_2O_3$)	$k_{app.}$ ($l.mole^{-1} min.^{-1}$)	x (%)	$k_{app.}$
0.00	2.6 [b]			
1.85	2.48	25	10	23
4.83	2.32	21	20	23
7.85	2.14	22	30	24
15.4	1.82	23	40	25
23.	1.54	24	50	28
31.37	1.24	25	60	31
42.	1.1	25	70	38

$k_{app.}$ = 23 $l.mole^{-1} min.^{-1}$ ($\pm$ 2).

III.

Initial concentrations:

Phenol = 0.0012 M

Bromine = 0.00106 M

Lithium bromide = 0.10

Lithium perchlorate = 0.10

Volume of each sample titrated = 5 ml.

Time (mins.)	Titre (ml.of 0.004N $Na_2S_2O_3$)	$k_{app.}$ ($l.mole^{-1}$ $min.^{-1}$)	x (%)	$k_{app.}$
0.00	2.65 [b]			
2.28	2.43	33	10	34
4.87	2.24	31	20	33
12.70	1.73	34	30	34
24.45	1.19	39	40	37
32.57	0.94	42	50	39
42.45	0.67	50	60	44
51.	0.47	61	70	52

$k_{app.}$ = 35 $l.mole^{-1}$ $min.^{-1}$ (± 4).

IV.

Initial concentrations:

Phenol	= 0.0012 M
Bromine	= 0.001066 M
Lithium bromide	= 0.05 M
Lithium perchlorate	= 0.15 M

Volume of each sample titrated = 5 ml.

Time (mins.)	Titre (ml.of 0.004N $Na_2S_2O_3$)	$k_{app.}$ ($l.mole^{-1}$ $min.^{-1}$)	x (%)	$k_{app.}$
0.00	2.665 [b]			
1.25	2.44	62	10	62
4.5	2.05	55	20	60
8.	1.71	57	30	60
11.7	1.43	59	40	59
15.55	1.23	59	50	62
20.8	0.95	66	60	67
30.2	0.61	79	70	79

$k_{app.}$ = 63 $l.mole^{-1}$ $min.^{-1}$ ($\pm$ 6).

2.4.b.1. Anisole in Acetic acid.

I.

Initial concentrations:

Anisole = 0.001485 M

Bromine = 0.00144 M

Lithium bromide = 0.20 M

Volume of each sample titrated = 5 ml.

Time (mins.)	Titre (ml.of 0.004N $Na_2S_2O_3$)	$k_{app.}$ ($l.mole^{-1}$ $min.^{-1}$)
0.00	3.6 [e]	
86.9	3.44	0.35
176.2	3.3	0.35
262.9	3.18	0.33
351.6	3.03	0.35
420.	2.96	0.33
480.5	2.87	0.35

e = Zero titre from first experimental point.

$k_{app.}$ = 0.34 $l.mole^{-1}$ $min.^{-1}$ (± 0.01).

II.

Initial concentrations:

Anisole = 0.001485 M

Bromine = 0.001264 M

Lithium bromide = 0.15 M

Lithium perchlorate = 0.05 M

Volume of each sample titrated = 5 ml.

Time (mins.)	Titre (ml.of 0.004N $Na_2S_2O_3$)	$k_{app.}$ ($l.mole^{-1} min.^{-1}$)
0.00	3.16 e	
40.37	3.07	0.50
79.49	2.97	0.51
121.8	2.88	0.53
169.8	2.78	0.54
220.2	2.68	0.54
276.8	2.59	0.54
322.7	2.48	0.56

$k_{app.}$ = 0.53 $l.mole^{-1} min.^{-1}$ ($\pm$ 0.03).

III.

Initial concentrations:

Anisole = 0.001485 M

Bromine = 0.001272 M

Lithium bromide = 0.10 M

Lithium perchlorate = 0.10 M

Volume of each sample titrated = 5 ml.

Time (mins.)	Titre (ml. of 0.004N $Na_2S_2O_3$)	$k_{app.}$ ($l.mole^{-1} min.^{-1}$)
0.00	3.18 [e]	
19.5	3.1	0.90
51.	2.96	0.93
90.	2.82	0.93
140.	2.65	0.94
199.7	2.49	0.91
261.	2.34	0.90
319.7	2.18	0.94

$k_{app.}$ = 0.92 $l.mole^{-1} min.^{-1}$ ($\pm$ 0.02).

IV.

Initial concentrations:

Anisole = 0.001485 M

Bromine = 0.001272 M

Lithium bromide = 0.05 M

Lithium perchlorate = 0.15 M

Volume of each sample titrated = 5 ml.

Time (mins.)	Titre (ml.of 0.004N $Na_2S_2O_3$)	$k_{app.}$ ($l.mole^{-1}\ min.^{-1}$)
0.00	3.18 [e]	
19.8	3.00	2.0
50.8	2.77	1.9
94.3	2.47	2.0
129.8	2.27	2.0
160.5	2.14	2.0
190.1	2.01	2.0
225.2	1.9	1.9

$k_{app.}$ = 1.95 $l.mole^{-1}\ min.^{-1}$ ($\pm$ 0.05).

V.

Initial concentrations:

Anisole = 0.003145 M

Bromine = 0.000758 M

Lithium bromide = 0.20 M

Volume of each sample titrated = 10 ml.

Time (mins.)	Titre (ml. of 0.004N $Na_2S_2O_3$)	$k_{app.}$ ($l.mole^{-1}\ min.^{-1}$)
0.00	3.79 [e]	
120.	3.34	0.34
240.	3.00	0.32
360.	2.61	0.34
450.	2.44	0.33
540.	2.24	0.33
600.	2.08	0.34

$k_{app.}$ = 0.33 $l.mole^{-1}\ min.^{-1}$ ($\pm$ 0.01).

VI.

Initial concentrations:

Anisole = 0.003145 M

Bromine = 0.000744 M

Lithium bromide = 0.15 M

Lithium perchlorate = 0.05 M

Volume of each sample titrated = 10 ml.

Time (mins.)	Titre (ml.of 0.004N $Na_2S_2O_3$)	$k_{app.}$ ($l.mole^{-1} min.^{-1}$)
0.00	3.72 e	
120.	3.12	0.48
240.	2.60	0.49
330.	2.28	0.50
450.	1.92	0.50
570.	1.64	0.49
630.	1.52	0.49

$k_{app.}$ = 0.49 $l.mole^{-1} min.^{-1}$ (± 0.01)

VII.

Initial concentrations:

Anisole = 0.003145 M

Bromine = 0.000745 M

Lithium bromide = 0.10 M

Lithium perchlorate = 0.10 M

Volume of each sample titrated = 10 ml.

Time (mins.)	Titre (ml.of 0.004N $Na_2S_2O_3$)	$k_{app.}$ ($l.mole^{-1} min.^{-1}$)
0.00	3.725 [e]	
90.	2.94	0.86
180.	2.34	0.86
271.	1.89	0.85
360.	1.53	0.86
450.	1.25	0.85
540.	1.01	0.86
600.	0.89	0.86

$k_{app.}$ = 0.86 $l.mole^{-1} min.^{-1}$

VIII.

Initial concentrations:

Anisole = 0.003145 M

Bromine = 0.000379 M

Lithium bromide = 0.05 M

Lithium perchlorate = 0.15 M

Volume of each sample titrated = 10 ml.

Time (mins.)	Titre (ml.of 0.004N $Na_2S_2O_3$)	kapp. ($l.mole^{-1} min.^{-1}$)
0.00	3.79 e	
60.3	2.64	1.9
90.	2.27	1.9
135.	1.8	1.9
165.	1.55	1.88
195.	1.33	1,88
240.	1.06	1.89
285.	0.86	1.88

$k_{app.}$ = 1.9 $l.mole^{-1} min.^{-1}$.

2.4.b.2. Anisole in Deuteroacetic acid.

I.

Initial concentrations:

Anisole = 0.00176 M

Bromine = 0.00155 M

Lithium bromide = 0.20 M

Volume of each sample titrated = 5 ml.

Time (mins.)	Titre (ml. of 0.004N $Na_2S_2O_3$)	$k_{app.}$ ($l.mole^{-1} min.^{-1}$)
0.00	3.88 e	
45.	3.61	0.96
105.	3.41	0.75
150.	3.06	1.00
195.	2.81	1.09
235.	2.69	1.04
275.	2.40	1.23
310.	2.30	1.20

e = Zero titre from first experimental point.

$k_{app.}$ = 0.9 $l.mole^{-1} min.^{-1}$ ($\pm$ 0.15).

II.

Initial concentrations:

Anisole = 0.00176 M

Bromine = 0.00155 M

Lithium bromide = 0.15 M

Lithium perchlorate = 0.05 M

Volume of each sample titrated = 5 ml.

Time (mins.)	Titre (ml. of 0.004N $Na_2S_2O_3$)	$k_{app.}$ ($l.mole^{-1} min.^{-1}$)
0.00	3.88 [e]	
30.	3.04	1.3
60.	3.46	1.2
90.	3.24	1.2
120.	3.02	1.3
155.	2.8	1.4
185.	2.65	1.4
220.	2.45	1.5
240.	2.35	1.5

$k_{app.}$ = 1.3 $l.mole^{-1} min.^{-1}$ ($\pm$ 0.1).

III.

Initial concentrations:

Anisole = 0.00176 M

Bromine = 0.00155 M

Lithium bromide = 0.10 M

Lithium perchlorate = 0.10 M

Volume of each sample titrated = 5 ml.

Time (mins.)	Titre (ml. of 0.004N $Na_2S_2O_3$)	$k_{app.}$ ($l.mole^{-1}\ min.^{-1}$)
0.00	3.875 [e]	
44.	3.48	1.48
90.	3.10	1.57
122.	2.77	1.83
150.	2.55	1.91
180.	2.34	2.01
215.	2.15	2.03
245.	2.00	2.06

$k_{app.}$ = 1.8 $l.mole^{-1}\ min.^{-1}$ ($\pm$ 0.3).

IV.

Initial concentrations:

Anisole = 0.00176 M

Bromine = 0.00167 M

Lithium bromide = 0.05 M

Lithium perchlorate = 0.15 M

Volume of each sample titrated = 5 ml.

Time (mins.)	Titre (ml. of 0.004N $Na_2S_2O_3$)	($l.mole^{-1} min.^{-1}$)
0.00	4.18 [e]	
21.	3.82	2.7
50.	3.44	2.5
80.	3.02	2.5
110.	2.70	2.8
140.	2.31	3.2
172.	2.00	3.4
200.	1.74	3.8

$k_{app.}$ = 3.4 $l.mole^{-1} min.^{-1}$ ($\pm$ 0.4).

SECTION (C)

PART 3.

DISCUSSION

3.1 Tribromide Ion in Acetic Acid and in Deuteroacetic Acid.

The magnitude of the equilibrium constant (K) for the dissociation of tribromide ion in acetic acid,

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

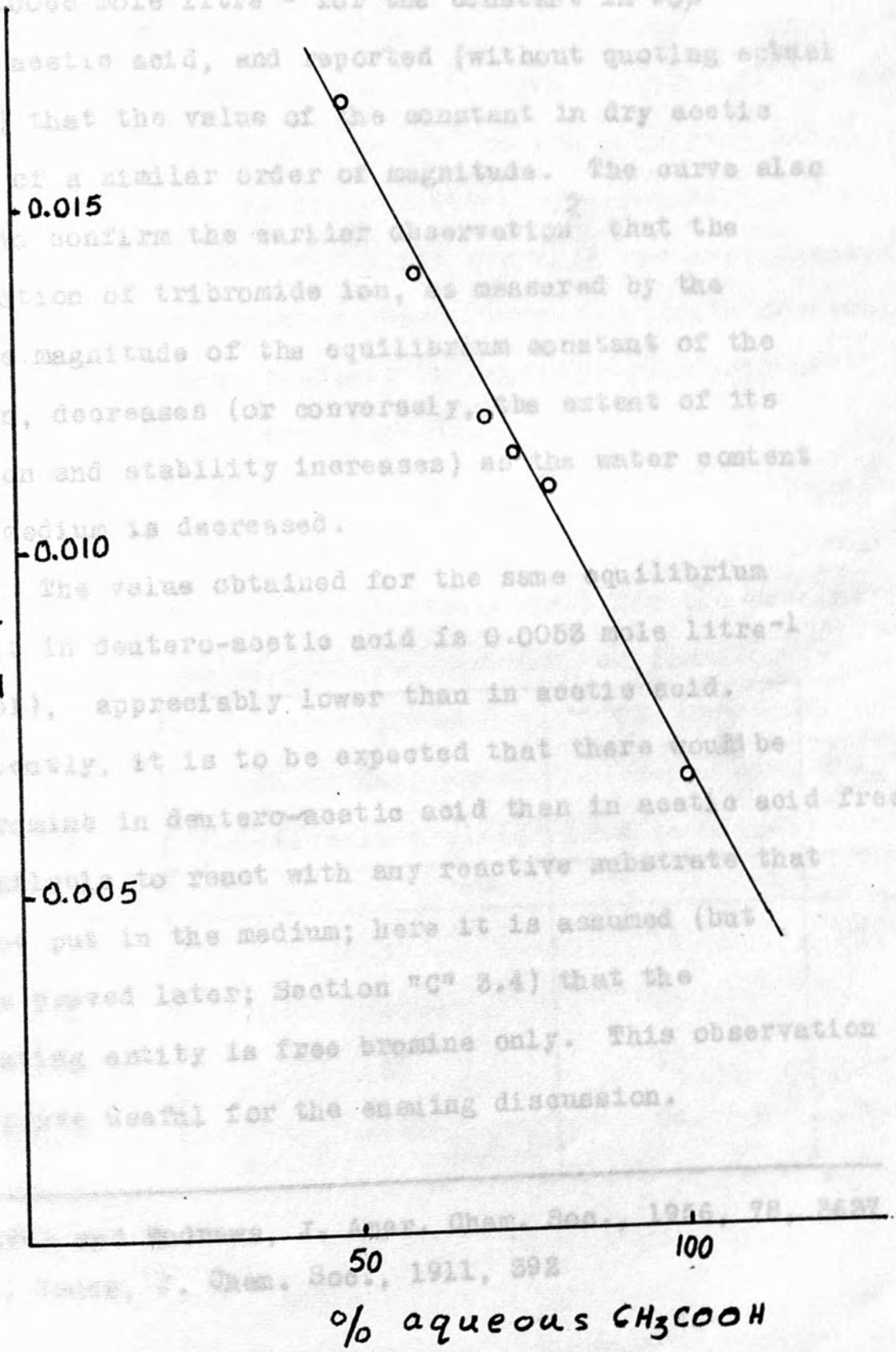
was found to be 0.0066 ± .001 mole litre^{-1} (Section "C", 2.2.6). This, together with the literature[1,2] values for 50, 60, 70, 75, and 80% aqueous acetic acid enable a graph (Fig. III) to be drawn for the relation between the magnitude of the equilibrium constant and the composition of the medium. It is to be noted that these measurements were made at constant ionic strength, by adding to the medium lithium perchlorate (the present work), sodium perchlorate[1] or perchloric acid[2].

From the graph it can be seen that a linear relationship exists between the magnitude of the equilibrium constant and the water content of the medium, especially when the difference in the experimental procedures, and the temperatures at which the different measurements were made, are born in mind. The graph also indicates that the value now assigned to the equilibrium constant in dry acetic acid does not seem to be unreasonable.

---

1. Berliner and Beckett, J.Amer.Chem.Soc., 1957, 79, 1425
   Berliner and Landry, J.Org.Chem., 1962, 27, 1083
2. E. Grovenstein, Jr., and U.V. Henderson, Jr., J.Amer. Chem.Soc., 1956, 78, 569.

Fig. III Plot of the equilibrium constant for the dissociation of tribromide ion in aqueous acetic acid mixtures



Furthermore, Keefer and Andrews[1] obtained a value of about 0.0068 mole litre^{-1} for the constant in 90% aqueous acetic acid, and reported (without quoting actual figures) that the value of the constant in dry acetic acid is of a similar order of magnitude. The curve also serves to confirm the earlier observation[2] that the dissociation of tribromide ion, as measured by the relative magnitude of the equilibrium constant of the reaction, decreases (or conversely, the extent of its formation and stability increases) as the water content of the medium is decreased.

The value obtained for the same equilibrium constant in deutero-acetic acid is 0.0053 mole litre^{-1} (± 0.001), appreciably lower than in acetic acid. Consequently, it is to be expected that there would be less bromine in deutero-acetic acid than in acetic acid free and available to react with any reactive substrate that might be put in the medium; here it is assumed (but will be proved later; Section "C" 3.4) that the brominating entity is free bromine only. This observation might prove useful for the ensuing discussion.

---

1. Keefer and Andrews, J. Amer. Chem. Soc., 1956, 78, 3637
2. W.J. Jones, J. Chem. Soc., 1911, 392

3.2. Kinetics of Bromination of Phenol in Acetic and in Deuteroacetic acid. ------.

The rate constants (Section "C", 2.4.a.1.) for molecular bromination of phenol in pure acetic acid at 25° and in presence of added bromide ion are tabulated below against the respective concentrations of bromide ion (Table 7.) In all these reactions the ionic strength was kept constant (0.20 M) by adding lithium perchlorate. The rate constants for the bromination of phenol in deuteroacetic acid under identical conditions are also given.

Table 7.

Summary of the rate coefficients (kapp.) for the bromination reactions of phenol.

Solvent	CH_3COOH	CH_3COOD	
LiBr (M)	$k_{app.}$ (l.mole min.$^{-1}$)	$k_{app.}$ (l.mole min.$^{-1}$)	$k_{CH_3COOH}/k_{CH_3COOD}$
0.20	32	19	1.7
0.15	43	23	1.9
0.10	65	35	1.9
0.05	122	64	1.9

These rate constants were calculated using the integrated rate equation for bimolecular reactions. For phenol in acetic acid the deviation within one kinetic run of the rate coefficients from the mean value was well within the limit of experimental error. The constancy of the rates could be taken to indicate that bromination reactions of phenol in acetic acid are of second-order overall, first-order in both bromine and phenol. Generally, bromination reactions in acetic acid, and in aqueous acetic acid are notable for yielding kinetic orders which are higher than one in bromine. However, intial addition of a large excess of bromide ion to the reaction medium has in many instances reduced the order to one with respect to bromine. A reason for this was given by Berliner and his coworkers.[1] They consider that the removal, though complexing, of part of the bromine (to Br_3^-), reduces free bromine concentration to the extent that the contribution from the term involving $[Br_2]^2$ in

$$-d(Br_2) / dt = k_2(ArH)(Br_2) + k_3(ArH)(Br_2)^2$$

to the overall rate of reaction becomes kinetically insignificant.

---

1. Zimmerman and Berliner, J. Amer. Chem. Soc., 1962, 84, 3953; and references therein

The corresponding rate coefficients of bromination of phenol in deuteroacetic acid were essentially constant over the first 40% of reaction, but were found to increase in the latter stages of bromination..

The reason why the rate of bromination of phenol should behave in this way in deuteroacetic acid is not yet clear. An explanation could be presented on the basis of an interference from p-bromophenol - the major product of substitution in this reaction.

The ratio of the ionization constant of acetic acid in water to that of deuteroacetic acid in deuterium oxide is given[1] as 3.3. If this is attributed mainly to the strengths of these acids, then deuteroacetic acid would be the weaker acid by roughly that factor.

It has also been shown[2] that phenol was not basic towards acetic acid. Furthermore, substitution of chlorine at the para- position in phenol led to an increase in the proton-donating property of phenol[3], and bromine should be expected to do the same.

---

1. Rule and La Mer, J. Amer. Chem. Soc., 1938, 60, 1974
2. M. Prytz, Acta Chem. Scand., 1947, 1, 510.
3. S. Nagakura, J. Chem. Soc. Japan, 75,743, from Chem. Abs. 1954, 48, L034h

If we consider that proton loss in hyperconjugation enhances, or its hindrance reduces, reactivity, and that this process is more important for p-bromophenol, as compared with phenol, in deuteroacetic acid rather than in acetic acid, then the contribution from p-bromophenol to the overall reaction rate could be appreciable when deuteroacetic acid is used as solvent. This contention can, of course, be tested by actually brominating p-bromophenol in both acids, and then comparing the results of the isotope effect with that of phenol. For the above argument to hold a slightly smaller isotope effect should be observed for p-bromophenol.

One other feature of the reaction in deuteroacetic acid is that protium ions are continually being produced in the reaction medium through the replacement of hydrogen by bromine. Exchange between protium ions and the solvent results in the formation of acetic acid in this medium. Since phenol brominates faster in the lighter acid, the overall rate would be expected to increase as the reaction progresses. However, this increase in rate can be appreciable only when a relatively high concentration of phenol is used. In the reactions conducted in this experiment the initial concentration of phenol never exceeded 0.0012 M; nevertheless useful information might be derived from a comparison of the behaviour in this respect of the reaction of phenol in deuteroacetic acid with

---

1. de la Mare, Dusouqui, Tillett, and Zeltner, J.Chem.Soc. 1964, 5306.

that of 2,4,6,-trideuterophenol in the same solvent.

The rate constants in Table 7 were calculated using the integrated form of the equation for bimolecular reactions,

$$-dx/dt = k_2[ArH][Br_2]_t$$

where $[Br_2]_t$ = total bromine concentration.

The rate constants refer to runs conducted at constant bromide ion concentration. As such, the results do not betray the nature of the brominating agents, i.e., whether it is molecular bromine, any entity derived from this, or both. However, a method of analysis has been developed[1] by which the rate of bromination by free bromine (uncomplexed) in a medium known to contain bromide ion in appreciable concentrations, can be assessed, and the participation and relative contribution to the overall rate of any other conceivable brominating entities could also be determined.

To begin with, the formation of the tribromide ion in the reaction medium is assumed to result from the complexing of free bromine with bromide ion:

$$Br_3^- \rightleftharpoons (Br_2)_f + [Br^-]$$

The equilibrium constant for this reaction would then be

---

1. Berliner and Beckett, J.Amer.Chem.Soc., 1957, 79, 1425.

given by the equation

$$K = [Br_2]_t \cdot [Br^-]/[Br_3^-]$$

It is further assumed that the total bromine concentration, $[Br_2]_t$, determined iodometrically, could be expressed essentially in terms of the concentrations of the following species,

$$[Br_2]_t = [Br_2]_f + Br_3^- \quad .$$

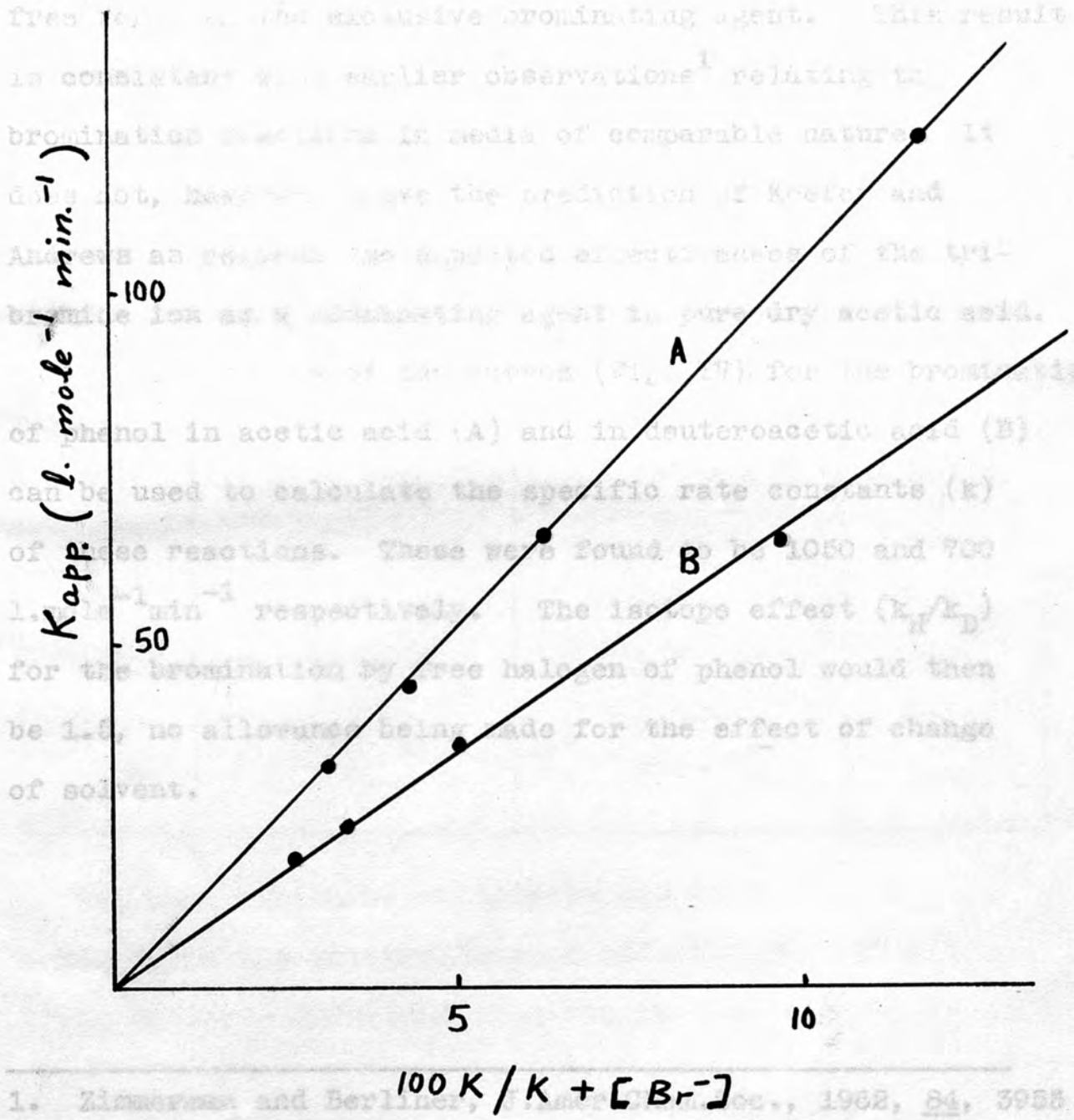
By suggesting that free bromine is the only effective brominating entity, the relationship given below could be formulated on the basis of the above assumptions, and it would be expected to hold:

$$k_{app} = kK/(K + [Br^-])$$

k being the specific rate constant for bromination by free bromine, K the equilibrium constant for the dissociation of tribromide ion, and $[Br^-]$ the concentration of the bromide ion. If k_{app} is then plotted against $K/(K + [Br^-])$, a straight line would be expected to result, and the slope of this would of course give the magnitude of k. For exclusive bromination by free bromine, the straight line should pass through the origin; and any appreciable positive intercept would then mean that some species other than free bromine is probably participating in the reaction.

Such a plot is given in Fig. IV for the bromination

Fig. IV Dependence on the tribromide ion concentration of the rate of bromination of phenol in acetic acid (A), and in deuteroacetic acid (B)



of phenol in acetic acid (A), and in deuteroacetic acid (B), using the rate constants given in Table 7, and the equilibrium constants obtained for the dissociation of tribromide ion in these two solvents.

From these plots it can be inferred that bromination of phenol in both acids involves molecular bromine, in its free form, as the exclusive brominating agent. This result is consistent with earlier observations[1] relating to bromination reactions in media of comparable nature. It does not, however, prove the prediction of Keefer and Andrews as regards the expected effectiveness of the tribromide ion as a brominating agent in pure dry acetic acid.

The slopes of the curves (Fig. IV) for the bromination of phenol in acetic acid (A) and in deuteroacetic acid (B) can be used to calculate the specific rate constants (k) of these reactions. These were found to be 1050 and 700 $l.mole^{-1}min^{-1}$ respectively. The isotope effect (k_H/k_D) for the bromination by free halogen of phenol would then be 1.5, no allowance being made for the effect of change of solvent.

---

1. Zimmerman and Berliner, J.Amer.Chem.Soc., 1962, 84, 3953

3.3 Kinetics of Bromination of Anisole in Acetic and in Deuteroacetic acid.

Anisole was brominated under conditions identical to those used for the bromination of phenol. The rate constants for the bromination reactions in these two acids are summarised below.

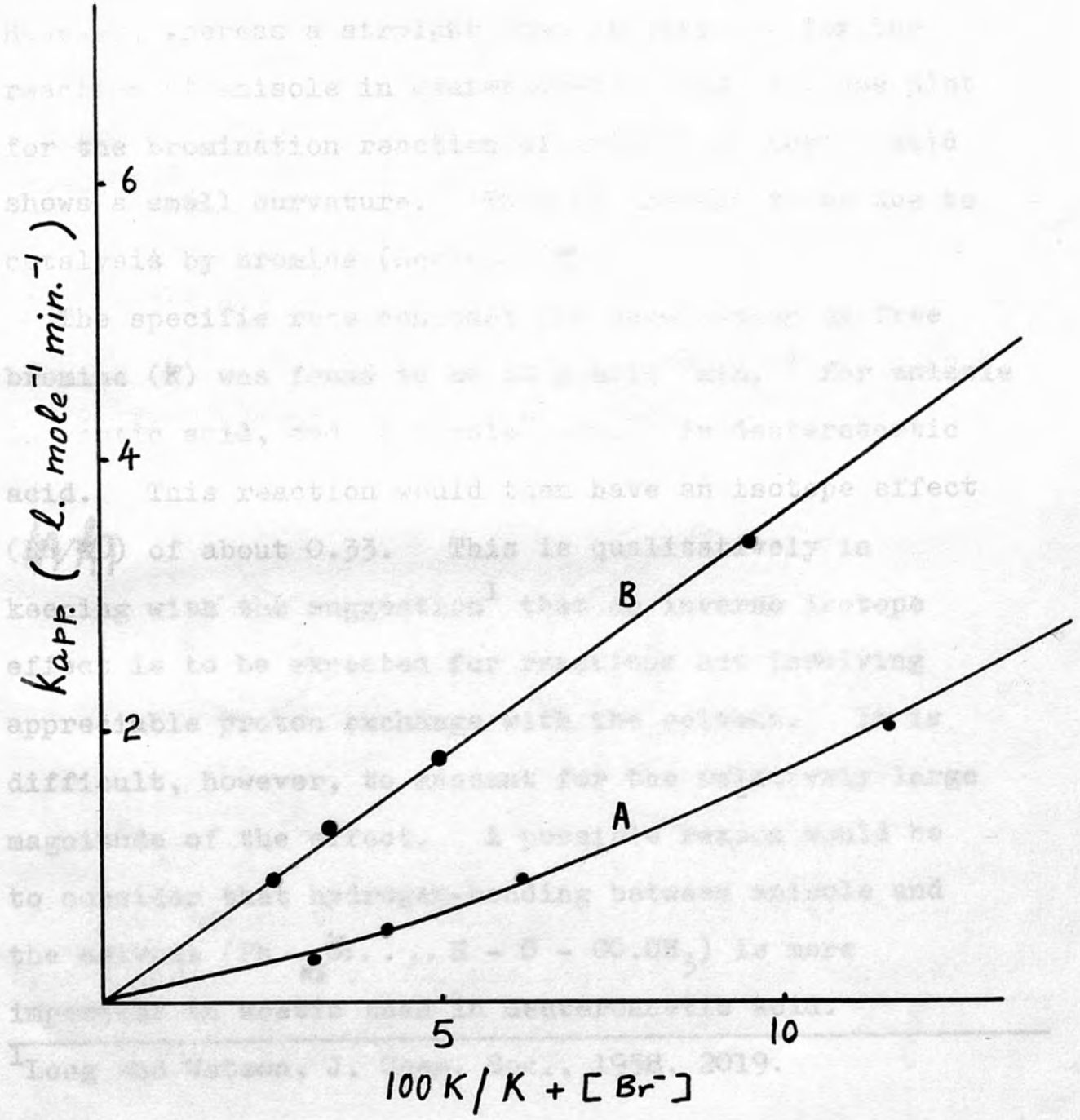
Table 8.

Summary of the rate coefficients ($k_{app.}$) for the bromination reactions of anisole.

SOLVENT	CH_3COOH	CH_3COOD	
Li Br (M)	$k_{app.}$ ($l.mole^{-1}min.^{-1}$)	$k_{app.}$ ($l.mole^{-1}min.^{-1}$)	$k_{CH_3COOH}/k_{CH_3COOD}$
0.20	0.34	0.9	0.4
0.15	0.53	1.3	0.4
0.10	0.92	1.8	0.5
0.05	1.96	3.4	0.6

The bromination of anisole is slower in acetic acid, hence the inverse isotope effect. A plot of $K_{app.}$ against $K/K+[Br^-]$ is given in Fig. V. It is

Fig. V Dependence on the tribromide ion concentration of the rate of bromination of anisole in acetic acid (A), and in deuteroacetic acid (B)



evident that the kinetics of the bromination reactions of anisole are identical with those of phenol (part 3.2., in this section). The brominating agent can again be identified as molecular bromine, in its uncomplexed form. However, whereas a straight line is obtained for the reaction of anisole in deuteroacetic acid (B), the plot for the bromination reaction of anisole in acetic acid shows a small curvature. This is thought to be due to catalysis by bromine (Section "E", 3.4.).

The specific rate constant for bromination by free bromine (k) was found to be 12 $l.mole^{-1}min.^{-1}$ for anisole in acetic acid, and 36 $l.mole^{-1}min.^{-1}$ in deuteroacetic acid. This reaction would then have an isotope effect (k_H/k_D) of about 0.33. This is qualitatively in keeping with the suggestion[1] that an inverse isotope effect is to be expected for reactions not involving appreciable proton exchange with the solvent. It is difficult, however, to account for the relatively large magnitude of the effect. A possible reason would be to consider that hydrogen-bonding between anisole and the solvent ($Ph - \underset{Me}{\ddot{O}}: \ldots H - O - CO.CH_3$) is more important in acetic than in deuteroacetic acid.

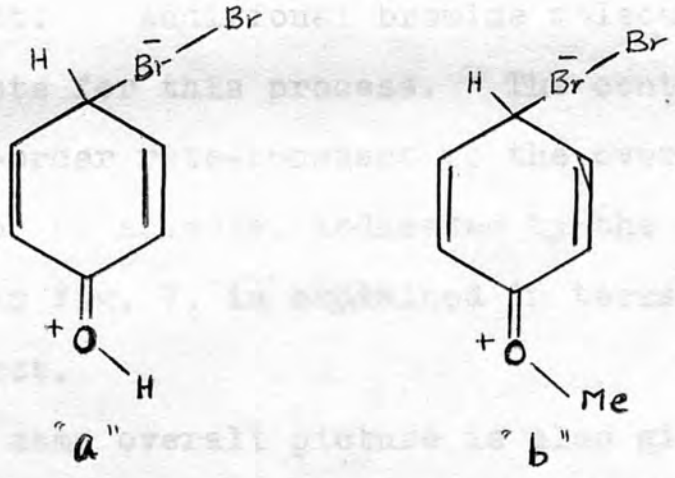
---

[1] Long and Watson, J. Chem. Soc., 1958, 2019.

3.4. <u>The Mechanism of the Bromination Reactions of Phenol and Anisole</u>. ————.

A preliminary discussion on the mechanism of the bromination reactions of phenol and anisole has been given in Section (B): 1.2.

If we assume that molecular bromination of phenol and anisole under the conditions of the present experiment (i.e., 25°, large excess of bromide ion in dry acetic acid as solvent) involves[1] formation of a complex between the aromatic substrate and a molecule of bromine, then the rate-determining stage of these two reactions could be approximated to the following structures,



The demand for resonance-stabilization of these transtion-states ("a" for phenol, and "b" for anisole)

---

[1] de la Mare, Dusouqui, Tillett and Zeltner, J. Chem. Soc., 1964, 5306.

is very large, and therefore, the activating powers of the OH and OMe groups would be expected to be fully utilized. The OH group in phenol copes with this demand by shifting part of the positive charge from the oxygen to the hydrogen atom. As the positive charge on the hydrogen atom increases, the potential acidic character of this atom increases as well, and hence its loss as a proton becomes imminent. The loss of this hydrogen atom would in turn facilitate the simultaneous loss of bromide ion in the transition state of the reaction. This does not happen in anisole, and the loss of the bromide ion from the complex of this compound would, therefore, require the participation of another species as catalyst. Additional bromine molecules could act as catalysts for this process. The contribution from the third-order rate-constant to the overall rate of bromination of anisole, indicated by the curvature in plot (A) in Fig. V, is explained in terms of this catalytic effect.

The same overall picture is also given by the reactions of these two compounds in dry acetic acid, in the absence of bromide ion. This finding is consistent with Berliner's[1] suggestion that bromination "reactions

[1] Zimmerman and Berliner, J. Amer. Chem. Soc., 1962, 84, 3953

in presence and absence of bromide ion, are kinetically, and presumably mechanistically, identical, and that the decisive factor is the reduced bromine concentration." This suggestion is further confirmed by the absence of such catalytic effects in the bromination of anisole in deuteroacetic acid.

The value of the equilibrium constant for the dissociation of the tribromide ion, as given by

$$K = [(Br_2)_f]\,[Br^-] \,/\, [Br_3^-] \,,$$

is 0.0066 mole litre^{-1} in acetic acid, but only 0.0053 mole litre^{-1} in deuteroacetic acid. Consequently, not enough bromine would be available for the contribution from third-order reaction to be significant when deuteroacetic acid is used as solvent.

3.5 Relative Reactivity of Phenol and Anisole

The rate constants for bromination by free bromine in dry acetic acid at 25° of phenol and anisole were found to be 1050 and 12 $l.mole^{-1}min^{-1}$ respectively. Accordingly, in this reaction phenol is at least 88 times more reactive than anisole. Comparing the rate of reaction of phenol with that of 2,6-dimethylphenol allowed a factor of roughly four to be assigned to the magnitude by which the rate of reaction is being reduced through steric hindrance of resonance[1]. It was also suggested[1] that the rate of bromination of anisole is expected to be reduced by about the same factor (by not more than four) if only steric hindrance were involved. Consequently, some other reason has to be furnished to account for the remaining rate discrepancy -- a factor of about 22. Recourse had to be made to -OH hyperconjugation to account for this extra reactivity in phenol. The acceptance of this postulate, however, poses some questions which, if answered successfully, would serve to strengthen the validity of the postulate.

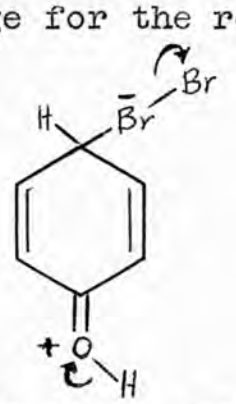
One of these questions concerns the possible occurrence of a normal isotope effect in the bromination of phenol, if the medium is changed from acetic to deuteroacetic acid.

---

1. de la Mare, Tetrahedron, 1959, 5, 107.

An isotope effect (k_H/k_D = 1.5) has in fact been observed for the bromination of phenol. This indicates that the O-H bond in phenol has been stretched considerably in the rate-determining step of the reaction. The stretching of this bond might have resulted from its engagement in releasing electrons conjugatively to the residue which it activates, and hyperconjugation could, therefore, be considered to be indirectly responsible for this isotope effect. Secondary isotope effects have in fact been used[1] before to corroborate the occurrence of hyperconjugative effects.

The fact that phenol was less susceptible than anisole to catalysis by bromine (Section "C", 3.4) indicates a simultaneous loss of the bromide and the hydrogen ions in the rate-determining stage for the reaction of phenol:



The loss of the latter ion could again be attributed to the engagement of O-H in hyperconjugation.

---

1. Olah, in "Organic Reaction Mechanisms - An International Symposium", Cork, Ireland, 1964. The Chemical Society, London, 1965, p. 21