ELECTROPHILIC SUBSTITUTION REACTIONS

by

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Abstract

The mechanistic investigations of certain electrophilic substitution reactions are briefly reviewed, with particular regard to C-nitrosation of aromatic substrates.

The kinetic principles of the investigation are then outlined.

An account of the C-nitrosation of a series of indoles in dilute aqueous acid is reported, in which nitrous anhydride, nitrosyl chloride, and the nitrousacidium ion are each deduced to be active electrophiles. An unusual change in the rate-determining step on variation of the basicity of the substrate is ascribed to the diffusion-controlled nature of reaction, when the reagent is either nitrosyl chloride or the nitrousacidium ion.

The nitrosation of both phenol and anisole in more concentrated acid are then reported, and the results interpreted in terms of a dienone intermediate in the case of phenol. The nitrosonium ion is demonstrated to be an active nitrosating agent.

Further studies are presented on the reaction of less reactive aromatic substrates with the nitrosonium ion, and the conclusion is made that the transition state of the aromatic C-nitrosation reactions generally involves loss of a proton from the Wheland intermediate to the solvent.

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DECLARATION

I declare that the contents of this thesis are a fair and truthful account of my own unaided endeavour, and that no part of the work has been submitted beforehand for any other higher degree.

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PART I.

INTRODUCTION

CHAPTER I .

THE HISTORICAL SURVEY.

(A). AROMATIC ELECTROPHILIC SUBSTITUTION.

The scope of this section will be limited to a brief presentation of the general features of some of the large range of electrophilic substitution reactions. A very detailed account of the history and conclusions of kinetic studies of aromatic halogenation and nitration has been written in recent years by De la Mare and Ridd[1] , while a later review, by Norman and Taylor,[2] covers other electrophilic substitutions in addition to those described by De la Mare and Ridd. A comprehensive review,[3] by Berliner, in 1964 , deals with the more theoretical aspects of the reaction.

A typical reaction, involving a general electrophile designated E^+ , is shown in FIGURE. (1.1).

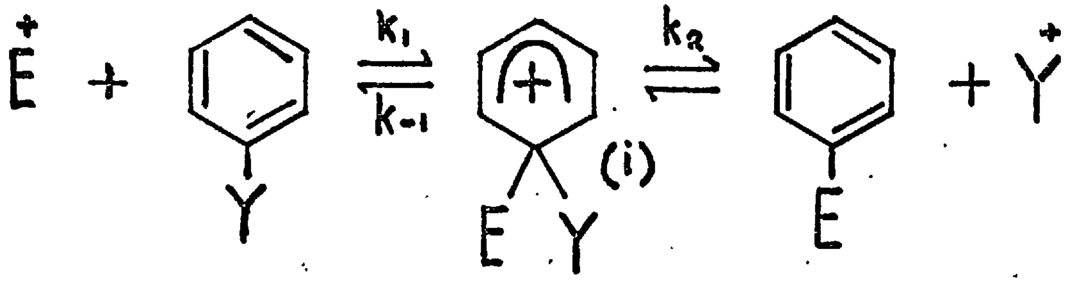

FIGURE (1.1).

Generally, though not exclusively, Y (FIG.1.1), represents a hydrogen atom. The intermediate (i) has a finite existence, albeit very transitory in most cases. Either k_1 or k_2 may be effectively rate controlling in most reactions. In the case where Y represents a hydrogen atom, the rate-determining step can usually be defined by comparison of the observed rate of reaction in substrates substituted with isotopes of hydrogen. A rate determining carbon/proton bond fission usually occurs between two and seven times faster than the corresponding carbon/deuteron bond fission.

Some reactions appear generally to involve a rate-determining k_1 , others a rate-controlling k_2 . It seems[4] that the criteria for this distinction are connected with the reactivity of the electrophile used. Thus, the more reactive reagents, (eg. the nitronium ion and the hypobromous-acidium ion ,) generally involve fast proton loss from the intermediate , while in less facile reactions, (eg.iodination and diazo coupling), the proton loss is often kinetically slow. Moreover, the nature of the aromatic substrate may also determine the rate-controlling step, particularly if the intermediate (i) becomes sterically crowded .

In this case, k_{-1} is increased relative to k_2, resulting in a rate-limiting proton loss from the intermediate (i).

Much interest has centered in the past on the exact nature of the electrophile, E^+, in a variety of related reactions carried out in aqueous solvent acid. In the general case, the reaction is accomplished by a solution of the typical acid, HOE, in mineral acid, such as $HClO_4$. In theory, such solutions may contain several possible electrophilic agents generated from the compound HOE by protonation.

eg. $$HOE + H^+ \rightleftharpoons H_2OE^+ \rightleftharpoons E^+ + H_2O$$

Attempts to ascribe the electrophilic reaction to either H_2OE^+ or E^+ have met with mixed success :

In nitration, the nitronium ion has been shown[6] to be the active nitrating agent over a wide range of conditions, while no convincing evidence for the nitricacidium ion, ($H_2ONO_2^+$), has been presented.

In halogenation, via an acidified solution of the hypohalous acid, the position is not so clear. Early[7] evidence indicated that both the hypochlorousacidium ion,

H_2OCl^+ , and the chlorinium ion , Cl^+ ,are effective electrophiles generated by theaction of mineral acid on aqueous solutions of hypochlorous acid. Objections have been raised[8] , however to this conclusion , on the grounds of thermodynamic calculations of the likely concentrations of these species in solution. Indeed, it has been suggested[9] that the necessary presence of silver salts in the original experimental conditions interfere with the reaction path by forming a species $AgCl_2^+$, and hence preclude any meaningful deductions on the nature of the electrophiles in solution .

The analogous reactions of the species generated by the acidification of hypobromous acid have been studied[10] in an attempt to distinguish between H_2OBr^+ and Br^+ as reagents. Acidity function correlation did not provide a definitive result.

Aromatic iodination , furthermore, has been observed to involve a large primary isotope effect[11] ,and consequently the nature of the iodinating species cannot be easily ascertained by acidity function correlations.

Recent work, in fact, on the iodination of indoles,[12] has indicated that the active agent in aqueous solution is molecular iodine , a conclusion earlier proposed by Grovenstein and coworkers .[13]

The uncertainty as to the electrophilic agents in halogenation is mirrored in the analogous nitrosation reaction. Nitrous acid reactions, in principle, should have proved the most tractable of all electrophilic reactions, since more data is known for the nitrosonium ion and its derivatives than for any of the series of electrophiles mentioned above. The nitrosonium ion is readily [14] formed in concentrated mineral acids, has a measurable ultraviolet absorption spectrum[15] , has a known pK_a[16], and the concentration of the species has been shown to follow the H_R acidity function[17] . Nevertheless, as is discussed in the next two sections below, separation of the reactions of the nitrosonium ion (NO^+) , and the nitrousacidium ion, (H_2ONO^+) , has not been achieved with any certainty.

(B). NITROSATING AGENTS FROM ACIDIC NITROUS ACID SOLUTIONS .

The nature of the various nitrous species generated from aqueous nitrous acid , and the effective role of each species in many electrophilic reactions , have been reviewed in recent years.[18, 19.] In this section, only a brief summary of these conclusions , with mention of more recent relevant work, is presented. Reference to the excellent review of Ridd[18], in particular, will present a clear account of the complex nature of the problems and findings in the reaction of nitrous acid with amines, prior to 1961 .

An aqeous acidic solution of nitrous acid may contain , (in various proportions depending on the exact composition of the medium,), the possible nitrosating agents shown in TABLE (1.1). Also shown in TABLE (1.1) , are the conditions which generally favour the predominance of the individual agents.

TABLE (1.1)

REAGENT	CONDITIONS
HNO_2	low acidity; low nitrite conc.s .
N_2O_3	low water activity; high nitrite conc.s.
NO.Hal.	high acidity; high conc.s halide ion.
H_2ONO^+	high acidity.
NO^+	high acidity; low water activity.
NO.X	high acidity; high conc.s of X^-

X^- represents acetate, phthalate, nitrate and thiocyanate ion.

The individual agents can each be regarded as carriers of the nitrosonium ion , and an order of reactivity as electrophilic reagents can be proposed on the basis of the basic strength of the moiety bound to the ion . Such an order of reactivity is shown in FIGURE (1.2).

$$NO^+ \rangle NO^+.H_2O \rangle NO^+.Cl^- \rangle NO^+.NO_3^- \rangle NO^+.NO_2^- \rangle NO^+.OAc^- \rangle\rangle NO^+.OH^-.$$

FIGURE (1.2).

The theoretical order of FIGURE (1.2). is in good agreement with the results observed in electrophilic reactions of nitrous species. The relative importance of each agent, however, depends on both the reactivity of that species, and the absolute concentration which it holds in solution under the conditions used. Thus, the most powerful nitrosating agent, the nitrosonium ion , is believed to contribute to only a negligible extent in reaction at low acidity, because this species is not present in solution to any great degree. Similarly, molecular nitrous acid, the weakest electrophile in the series, does not nitrosate even the most reactive amines, although this reagent is always the major nitrous component by far at low acidities.

The identity of the active electrophile under a particular set of conditions can usually be determined by examination of the rate equation which governs the reaction, since each reagent has a specific kinetic form, as is illustrate below, in CHAPTER II. A knowledge of the pre-equilibria governing the concentration of the nitrosating species, therefore,enables molecular rates to be calculated. Molecular rate-coefficients for the various nitrosating species are directly comparable, since corrections for concentration and acidity effects are inherent in the calculation of the molecular reagent.

An analysis of this type breaks down, however, when applied to comparison of the nitrousacidium ion and the nitrosonium ion. These two species present identical rate expressions in reaction. Furthermore, no information is available on the pre-equilibrium which controls the concentratio of the nitrousacidium ion in solution, although the analagous pre-equilibrium for the nitrosonium ion is well defined.[16]. Nevertheless, a correlation of the rate of reaction with acidity functions , as disscussed below in CHAPTER II, was believed to be a possible method of separating the roles of these two distinct reagents. Acidity functions could not be successfully applied, however, in the study of amine nitrosation in moderate solvent acidities, since a reaction path was observed[20] which involved the conjugate acid of the amine , and in which the transition state could be a proton transfer to the medium, if the solvent acidity were sufficiently high[21]. Similar limitations were observed in the study of the reaction of nitrous acid with hydroxylamines,[22] with the additional possibility of nitrosation occurring at Oxygen, involving a potentially slow rearrangement in this reaction. Such complications make acidity function correlations difficult to interpret, particularly when the rate-determining step was not known with certainty.

In a study of the ntrosation of benzamide, however, Ladenheim and Bender[23] assumed that the rate-controlling stage of reaction involved the initial nitrosation of the free amide substrate, with no reaction proceeding through the amide conjugate acid.

Correlation of the reaction rate with the acidity function H_R indicated to these workers that the nitrosonium ion was the active species in moderately concentrated acid.

Hughes and Stedman[24], however, studying the nitrosation of acetamide, reinterpreted Bender's data, and concluded that the nitrousacidium ion was operative in the nitrosation of both benzamide and acetamide at moderate acidities, although in higher acidities a change in the rate-determining step was possible.

In neither of these studies of amide nitrosation, however, was any account taken of the possibility that reaction may occur via nitrosation at the Oxygen atom,with a potentially slow rearrangement of the fragment NO^+ to the amide nitrogen. Such a mechanism can be declared to be generally operative in the reaction of electrophiles with amides.[25]

Considerable uncertainty exists, therefore, in the nature of the nitrosating species in moderately concentrated solvent acid. At low acidities , however, the nitrousacidium ion has been shown conclusively to exist as a nitrosating agent. In particular, the results of studies of oxygen exchange[26] between labelled nitrous acid and water have excluded the nitrosonium ion as the active , positively charged electrophile in dilute mineral acid,(pH $>$4.0) . This conclusion was first proposed by Hughes, Ingold and Ridd[27] in 1958, on the basis of a complex but apparently rigourous argument derived from the results of the diazotisation of amines, catalysed by the anions moderately strong acids.

Consequently, the bulk of the results of nitrous acid reactions to date have been interpreted in terms of the nitrousacidium ion as the positively charged electrophile, despite the possibility that the conclusions of Hughes, Ingold and Ridd may not necessarily apply to solutions of greater solvent acidity.

(C.). AROMATIC C-NITROSATION.

The mechanism of the reaction of aqueous nitrous acid with aromatic substrates to yield C-nitroso compounds has been accorded little attention to date. Indeed, the first recorded kinetic data of aromatic electrophilic C-nitrosation was published as recently as 1955[29]. Prior to this date, interest in the reaction had centred primarily on the various preparative methods of producing C-nitroso compounds, and on the properties of the nitroso compounds themselves. In a series [30] of papers in the period 1923 to 1943, for instance, Hodgson and coworkers prepared a number of substituted nitrosophenols by direct nitrosation , and speculated on the possible tautomeric forms of these compounds. Blongey, in 1938, observed [31] that the reaction of certain substituted anilines with nitrous acid in concentrated sulphuric acid produced C-nitroso compounds, and not the expected diazonium ions. Aside from phenols and a few indoles, however,[32,33]. direct nitrosation of the aromatic substrate was not generally used as a preparative method for C-nitroso compounds, since many substrates were found to react very slowly, and many nitroso compounds react further with extreme facility , under the conditions of direct nitrosation.

This latter observation , that many nitroso derivatives undergo further reaction, doubtless diverted interest for many years from any mechanistic study of aromatic C-nitrosation yet, paradoxically, it was this very property which attracted the attention of Hughes, Ingold and coworkers in the early 1950's. In a series of very comprehensive studies [34] of the mechanism of the nitration of aromatic substrates, they analysed an observed catalysis by nitrous acid in terms of a special mechanism of nitration , involving prior C-nitrosation [35]. The nitroso compound so formed was rapidly oxydised by nitric acid to the nitro compound, with concomitant regeneration of the nitrous acid. Thus the kinetic data for many nitrosation reactions was latent in the results of the nitration studies, but this was rather difficult to analyse, due to the contribution from a different, competing process, the "general" mechanism of nitration, involving attack by the nitronium ion.

Suzawa and coworkers , in 1955, were the first to report the rate of a simple aromatic C-nitrosation by aqueous nitrous acid[29]. They established the rate-law for the nitrosation of phenol , as shown in equation (1.1).

$$\text{rate} = \bar{k}_2.(\text{phenol}).(HNO_2). \quad ----- \quad (1.1).$$

The nitrosation of phenol was studied further by Morrison and Turney[36], in1960, who correlated $\bar{k}_2$,(eq.1.1), with the solvent acidity , as measured by the acidity functions H_0 and H_R [46] , in an attempt to differentiate between the nitrosonium ion and the nitrousacidium ion as possible electrophilic agents in the medium of moderately concentrated $HClO_4$. They concluded that the nitrosonium ion could be excluded as an active electrophile ,and postulated that reaction occurred between either phenol and the nitrousacidium ion, or molecular nitrous acid and the conjugate acid of phenol.

Schmid and coworkers , [37] in 1966 , reported studies of the nitrosation of phenol in more dilute acid ,(viz pH 5.0 to pH 1.0 HCl), and found that the kinetic form of equation (1.1) was rigourously obeyed at all concentrations of reagents, and furthermore that the value of $\bar{k}_2$ was independent of the bulk concentration of acid , although the observed rate increased with increasing ionic strength. To explain this observation , Schmid proposed reaction between molecular nitrous acid, (HNO_2), and molecular phenol. Reaction between the phenate anion , (PhO^-), and the nitrousacidium ion was ruled out on the grounds that such a reaction rate would greatly exceed the limiting encounter rate of the two species in solution . For this calculation , Schmid apparently used thermodynamic functions for the nitrousacidium ion , which are more commonly associated with the nitrosonium ion.[16] The reaction in 70.0 % H_2SO_4 was concluded to proceed via attack of the nitrousacidium ion on molecular phenol; surprisingly, in view of Morrison and Turney's earlier proposals, no justification was made by Schmid for this assumed mechanistic path.

Schmid also made no mention, in his conclusions, of the earlier work by Ibne-Rasa[38],who studied the nitrosation of 2,6-dibromophenol, and the nitrosodecarboxylation of 3,5-dibromo-4-hydroxybenzoic acid. In a kinetic study of these closely related reactions, Ibne-Rasa concluded that in the case of nitrosodeprotonation, reaction occurs in a fast pre-equilibrium between the anion of the phenol and either the nitrousacidium ion or nitrous anhydride. The rate-controlling step, he claimed , was the fission of the carbon/hydrogen bond at the site of reaction. This conclusion was justified in particular by the observation,by Ibne-Rasa, of a large primary isotope effect, $k^H/k^D = 3.6$. The nitrosodecarboxylation was shown to pass through the dianion of the benzoic acid, although no new definition of the active species could be made, in view of the postulated formation of a quinonoid intermediate, which loses carbon dioxide in the slow step.

A SUMMARY.

No conclusive evidence has been presented to define the nature of the active reagents in aromatic C-nitrosation, either at low or high solvent acidity. All postulated mechanisms are in contradiction in their conclusions with other existing work. The observation of Ibne-Rasa [38], that proton loss may be rate-controlling in a C-nitrosation reaction, may explain much of the discordancy,since all other workers assume a fast fission of the carbon/hydrogen bond, despite the shrewd postulate of Veibel, [39] in 1930 , who foresaw the possibility of a slow proton transfer in the case of the nitrosation of phenol.

CHAPTER II.

THE KINETIC PRINCIPLES.

(A). ACIDITY FUNCTION CORRELATIONS IN STUDIES OF NITROSATION.

The generation of molecular nitrous acid and the nitrousacidium ion, which are both formed by prototropic equilibria from the initial sodium nitrite, cannot be the rate limiting step in any nitrosation reaction[40], since proton transfer to oxygen is generally a fast process. Formation of the reagents N_2O_3[41] and NOCl[42], however, have been observed to be slow processes under the correct conditions. In theory, the formation of the nitrosonium ion may also be rate-limiting, although this has not been observed, to date, in practice. The rate-expressions listed in TABLE (2.1) summarise the kinetic forms found in nitrosation reactions by the various reagents under suitable conditions, when all reaction stages after the initial nitrosation are fast.

It will be appreciated from a study of TABLE (2.1), that reaction involving a rate-controlling attack by the nitrousacidium ion or the nitrosonium ion produces an identical rate law in dilute acid. It should be possible, however, to differentiate between these reagents in more concentrated mineral acid by relating the reaction rate with the acidity functions H_0 and H_R[46], in the manner described in this section.

TABLE (2.1).

Reagent	Slow step.	Rate-law.	Comment.
HNO_2	Attack.	$v \alpha (S).(HNO_2)$	Reported Once[37].
N_2O_3	Formation.	$v \alpha (HNO_2)^2$	Well established
	Attack.	$v \alpha (S).(HNO_2)^2$	Well established
NOCl	Formation.	$v \alpha (H^+).(HNO_2).(Cl^-)$	
	Attack.	$v \alpha (H^+).(HNO_2).(Cl^-).(S).$	
NO^+	Formation.	$v \alpha (H^+).(HNO_2).$	Unreported
	Attack.	$v \alpha (H^+).(HNO_2).(S).$	
H_2ONO^+	Attack.	$v \alpha (H^+).(HNO_2).(S).$	

"S" represents the substrate in reaction.

The activity of the nitrousacidium ion will be governed by equation (2.1).

$$a_{H_2ONO^+} = \frac{a_{HNO_2} \cdot a_{H^+}}{K_a} \quad \text{-----(2.1).}$$

In common with other oxygen acids[44], the nitrousacidium ion can be assumed to follow the h_0 acidity function, defined by equation (2.2).

$$h_0 = \frac{a_{H^+} \cdot f_B}{f_{BH^+}} \qquad \text{--------(2.2).}$$

in which B is the indicator base used to measure the acidity function.

Combining equations (2.1) and (2.2):-

$$a_{H_2ONO^+} = \frac{a_{HNO_2} \cdot f_{BH^+} \cdot h_0}{K_a \cdot f_B} \qquad \text{----(2.3).}$$

The Brønsted rate-expression for a rate-controlling attack of the nitrousacidium ion on the free base form of the substrate (S), is shown in equation (2.4).

$$\text{rate} = k. \frac{a_{H_2ONO^+} \cdot a_S}{f^{\ddagger}} \qquad \text{--------(2.4).}$$

Combining equations (2.4) and (2.3) :-

$$\text{rate} = \frac{k.(S).(HNO_2).}{K_a} \; x. \; \frac{f_{HNO_2} \cdot f_S \cdot f_{BH^+} \cdot h_0}{f_B \cdot f^{\ddagger}} \qquad \text{----(2.5)}$$

Provided that the activity -coefficient ratio is independent of the medium, and in conditions such that the nitrousacidium ion does not constitute a major part of the total nitrous acid species, equation (2.5) reduces to equation (2.6).

$$\text{rate} = k_3 .\ (S).(HNO_2).h_0 \qquad ------- (2.6).$$

The experimentally observed rate-coefficient is defined by equation (2.7).

$$\text{rate} = \overleftarrow{k}_2 . (S).(HNO_2) \qquad ------- (2.7).$$

Thus , if the nitrousacidium ion is the active reagent, the rate-coefficient $\bar{k}_2$ (equation 2.7) , should be related to the acidity function h_0 by equation (2.8).

$$\overleftarrow{k}_2 \ \alpha \ h_0 \qquad ------- (2.8).$$

The nitrosonium ion, however, has been shown[16] to follow a different acidity function, h_R , defined by equation (2.9).

$$h_R = \frac{a_{H^+} \cdot f_{ROH}}{a_{H_2O} \cdot f_{R^+}} \qquad ------------- (2.9).$$

where ROH is the indicator used to measure the acidity function. By an entirely analogous calculation to that expressed above for the nitrousacidium ion, equation (2.10) can be derived for a rate-determining attack of the nitrosonium ion on the free base form of any substrate.

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$$\text{rate} = \frac{k.\ (S).(HNO_2).}{K_{a,NO^+}} \quad x.\ \frac{f_S \cdot f_{HNO_2} \cdot h_R}{f_{ROH} \cdot f^{\ddagger}} \quad ---(2.10).$$

Assuming again that the activity coefficient ratio is independent of the medium, equation (2.10) reduces to :-

$$\text{rate} = k_3.(S).(HNO_2).\ h_R \quad ---------- (2.11).$$

and thus:-

$$\bar{k}_2 \propto h_R \quad ---------- (2.12).$$

The numerical value of h_R increases by a much greater factor [45] than the corresponding increment in h_0 , on increasing the stoicheiometric concentration of perchloric or sulphuric acids in the range 1.0 to 7.0 M. , and so, from these arguments, distinction can be made between reaction of the nitrosonium and the nitrousacidium ions , provided the reaction involves a slow nitrosation of the free base form of the substrate.

(B). DIFFUSION CONTROLLED REACTIONS.

A bimolecular reaction cannot take place faster than the frequency of encounter of the two reactants in solution. The rate of encounter of two solute molecules is expressed by the bimolecular rate-coefficient ($k_{en.}$) defined by the equation of Debye[47] :-

$$k_{en.} = \frac{8NkT}{3000.} \text{ x. } \frac{1}{4\eta} \left(2 + \frac{R_2}{R_1} + \frac{R_1}{R_2} \right)$$

where N is Avogadro's number,

k is the Boltzman constant,

η is the specific viscosity of the medium,

and R_1 and R_2 are the molecular diameters of the reacting particles.

k_{en}, calculated in this way ,has a value of ca. 10^{10} $1.mol.^{-1}sec.^{-1}$, [48] for aqueous solutions at 25.0°C.

Reactions which are thus "diffusion controlled" show only small[49] energies of activation, arising from viscosity changes in the solvent , with temperature. Also, the rates of such reactions are insensitive to the reactivity of the reactants involved.

(c). THE HAMMETT $\sigma^+.\rho$ RELATIONSHIP.

The linear free energy relationship of Hammett[51], (equation 2.13), measures quantitatively the effect of an aromatic substituent on reaction rates, relative to hydrogen.

$$\log.(k^X/k^H) = \sigma_X.\rho \qquad ----- (2.13).$$

σ_X is a constant for the substituent X, in a particular ring position, measuring the electronic interaction of the group as the logarithm of the ratio of the ionization constants of the substituted and unsubstituted benzoic acid. The value of ρ is constant for a given reaction, the numerical value and sign being a relative measure of the degree of positive or negative charge developed in the transition state of reaction.

The original model for measurement of σ values, given in equation (2.13), has been found to be inadequate in representing the substituent effect in reactions, such as aromatic substitution, which involve a transition state in which the site of reaction is directly conjugated to the substituent. Consequently, a new model[52] for the measurement of substituent parameters, (designated σ^+), has been proposed, to determine values for electrophilic substitution, and other reactions in which a directly conjugated substituent can stabilize a transition state by electron donation <u>via</u> resonance delocalization.

Thus, for an electrophilic substitution reaction:-

$$\log.(k^X/k^H) = \sigma_X^+ . \rho \qquad ----- (2.14).$$

where :

k^X is the rate-coefficient for reaction of the substituted benzene;

k^H is the analogous rate coefficient for benzene itself.

ρ values for various electrophilic substitutions have been determined[53]. All are of negative sign, indicating a positively charged transition state in each case. In general, a larger negative value of ρ indicates a greater selectivity in the attacking electrophile, and hence a less reactive reagent. Thus, bromination in perchloric acid has a ρ of $-5{\cdot}78$[54], while the less reactive diazonium ion in diazo coupling reactions, has a ρ value of ~ -12 .[55]

(D). CONVENTIONS USED IN THE PRESENT WORK.

(i). Rate-coefficients defined from the total stoicheiometric concentrations of reactants are denoted by barring. eg. $\overleftarrow{k}_3$

(ii). The stoicheiometric concentrations of reactants are designated by round brackets. eg. (HNO_2).

(iii) Molecular rate-coefficients, (calculated from the stoicheiometric counterparts by adjustment of reactant concentration terms), have been written unbarred. eg. k_3

(iv). Molecular concentrations of reactants , specified in either the free base or the conjugate acid form, have been denoted by squared brackets . eg. $[NO^+]$.

(v). The term " indole " , abbreviated on occasion to the symbol, IND., is a generic name in the present work, and does not in any instance refer to the parent unsubstituted molecule, Indole.

PART II.

DISCUSSION OF THE EXPERIMENTAL RESULTS.

CHAPTER III.

C-NITROSATION IN DILUTE MINERAL ACID.

The mechanism of the electrophilic reaction of aqueous nitrous acid with aromatic and aliphatic amines is now well defined. In particular, a number of active nitrosating species have been identified under various conditions of solvent acidity and reactant concentrations. In the few studies which have been performed on the C-nitrosation of aromatic substrates however, insufficient evidence is available to define the nature of the active electrophile.

Consequently, a study of the nitrosation of a series of indoles has been undertaken in the expectation that the reactivity of the indole nucleus in C-nitrosation should approximate to that of the aromatic amines in diazotisation, and hence the role of the various nitrosating species can be compared in the reaction of nitrous acid with Carbon and Nitrogen bases of similar basicity. The indole molecule is suitable for such a study, since it is known[57] to react with electrophilic reagents very readily at the 3-position (FIGURE(3.1).) specifically; also the basicity of the 3-position in many indoles has been measured[58] and correlated with an acidity function, H_I, for both perchloric and sulphuric acids.

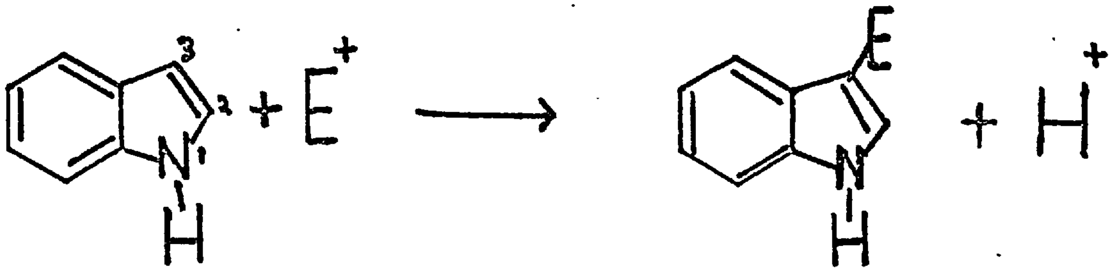


FIGURE (3.1).

(A.). THE NITROSATION OF 1,2-DIMETHYLINDOLE IN DILUTE $HClO_4$.

(i.). The zero order path.

Under conditions of low solvent acidity, (ca. pH.3.0), low concentrations of the indole, (ca. 10^{-5}M.), and moderate concentrations of nitrous acid, (~3x 10^{-5}M.), the rate of nitrosation of 1,2 dimethylindole has a second order dependence on the nitrous acid concentration, but is independent of the concentration of the indole.

$$\text{rate} = \bar{k}.(HNO_2)^2. \qquad --- (3.1).$$

Evidence that the reaction rate depends only on the nitrous acid concentration is presented in TABLE (3.1), which lists the percentage reaction versus time for a kinetic run carried out under conditions of excess nitrous acid. The slight deviation from linearity probably arises from a small contribution from a different, acid-catalysed path, which is discussed in detail below.

TABLE (3.1).

Nitrosation of 1,2-dimethylindole at 3.0°.C.

Run.323.

(Reactant.) = initial stoicheiometric values.

$(HClO_4) = 1.45x.10^{-3}M.$ (indole.) = $1.13x.10^{-5}M.$

$(HNO_2) = 1.00x.10^{-4}M.$

t. (min.)	(Prod.) $x.10^6M.$	% reaction.	d(% react.)/dt.
1.5	1.37	12.1	-
3.0	2.25	19.9	5.2
4.5	3.38	29.9	6.7
6.0	4.15	36.7	4.5
7.5	5.04	44.7	5.3
9.0	5.67	50.2	3.7
10.5	6.47	57.2	4.7
12.0	7.15	63.3	4.1
13.5	7.78	68.9	4.6
15.0	8.44	74.7	3.9
16.5	9.02	79.9	3.5
18.0	9.61	85.1	3.5
19.5	1.01	89.0	2.6
22.5	1.09	96.5	2.5
∞	1.13	100.0	

The second order dependence on the nitrous acid concentration is demonstrated by the data in TABLE (3.2), where variation in the absolute value of the initial concentration of the nitrous acid is recorded together with the concomitant values of d(% react.)/dt. , and the deduced values of $\bar{k}$, equation (3.1).

TABLE (3.2).

Nitrosation of 1,2-dimethylindole at 3.0° C.

(Reactant.) = initial stoicheiometric values.

(indole.) = 1.13×10^{-5}M. throughout.

Run	$(HClO_4)$.M. $\times 10^4$	(HNO_2).M. $\times 10^5$	-d(indole.)/dt. $\times 10^8$	$\bar{k}$(eq.3.1) $\text{l.mol.}^{-1}\text{min}^{-}$
321	14.5	3.1	5.93	61.8
322	14.5	5.0	13.0	51.4
323	14.5	10.0	51.4	51.4
324	14.5	15.6	125.0	51.4
338	5.8			53.6
			mean =	53.9

(ii). The acid-catalysed path. At acidities higher than 10^{-3}M. the rate of nitrosation of 1,2 dimethylindole shows the incursion of an additional path, with only a first order dependence on both nitrous acid and indole concentrations, in accordance with equation (3.2).

$$\text{rate} = \bar{k}_2.(\text{indole.}).(HNO_2). \qquad --- (3.2)$$

Reaction orders for the indole and nitrous acid were determined in this instance by the method of initial rates.[59] This evidence is given in TABLE (3.3); dx/dt_0 represents the rate of formation of the product at time zero in individual kinetic runs. The consistency of the values of $\bar{k}_2$, (equation (3.2)), calculated by this method, justify the adoption of the kinetic form of equation (3.2).

TABLE (3.3).

Nitrosation of 1,2-dimethylindole at 3.0°C.

(reactant.) = initial stoichiometric values.
$(HClO_4)$ = 4.0×10^{-1} throughout.

Run	(indole).M. $\times 10^6$	(HNO_2).M. $\times 10^5$	dx/dt_0 $\times 10^7$	$\bar{k}_2$(eq. (3.2) $l.mol.^{-1}min^{-1}$
325	10.6	3.10	28.6	8700
327	7.1	2.06	10.8	7400
326	10.6	1.04	8.5	7700
328	11.3	2.06	16.2	6940
329	18.8	2.06	30.0	7750

mean = 7700

The first order dependence on acidity is reflected by the rate coefficients listed in TABLE (3.4), for concentrations of solvent acid up to ca. 10^{-1}M. $HClO_4$.

TABLE (3.4).

Nitrosation of 1,2-dimethylindole at 3.0° C.

Acidity dependence of $\bar{k}_2$, (eq.3.2).

Run	$(HClO_4)$.M. x.10^2	$\bar{k}_2$ (eq.3.2) l.mol.$^{-1}$min.$^{-1}$
270	1.03	253
183	4.8	1510
182	13.5	4350

Thus the full kinetic form for nitrosation via this path is given by equation (3.3).

$$\text{rate} = \bar{k}_3.(\text{indole.}).(HNO_2).(H^+). \qquad ---(3.3).$$

At higher acidities, however, the value of $\bar{k}_2$, (eq.3.2), passes through a maximum, finally decreasing on raising the acidity. This non-linear dependence is discussed in Chapter IV. below.

(iii). Catalysis by Chloride ion. Addition of sodium chloride strongly accelerates the rate of nitrosation of 1,2-dimethylindole, and the reaction then follows equation (3.4).

$$\text{rate} = \bar{k}_3.(\text{indole}).(HNO_2).(H^+) + \bar{k}_4.(\text{indole}).(HNO_2).(H^+).(Cl^-). \quad --- (3.4)$$

The first term is identical to that observed in the absence of halide ion, and the second term represents an additional reaction path. Since the overall reaction rate can be expressed by equation (3.5),

$$\text{rate} = \bar{k}_2.(\text{indole}).(HNO_2). \quad ---- (3.5)$$

equation (3.6) may be easily deduced.

$$\bar{k}_2 = [\bar{k}_3 + \bar{k}_4.(Cl^-)\ ].(H^+) \quad --- (3.6)$$

At constant acidity , therefore, $\bar{k}_2$ varies linearly with the concentration of added chloride ion, as is shown in TABLE (3.5).

TABLE (3.5).

Nitrosation of 1,2-dimethylindole at 3.0° C.

Chloride ion Catalysis.

$(HClO_4) = 1.03 \times 10^{-2}$M.

Run	(Cl^-).M. x.10^3	$\bar{k}_2$ (eq.3.5) l.mol.$^{-1}$min.$^{-1}$	$\bar{k}_4$ (eq.3.6) l.mol.$^{-1}$min.$^{-1}$
270	0.0	253	-
278	7.2	2960	3.65
279	12.0	4870	3.73
280	24.0	9130	3.63
		mean =	3.67

(iv). A Summary of the Nitrosation of 1,2-dimethylindole.

Depending on the experimental conditions, the reaction rate follows three different kinetic laws, defined by equation (3.1), page 40, equation (3.3), page 44, and equation (3.7).

$$\text{rate} = \bar{k}_4.(\text{indole}).(HNO_2).(H^+).(Cl^-) \quad - - \quad (3.7)$$

As was discussed in the Introduction, page 30, nitrosation according to equation (3.1) has been observed previously for several species, including certain amines and inorganic ions[60]. This behaviour is commonly attributed to a slow formation of the reagent nitrous anhydride from two molecules of nitrous acid, followed by a rapid nitrosation of the substrate. This mechanism must also operate with 1,2-dimethylindole, and this conclusion is strongly supported by the close correspondence between the value of $\bar{k}$. (eq.3.1) obtained in the nitrosation[61] of aniline , ($\bar{k}$. =51.0 l.mol.$^{-1}$min at 0.0° C.) , and 1,2-dimethylindole. ($\bar{k}$. = 53.9 l. mol.$^{-1}$min.$^{-1}$ at 3.0° C.). Perhaps the most surprising feature of this result is that previously, slow formation of nitrous anhydride has been reported only with much more basic compounds than 1,2-dimethylindole.

Nitrosation according to equations (3.3) and (3.7) have been ascribed, in the analogous previous studies, to rate-determining nitrosation reactions involving the nitrousacidium ion ,(H_2ONO^+), and nitrosyl chloride, (NOCl), respectively.

(B). THE NITROSATION OF 2-METHYLINDOLE IN $HClO_4$

Similarly to 1,2-dimethylindole, the nitrosation of this substrate predominantly follows equation (3.8) in the absence of chloride ion.

$$\text{rate} = \bar{k}_3.(\text{indole}).(HNO_2).(H^+) \quad ---- \quad (3.8).$$

$$\equiv \bar{k}_2.(\text{indole}).(HNO_2). \quad ---- \quad (3.9).$$

TABLE (3.6) demonstrates the variation of the initial rate with variation of the reactant concentrations, and the ensueing constancy of $\overleftarrow{k}_2$, (eq. 3.9).

TABLE (3.6).

Nitrosation of 2-methylindole at 15.2° C.

(reactant) = initial stoicheiometric values.

$(HClO_4)$ = 1.0×10^{-2} M.

Run	(indole).M.	(HNO_2).M.	dx/dt_0	$\overleftarrow{k}_2$ (eq.3.9)
	$\times 10^5$	$\times 10^5$	$l.^{-1}mol.\ min.^{-1}$	$l.mol.^{-1}min.^{-1}$
21	5.7	5.7	5.65	1730
23	11.4	5.7	11.0	1690
24	5.7	11.4	11.3	1740
20	11.4	11.4	20.9	1610
22	17.1	17.1	56.5	1930

The acidity dependence of $\overleftarrow{k}_2$ is illustrated by the data of TABLE (3.7).

TABLE (3.7).

Nitrosation of 2-methylindole at 22.0° C.

Run	$(HClO_4)$.M.	$\bar{k}_2$(eq.3.9).	$\bar{k}_3$(eq.3.8).
	x.10^4	l.mol.$^{-1}$min.$^{-1}$	l.mol.$^{-1}$min.$^{-1}$
8	9.6	350	3.65x.10^5
9	19.2	732	3.81x.10^5
11	96.0	3420	3.57x.10^5
		mean =	3.77x.10^5

(C). NITROSATION OF 2-PHENYLINDOLE IN $HClO_4$

(i). The contribution due to nitrous anhydride.

The reaction of 2-phenylindole with aqueous nitrous acid in dilute $HClO_4$ (ca.10^{-2}M.), shows the incursion of at least two reaction paths , since the apparent order in nitrous acid is non-integral, being between 1.0 and 2.0 . The empirical relationship is shown in equation (3.10). ,

$$\text{rate} = \bar{k}.(\text{indole}).(HNO_2).^{1.3} \quad --- \quad (3.10)$$

which refers to measurements of the

reaction in 0.024M. $HClO_4$. That the reaction is first order in the indole is demonstrated by the dependence of the rate on the indole concentration throughout a typical kinetic run shown in TABLE (3.8).

TABLE (3.8).

Nitrosation of 2-phenylindole at 3.0°C. Run. 311

(reactant) = initial stoicheiometric values.

$(HClO_4)$ =2.4x.10^{-2}M. (indole) = 1.76x.10^{-6}M.

(HNO_2) = 8.0x.10^{-5}M.

t. min.	(indole).M. x.10^6	7+$\log_{10}$(indole).	d[log(indole)]/dt
1.5	1.41	1.141	0.070
2.25	1.24	1.093	0.068
3.0	1.11	1.045	0.067
4.5	0.91	0.959	0.064
6.0	0.733	0.865	0.064
9.0	0.452	0.655	0.066
12.0	0.312	0.494	0.063
15.0	0.209	0.320	0.062
∞	0.0		

If the initial concentration of the nitrous acid is maintained constant, in excess, in individual kinetic runs, then equation (3.10) can be rewritten as equation (3.11).

$$\text{rate} \quad = \quad \bar{k}_1.(\text{indole}). \qquad\qquad ----- (3.11).$$

A reasonable interpretation of the non-integral order in nitrous acid is that reaction via nitrous anhydride and the nitrousacidium ion occur concurrently. Thus the rate law is more correctly expressed by equation (3.12).

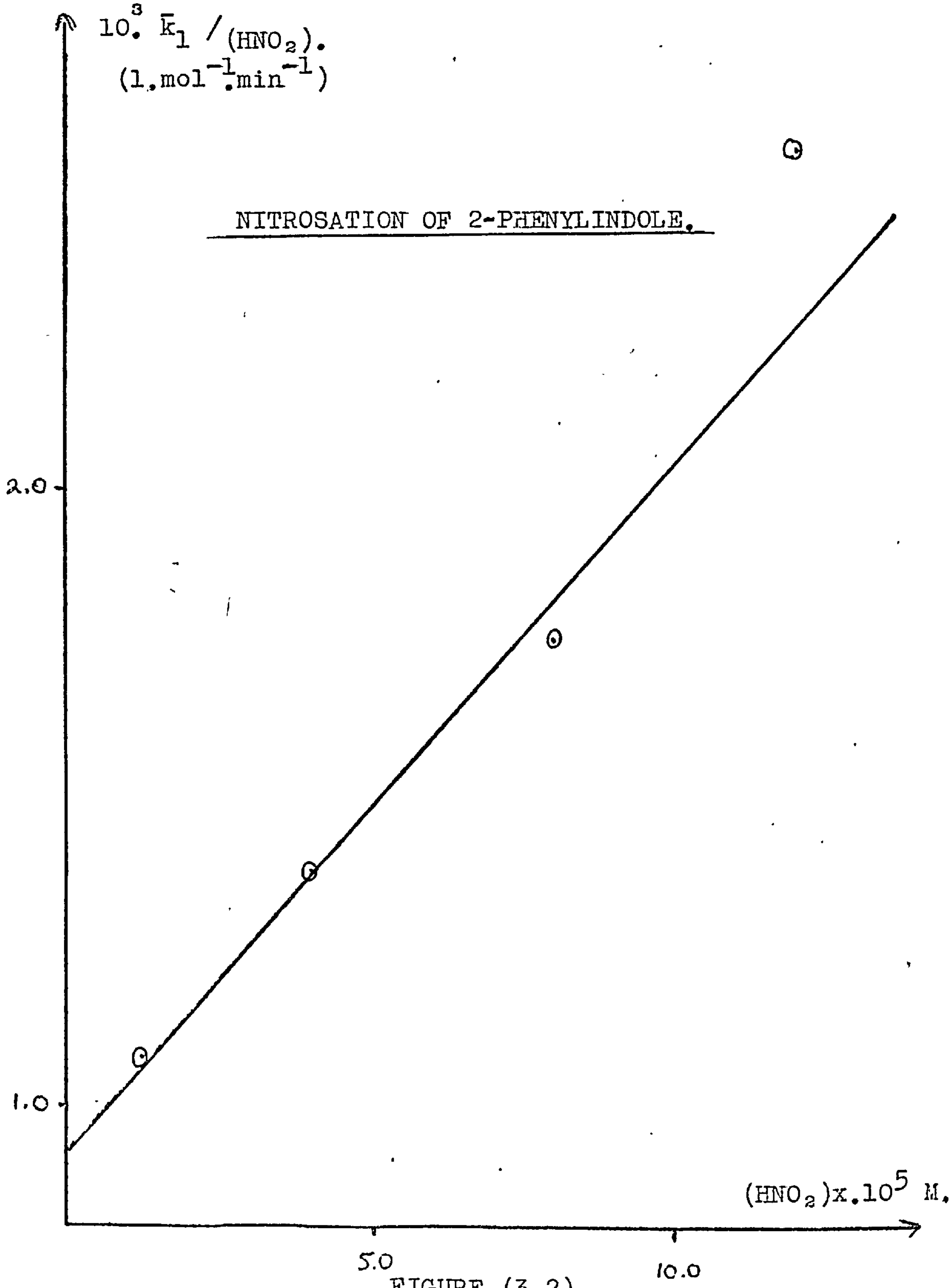
$$\text{rate} \quad = \quad \bar{k}_3.(\text{indole}).(HNO_2).(H^+) + \bar{k}_4.(HNO_2)^2.(\text{indole}) \;--\; (3.12).$$

Combineing equations (3.11) and (3.12),

$$\bar{k}_1 = \bar{k}_3.(H^+).(HNO_2) + \bar{k}_4.(HNO_2)^2 \qquad\qquad ----- (3.13).$$

$$\text{and} \quad \bar{k}_1/(HNO_2) \quad = \quad \bar{k}_3.(H^+) \quad + \quad \bar{k}_4.(HNO_2) \qquad\qquad ----- (3.14).$$

Hence a graph of $\bar{k}_1/(HNO_2)$ against (HNO_2) should be linear for runs performed at constant acidity, and under conditions where the concentration of nitrous acid remains effectively constant throughout each run. A graph of this type is shown in FIGURE (3.2), the relevant coefficients being listed in TABLE (3.9).



$10^3\ \bar{k}_1\ /(HNO_2)$.
(l.mol^{-1}.min^{-1})
NITROSATION OF 2-PHENYLINDOLE.
2.0
1.0
$(HNO_2)\times10^5$ M.
5.0
10.0

FIGURE (3.2).

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TABLE (3.9).

Nitrosation of 2-phenylindole at 3.0° C.

Variation of $\bar{k}_1$ (eq.3.15) with nitrous acid concentration.

(reactant) = initial stoicheiometric values.

$(HClO_4)$ = 2.4×10^{-2}M. (indole) = 1.76×10^{-6}M.

Run	(HNO_2) M. x.10^5	$\bar{k}_1$(eq.3.11) x.10^2, min.$^{-1}$	$\bar{k}_1/(HNO_2)$ l.mol.$^{-1}$min.$^{-1}$
308	1.2	1.29	1080
309	4.0	5.52	1380
311	8.0	14.1	1760
310	12.0	30.7	2560

From FIGURE (3.2).,

$\bar{k}_3.(H^+)$ = 950 l.mol.$^{-1}$min.$^{-1}$

and $\bar{k}_4$. = 1.1×10^7 l.^{2}mol.$^{-2}$min.$^{-1}$

(ii). The acid-catalysed path . At higher solvent acidities, reaction via the nitrousacidium ion should predominate , especially if the initial concentration of nitrous acid is low, (ca. 10^{-5} M.). Under these conditions, equation (3.12) effectively reduces to equation (3.15),

$$\text{rate} = \bar{k}_3.(\text{indole}).(HNO_2).(H^+) \quad ---- \quad (3.15)$$

which can be rewritten as equation (3.16).

$$\text{rate} = \bar{k}_2.(\text{indole}).(HNO_2) \qquad ----(3.16)$$

The variation in $\bar{k}_2$, with acidity , is shown in TABLE (3.10).

TABLE (3.10).

Nitrosation of 2-phenylindole at 3.0° C.

Variation of $\bar{k}_2$ (eq.3.16) with solvent acidity.

Run	$(HClO_4)$.M. $x.10^2$	$\bar{k}_2$ (eq.3.16) $l.mol.^{-1}min.^{-1}$	$\bar{k}_3$ (eq.3.15). $l.^2mol.^{-2}min.^{-1}$
308-311	2.4	950	$3.96x.10^4$
316	6.7	2420	$3.61x.10^4$
307	20.0	8450	$4.23x.10^4$
		mean =	$3.93x.10^4$

It is interesting to note in TABLE (3.10), that the value of $\bar{k}_2 \equiv \bar{k}_3.(H^+)$, obtained from the graphical intercept of FIGURE (3.2)., is quite consistent with the values of $\bar{k}_2$ obtained directly at higher acidities. This can be regarded as evidence to support the general treatment of the results.

(iii). Catalysis by added Chloride ion.

Added sodium chloride

strongly catalyses the reaction rate , which then is controlled by equation (3.17), by analogy with 1,2-dimethylindole.

$$\text{rate} = \bar{k}_3.(\text{indole}).(\text{HNO}_2).(\text{H}^+) + \bar{k}_4.(\text{indole}).(\text{HNO}_2).(\text{H}^+).(\text{Cl}^-). \qquad \text{------(3.17).}$$

At constant solvent acidity, and with an excess of chloride ion, equation (3.17) reduces to equation (3.18).

$$\text{rate} = \bar{k}_2.(\text{indole}).(\text{HNO}_2) \qquad \text{--------(3.18).}$$

$$\text{where } \bar{k}_2 = \bar{k}_3.(\text{H}^+) + \bar{k}_4.(\text{H}^+).(\text{Cl}^-). \qquad \text{---(3.19).}$$

A graph of $\bar{k}_2$ against (Cl^-) at constant acidity will therefore be linear, with gradient of $\bar{k}_4.(\text{H}^+)$ and intercept of $\bar{k}_3.(\text{H}^+)$. A graph of this kind is shown in FIGURE (3.3)., the relevant coefficients being listed in TABLE (3.11).

NITROSATION OF 2-PHENYLINDOLE.

HALIDE ION CATALYSIS.

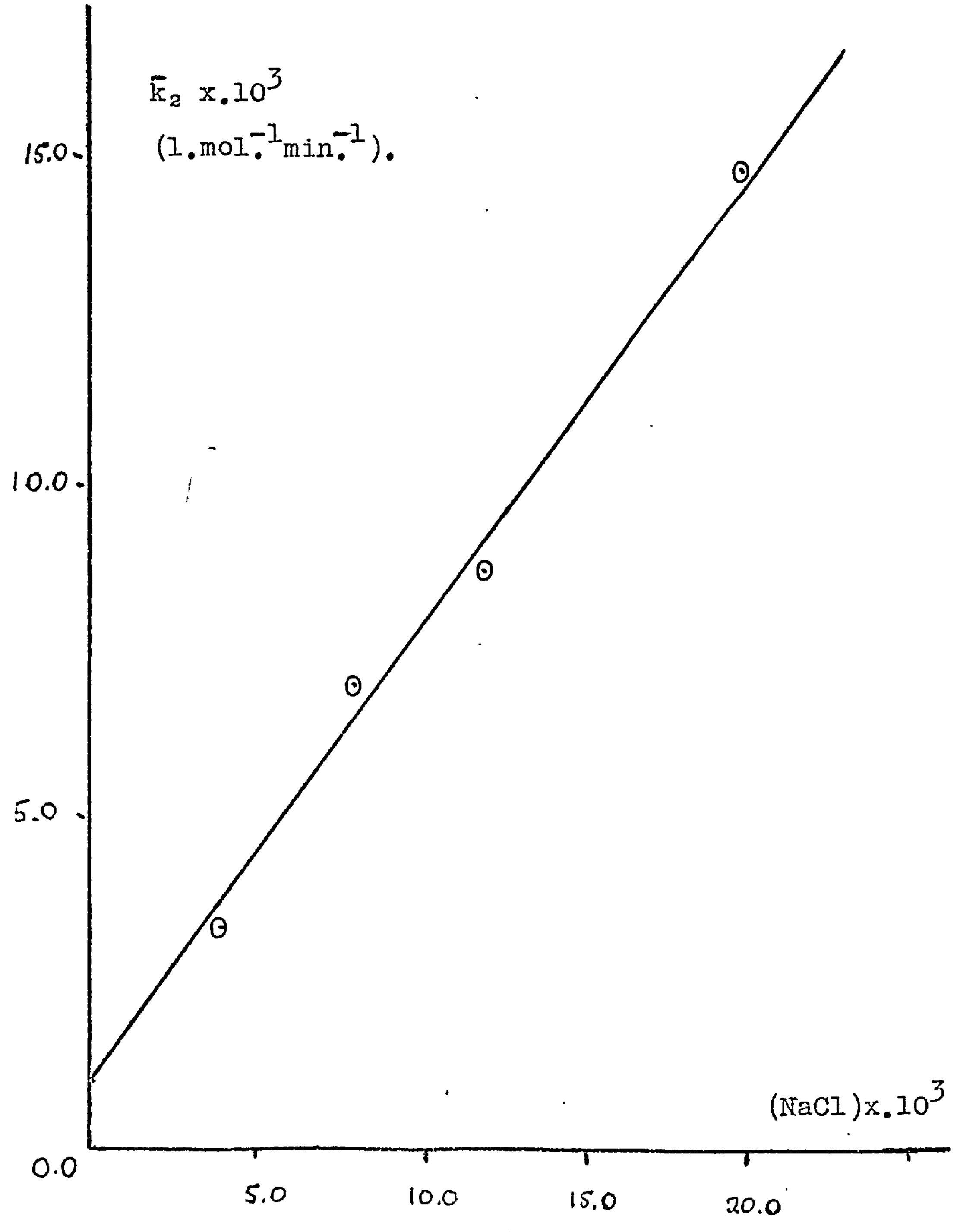

FIGURE (3.3).

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TABLE (3.11).

Variation of $\bar{k}_2$(eq.3.19) with concentration of sodium chloride.

$(HClO_4) = 2.4x.10^{-2}M.$

Run	$(Cl^-).M.$ x.10^3	$\bar{k}_2$(eq.3.19) l.mol.$^{-1}$min.$^{-1}$	$\bar{k}_4.(H^+)$. l^2.mol.$^{-2}$min.$^{-1}$
314	4.0	3360	6.02x.10^5
315	8.0	7000	7.57x.10^5
312	12.0	8750	6.35x.10^5
313	20.0	14800	7.40x.10^5
		Mean =	6.83x.10^5

The observed intercept value from FIGURE (3.3) leads to:- $\bar{k}_3.(H^+)$ = 950 l.mol.$^{-1}$min.$^{-1}$ at 3.0°C. and 2.4x.10^{-2}M. $HClO_4$. This corresponds exactly to the value of $\bar{k}_3.(H^+)$, already obtained from the graphical intercept of FIGURE (3.2)., thus generally establishing the consistency of the graphical treatments used for this compound.

(D). NITROSATION OF 2-METHYL-5-NITROINDOLE .

(i). The acid-catalysed path. The kinetic method used for this reaction, combined with the relative insolubility of the substrate, prohibited a rigorous study of the reactant orders. The experimental conditions of solvent acidity, (ca.pH 1.0), and low nitrous acid concentration (ca.10^{-5}M.), would, however, in combination, prevent any appreciable interference from a mechanism involving nitrous anhydride. By analogy with the other indoles, already described, it was assumed that the reaction rate also follows equation (3.20).

The data of TABLE (3.12) fits this assumption appropriately.

$$\text{rate} = \bar{k}_3.(\text{indole}).(HNO_2).(H^+) \qquad \text{------(3.20).}$$

$$= \bar{k}_2.(\text{indole}).(HNO_2) \qquad \text{------(3.21).}$$

TABLE (3.12).

Nitrosation of 2-methyl-5-nitroindole at 0.5°C.

Run	$(HClO_4)$.M. x.10	(indole)M. x.10^6	(HNO_2).M. x.10^6	$\bar{k}_2$(eq.3.21). l.mol.$^{-1}$min.$^{-1}$
249	7.2	40.0	6.0	> 6000
250	1.19	7.8	10.0	1800
265	1.13	20.8	11.2	1700

Analysis of individual runs employing equation (3.22) always resulted in good linear dependence of the logarithmic function, plotted against time, to over 90% reaction.

$$\bar{k}_2.(t-t_0) = \frac{2.303}{a-b} \cdot \log_{10}\left[\frac{b}{a} \cdot \frac{(a-x)}{(b-x)}\right] \quad --(3.22)$$

– where all the symbols have their usual significance. Equation (3.22) is sensitive to the validity of equation (3.21), especially if the initial concentrations of reactants are of the order of 2:1 . , which was the case in these studies.

(ii). <u>Catalysis by chloride ion</u> .

Added chloride ion catalyses the rate according to equation (3.23).

$$\text{rate} = \bar{k}_3.(\text{indole}).(HNO_2).(H^+) + \bar{k}_4.(\text{indole}).(HNO_2).(H^+).(Cl^-) \quad -------(3.23).$$

At constant acidity, equation (3.23) reduces to equation (3.24) , when the individual runs maintain a constant concentration of chloride ion throughout reaction, by virtue of the catalytic nature of this ion.

$$\text{rate} = \bar{k}_2.(\text{indole}).(HNO_2) \quad -------(3.24).$$

Combining equations (3.23) and (3.24) :-

$$\bar{k}_2 \quad = \quad \bar{k}_3.(H^+) \quad + \quad \bar{k}_4.(H^+).(Cl^-) \qquad ------(3.25).$$

A graph of $\bar{k}_2$, (equation 3.25), a gainst tha concentration of added chloride ion is shown in FIGURE (3.4), the relevant coefficients being listed in TABLE (3.13).

TABLE (3.13).

Nitrosation of 2-methyl-5-nitroindole at 0.5°C.

Catalysis by added chloride ion.

$(HClO_4) = 0.10$ M.

Run	(NaCl).M. x.10^3	$\bar{k}_2$ (eq.3.25) $l.mol.^{-1}min.^{-1}$	$\bar{k}_4.(H^+)$ (eq.3.25) $l.^2mol.^{-2}min.^{-1}$
250, 265	0	1510	-
284	1.67	3320	1.08x.10^6
285	3.44	5400	1.13x.10^6
283	5.00	7500	1.20x.10^6
282	7.20	8800	1.01x.10^6
		mean =	1.10x.10^6

The value of $\bar{k}_3(H^+)$, =1600 $l.mol.^{-1}min.^{-1}$, obtained from the intercept of FIGURE (3.4), leads to the value of $\bar{k}_3$ =16000 $l.^2mol.^{-2}min.^{-1}$ at 0.5°C., which is in good agreement with the value of $\bar{k}_3$ measured in the absence of chloride ion,

NITROSATION OF 2-METHYL-5-NITROINDOLE.

HALIDE ION CATALYSIS.

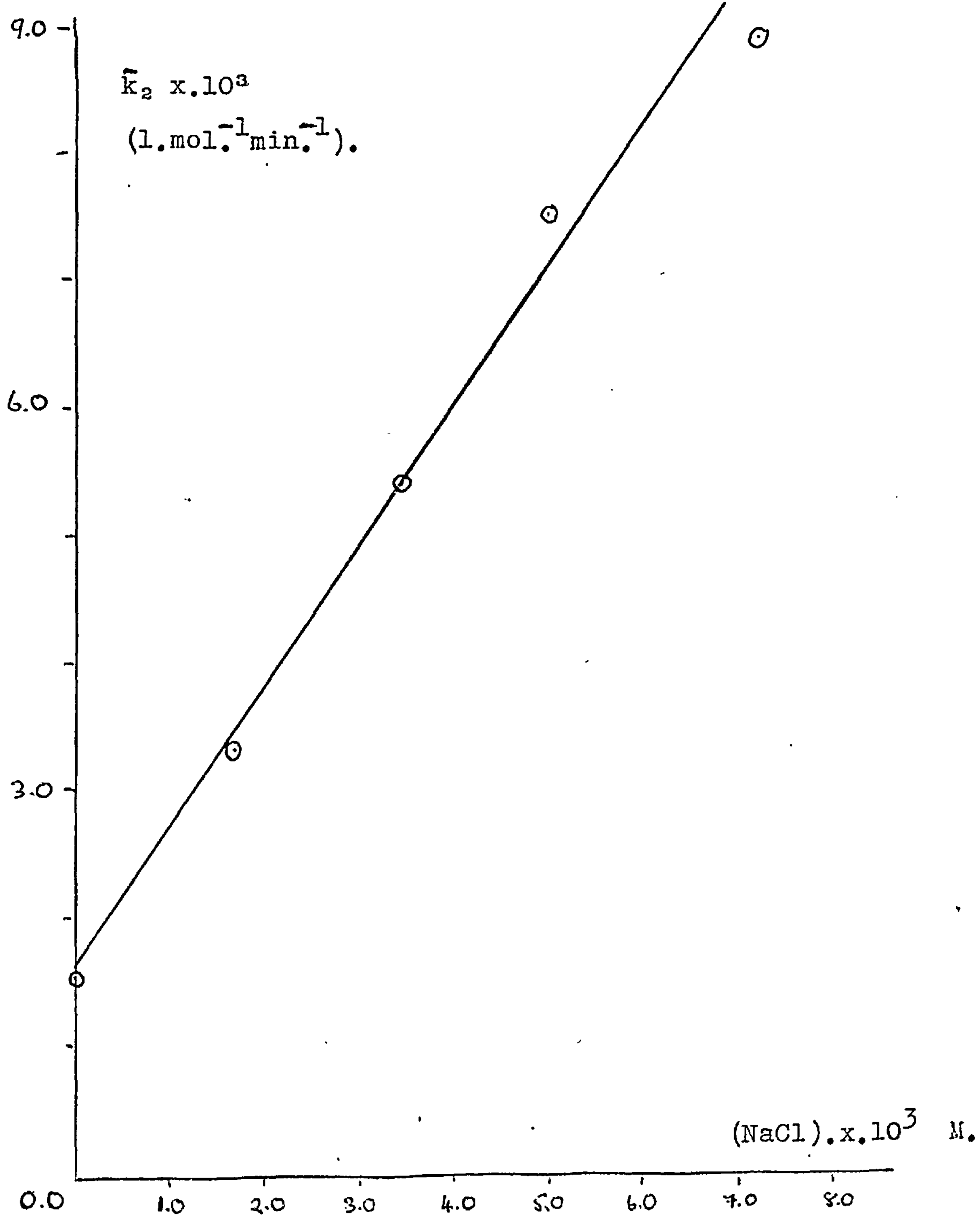


FIGURE (3.4).

($\bar{k}_3$ = 15100 $l.^2mol.^{-2}min.^{-1}$), and listed above in TABLE (3.12).

(E). NITROSATION OF 5-CYANOINDOLE.

(i). The acid-catalysed path.

The reaction has been studied over an acidity range of 10^{-2} to 10^{-1} M. $HClO_4$. In this acidity range, with a large excess of the indole over nitrous acid, the rate expression for individual runs was always that of equation (3.26).

$$\text{rate} = \bar{k}_1.(HNO_2) \qquad ------(3.26).$$

Good linearity was always observed in a graph of $\log.(HNO_2)_t$ against time, up to at least 90% reaction.

The variation in $\bar{k}_1$ (equation 3.26), with the initial stoicheiometric concentration of substrate, is shown in TABLE (3.14).

TABLE (3.14).

Nitrosation of 5-cyanoindole at 25.0°C.

(reactant) = initial stoich. values.

Run	(indole).M. x.10^4	(HNO_2).M. x.10^5	$\bar{k}_1$ $min.^{-1}$	$\bar{k}_2$ (eq.3.27). $l.mol.^{-1}min.^{-1}$
346	8.0	1.0	$5.37x.10^{-2}$	67.0
347	4.0	1.0	$2.77x.10^{-2}$	69.0

The observed first order dependence of $\bar{k}_1$ on the concentration of the indole implys that reaction follows equation (3.27).

$$\text{rate} = \bar{k}_2.(\text{indole}).(\text{HNO}_2) \qquad \text{-----(3.27).}$$

The acidity dependence of $\bar{k}_2$ is shown in TABLE (3.15).

TABLE (3.15).

Nitrosation of 5-cyanoindole in $HClO_4$ at 0.5°C.

Variation of $\bar{k}_2$ (eq.3.27) with acidity.

Run	$(HClO_4)$.M. x.10^2	$\bar{k}_2$ (eq.3.27) l.mol.$^{-1}$min.$^{-1}$	$\bar{k}_2/(H^+)$. l^2.mol.$^{-2}$min.$^{-1}$
286	1.0	12.7	1.27x.10^3
348	4.9	59.0	1.20x.10^3
287	10.0	126.0	1.26x.10^3
		mean =	1.24x.10^3

Thus the total rate law for this reaction is that of equation (3.28).

$$\text{rate} = \bar{k}_3.(\text{indole}).(\text{HNO}_2).(H^+) \qquad \text{----(3.28).}$$

(ii). Chloride ion catalysis. Unlike the previously mentioned indoles, only a small increase in reaction rate was observed on the introduction of chloride ion.

TABLE (3.16).

Nitrosation of 5-cyanoindole at 0.5°C.

Chloride ion catalysis.

$(HClO_4)$ = 0.10 M.

Run	(NaCl).M.	$(NaClO_4)$.M.	$\bar{k}_2$ (eq.3.27)
	x.10	x.10	$l.mol.^{-1}min.^{-1}$
287	0.0	0.0	126.0
349	0.0	4.0	226.0
350	0.0	8.0	350.0
288	1.0	0.0	170.0
289	7.5	0.0	314.0

The catalytic effect of sodium chloride is of the same order of magnitude as that of sodium perchlorate, which is known[62] to form no covalently bonded nitrosating agent with nitrous acid, and hence can only exert a medium effect on the rate of reaction. Thus the logical conclusion is that sodium chloride , in this case, mildly accelerates the rate by a salt effect.

(F.). NITROSATION OF 1-METHYL-5-NITROINDOLE AND 5-NITROINDOLE.

By analogy with the results for 5-cyanoindole and

2-methyl-5-nitroindole, the rate law for these reactions is assumed to be that of equation (3.29).

$$\text{rate} = \bar{k}_3.(\text{indole}).(\text{HNO}_2).(\text{H}^+) \quad \text{-----}(3.29).$$
$$= \bar{k}_2.(\text{indole}).(\text{HNO}_2) \quad \text{-----}(3.30).$$

This assumption is supported by the observation that individual kinetic runs follow equation (3.22) exactly, and that the value $\bar{k}_2$ (eq.3.30) is directly proportional to the concentration of perchloric acid in dilute solution, as is shown by TABLES (3.17) and (3.18).

TABLE (3.17).

The Nitrosation of 1-methyl-5-nitroindole.

Temperature = 0.5°C.

Run	(HClO_4).M. x.10	(NaCl).M. x.10	$\bar{k}_2$ (eq.3.30). $\text{l.mol.}^{-1}\text{min.}^{-1}$
358	1.0	0.0	70.0
351	2.0	0.0	195.0
352	2.0	1.0	221.0

TABLE (3.18).

Nitrosation of 5-nitroindole at 0.5°C.

Run	$(HClO_4)$.M. x.10	(NaCl).M. x.10	$\bar{k}_2$ (eq.3.30). $l.mol.^{-1}min.^{-1}$
266	12.0	0.0	1100
252	1.19	0.0	35
281	1.00	1.0	24

For both indoles, the extent of specific chloride ion catalysis , as listed above , is too small to be detected, the observed variations in the rate, with added chloride, being well within the expected medium effect.

(G). THE RATE-DETERMINING STEP IN THE NITROSATION OF INDOLES.

(i). Nitrosation of 1,2-dimethyl-3[^{2}H]-indole.

The nitrosation of this indole could not be carried out directly in H_2O, because of the extremely rapid rate of protodedeuteriation . Consequently, the reaction has been conducted in D_2O, and the rate compared with that obtained from reaction of 1,2-dimethylindole in H_2O. The results are shown in TABLE (3.19), in which the second order rate coefficients are defined by equation (3.31).

rate = $\bar{k}_2$.(indole).(nitrous acid). - - - (3.31).

TABLE (3.19).

Nitrosation of 1,2-dimethylindole at 3.0°C.

Runs in D_2O and H_2O.

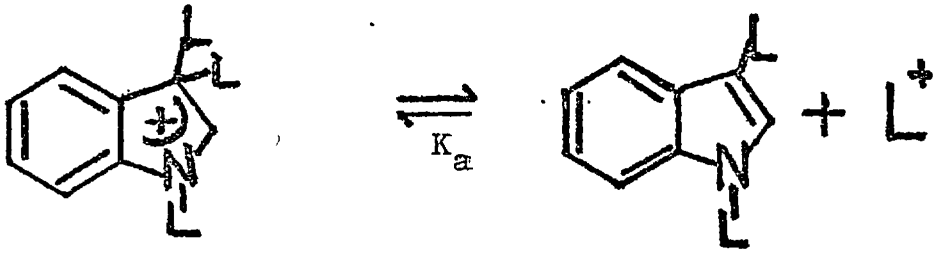
Run	$(DClO_4)$.M. x.10^2	$(HClO_4)$.M. x.10^2	$\bar{k}_2$ (eq.3.31). l.mol.$^{-1}$min.$^{-1}$
269	1.02	0.0	416
270	0.0	1.03	253

The concentrations employed in equation (3.31), however, are stoicheiometric values, and consequently the magnitude of any primary isotope effect will be compounded with solvent isotope effects [63] on the fast pre-equilibria involved in this reaction.

The solvent isotope effect on the concentration of the nitrousacidium ion is known [64] under similar conditions to the above measurements, and the result is expressed in equation (3.32).

$$\frac{[\ D_2ONO^+]^{D_2O}}{[\ H_2ONO^+]^{H_2O}} = 2.2 \quad ----- (3.32).$$

The solvent isotope effect on the indole protonation , moreover, has been determined in the present work, by direct measurement of the basicities in H_2O and D_2O as solvents , and is expressed in terms of pK_a (eq.3.33), in TABLE (3.20).



INDL$^+$. IND. - - (3.33).

TABLE (3.20).

Values of pK_a (eq.3.33) for 1,2-dimethylindole.

Solvent	pK_a
H_2O	+ 0.3 [58]
D_2O	+ 0.8 ± 0.1

The symbol " L", at this point , is used to represent either the deuterium or hydrogen atoms.

Thus, :-

$$\text{rate} = \overleftarrow{k}^{L}_{obs}\,.\,(\text{indole}).(LNO_2) \qquad ------(3.34).$$

$$= \quad \bar{k}^L_{obs} \,.\, ([IND] + [INDL^+]).\ (LNO_2). \qquad \text{-- --}(3.35).$$

$$= \quad k^L_2.\ [IND].[L_2ONO^+] \qquad \text{-- -- -- -- -- -- -- --}(3.36).$$

where $\bar{k}^L_2$ is the molecular rate coefficient for reaction, and is therefore corrected for solvent isotope effects.

Then:-

$$k^L_2 \quad = \quad \bar{k}^L_{obs} \,.\, \langle 1 + \frac{[INDL^+]}{[IND]} \rangle .\ \frac{(LNO_2)}{[L_2ONO^+]} \qquad \text{-- -- --} \quad (3.37).$$

and, since $\quad K^L_a \quad = \quad \dfrac{[IND].(L^+)}{[INDL^+]}$,

$$k^L_2 \quad = \quad \bar{k}^L_{obs} \,.\, \langle 1 + \frac{(L^+)}{K^L_a} \rangle .\ \frac{(LNO_2)}{[L_2ONO^+]} \qquad \text{-- -- -- --} \ (3.38).$$

If $(D^+) = (H^+)$, both being greater than 10^{-3}M., then $(DNO_2) = (HNO_2) =$ total stoichèiometric value.

Thus :-

$$\frac{k^H_2}{k^D_2} \quad = \quad \frac{\bar{k}^H_{obs}}{\bar{k}^D_{obs}} \,.\, \frac{\langle 1 + \frac{(H^+)}{K^H_a} \rangle}{\langle 1 + \frac{(D^+)}{K^D_a} \rangle} \,.\, \frac{[D_2ONO^+]}{[H_2ONO^+]} \qquad \text{-- -- --} \ (3.39).$$

When the data recorded in TABLES (3.19) and (3.20) are combined with the result of equation (3.32), and substituted into equation (3.39), the numerical answer is that presented in equation (3.40).

$$k_2^H/k_2^D = 1.26 \pm 0.2 \quad \text{---------} \quad (3.40).$$

The assumption , inherent in the above calculation, that reaction occurs through the base form of the indole, and not through the conjugate acid, is justified below in CHAPTER IV.

The calculated ratio of the rate-coefficients of equation (3.40) is less consistant with a primary isotope effect than with a secondary isotope effect. Thus, for the nitrosation of 1,2-dimethylindole, the rate-determining step is concluded to involve very little stretching of the carbon/hydrogen bond at the site of reaction.

(ii). Nitrosation of 5-cyano-3[^{2}H]-indole. The magnitude of the primary isotope effect for the nitrosation of this indole was determined directly,without resorting to D_2O as solvent. This was possible by virtue of the relatively high solubility of this substrate in water, and the relatively slow rate of protodedeuteriation[65] in cold dilute $HClO_4$.

Under carefully controlled experimental conditions, the nitrosation reaction of an aqueous solution of 5-cyano-3[^{2}H]-indole will be complete before a significant fraction of the isotopic label has exchanged. The resulting rate-coefficients, defined by equation (3.41), are listed in TABLE (3.21).

$$\text{rate} = \overleftarrow{k}^{L}_{obs}.(\text{indole}).(\text{HNO}_2) \qquad ---(3.41).$$

TABLE (3.21).

Nitrosation of 5-cyanoindole in $HClO_4$.

Primary isotope effect .

$(HClO_4) = 1.2x.10^{-2}$

Run	Indole	$T^{\circ}C.$	$\overleftarrow{k}^{L}_{obs.}$ $l.mol.^{-1}min.^{-1}$	$\overleftarrow{k}^{H}/\overleftarrow{k}^{D}$
341	-3[^{2}H]	0.5	8.0	1.86
TABLE (3.15)	-3[^{1}H]	0.5	14.9	
342	-3[^{2}H]	25.0	38.1	1.75
343	-3[^{1}H]	25.0	66.5	

The observed ratio of rate-coefficients, $\overleftarrow{k}^{H}/\overleftarrow{k}^{D} = 1.8 \pm 0.1$

is large enough to justify interpretation as a primary isotope effect. In contrast to the more basic 1,2-dimethylindole, described above , the transition state for nitrosation of 5-cyanoindole apparently involves considerable stretching of the carbon/hydrogen bond at the reaction site.

(H). DISCUSSION.

The following rate-laws have been described in the nitrosation of indoles :-

$$\text{rate} = \bar{k}_1.(\mathrm{HNO_2})^2 \qquad \text{------}(3.42).$$

$$\text{rate} = \bar{k}_2.(\mathrm{HNO_2})^2.(\text{indole}) \qquad \text{------}(3.43).$$

$$\text{rate} = \bar{k}_3.(\mathrm{HNO_2}).(\text{indole}).(\mathrm{H^+}) \qquad \text{------}(3.44).$$

$$\text{rate} = \bar{k}_4.(\mathrm{HNO_2}).(\text{indole}).(\mathrm{H^+}).(\mathrm{Cl^-}) \qquad \text{------}(3.45).$$

Values of the various rate-coefficients for the series of indoles are summarised in TABLE (3.22)., along with the relevant pK_a values for the indoles, protonated at the 3-position.

TABLE (3.22).

Summary of the rate-coefficients for the nitrosation of indoles

Units of coefficients = $l^{n}.mol.^{-n}min.^{-1}$

Indole	pK_a	T°C.	$\overleftarrow{k}_1$ n=1	$\overleftarrow{k}_2$ $x.10^{-7}$ n=2	$\overleftarrow{k}_3$ $x.10^{-4}$ n=2	$\overleftarrow{k}_4$ $x.10^{-7}$ n=3
1,2-dimethyl	$+0.3$[a]	3.0	53.9		3.2	3.67
2-methyl	-0.28[a]	3.0			3.0	
2-phenyl	-1.85[c]	3.0		1.1	3.9	2.85
2-methyl-5-nitro	-3.58[a]	0.5			1.5	1.10
5-cyano	-6.0[b]	0.5			0.124	<0.000
1-methyl-5-nitro	-6.6[d]	0.5			0.07	<0.000
5-nitro	-7.4[a]	0.5			0.027	<0.0001

a - reference 58. b - reference 71.

c - measured in the present work.

d - estimated value, see reference 58.

Some of these results are also shown in graphical form in FIGURE (3.5).

The various kinetic forms listed above all have their analogues in the diazotization of amines, when they have been attributed to nitrosation <u>via</u> a series of carriers of the nitrosonium ion, and presumably, the same conclusions can be drawn in the present study.

Thus:-

$\bar{k}_1$ (eq.3.42) refers to a rate-determining formation of the reagent, nitrous anhydride.

$\bar{k}_2$ (eq.3.43) refers to a rate-determining attack of the reagent, nitrous anhydride.

$\bar{k}_3$ (eq.3.44) refers to the nitrousacidium ion as reagent.

$\bar{k}_4$ (eq.3.45) refers to the reagent nitrosyl chloride.

It is therefore interesting to see how far this analogy applies in terms of the reactivity of the various nitrosating agents towards the amines and the indoles.

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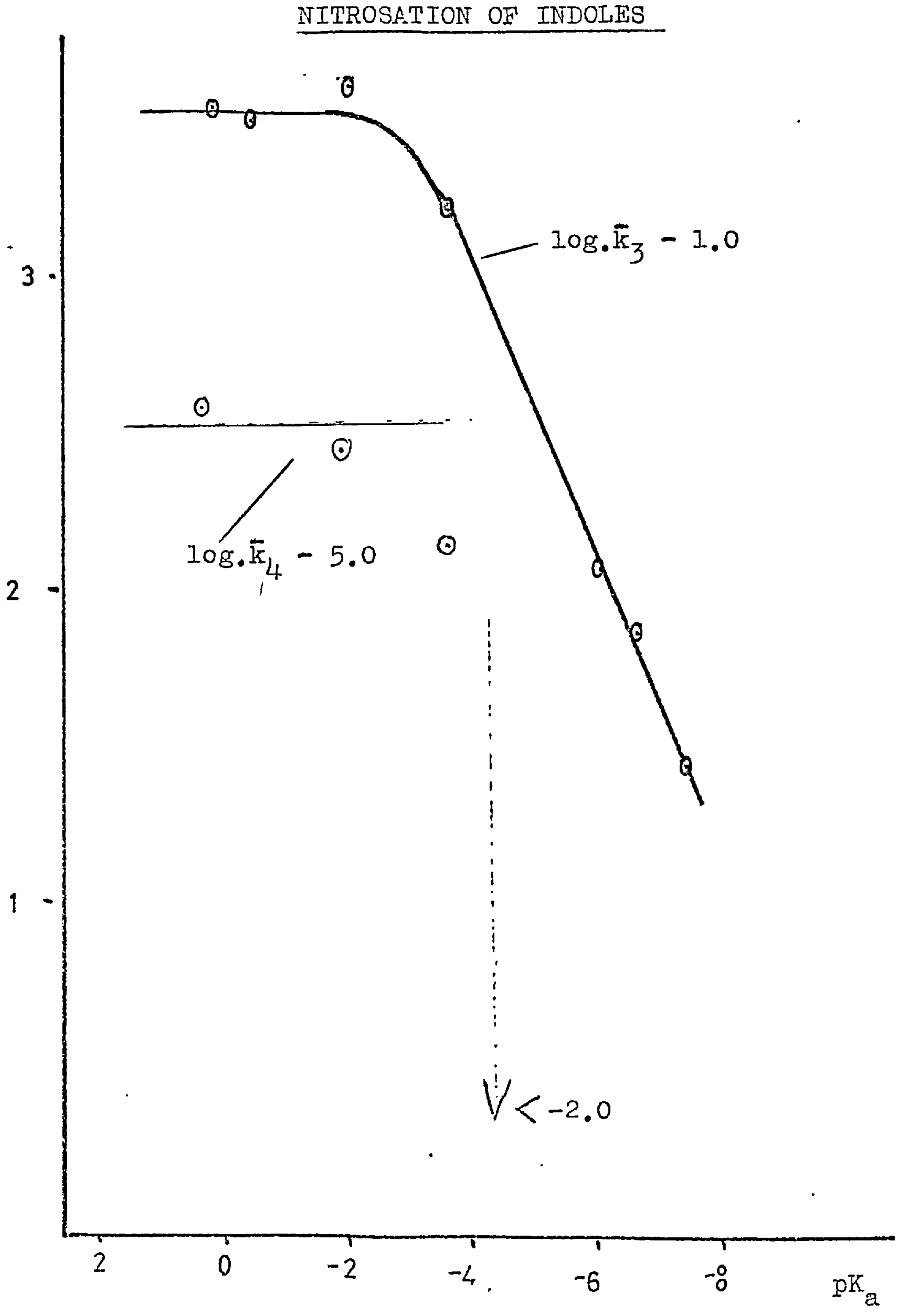


FIGURE (3.5).

(i). Nitrous anhydride. Nitrosation *via* this species is observed only for the most basic ,(and therefore most reactive), substrates. 1,2-dimethylindole apparently reacts with nitrous anhydride as fast as the species is formed, whereas 2-phenylindole reacts with an equilibrium-controlled concentration of the reagent in the rate-determining step. The discovery of these pathways is surprising, since comparable reactions of amines are observed only with more basic species. This is evident from a comparison of the molecular rate-coefficients for reaction of nitrous anhydride with the substrates listed in TABLE (3.23).

TABLE (3.23).

Nitrous anhydride reaction with anilines[18] and indoles.

Substrate	pKa	$\bar{k}_1$ (eq3.42) $l.mol^{-1}min^{-1}$	$\bar{k}_2$ (eq3.43) $l^2 mol^{-2} min^{-1}$	$T^\circ C.$
aniline .	4.6	51.0	$1.8x.10^7$	0.0
4-Cl-aniline.	4.0		$5.5x.10^6$	0.0
$4-NMe^+$-aniline .			$8.4x.10^5$	0.0
$4-NO_2$-aniline.	0.99		undetected	
1,2-dimethylindole.	0.3	53.9		3.0
2-phenylindole .	-1.85		$1.1x.10^7$	3.0

This implies that either the reactivity of the site toward nitrous anhydride is not adequately reflected in the basicity as measured by the pK_a, or that the nitrosation of indoles by nitrous anhydride does not involve rate-determining attack by nitrous anhydride at the 3-position. Further discussion of these possibilities is deferred until later.

(ii). The nitrousacidium ion. The form of equation (3.44) has been previously interpreted in terms of reaction through the nitrousacidium ion. As discussed earlier , reaction through the nitrosonium ion would give an identical rate-expression, but the bulk of the work to date on nitrosation reactions suggests that the nitrosonium ion is not the active electrophile in dilute mineral acid. In particular, the experiments of Stedman and coworkers[26] on the rate of oxygen exchange between labelled nitrous acid and water, seem to be quite exclusive of this agent. The present results do not materially alter these conclusions, and therefore the nitrousacidium ion will be assumed to be the active species for nitrosation in accord with equation (3.44).

The numerical values of $\bar{k}_3$ (eq.3.44), measured for a series of indoles , show a striking lack of variation with pK_a in the case of the four most basic substrates studied,as is shown in FIGURE (3.5). This behaviour is similar to that observed in the diazotisation of the aromatic amines by the nitrousacidium ion. Values of the rate-coefficient , ($\overleftarrow{k}_3'$), equivalent to $\overleftarrow{k}_3$, (eq.3.44), for the diazotisation of some aromatic amines of known basicity are reproduced in TABLE (3.24). It will be readily appreciated that $\overleftarrow{k}_3$ and $\overleftarrow{k}_3'$ are directly comparable, since they both refer to reaction of the nitrousacidium ion on the neutral base form of the substrate.

TABLE (3.24).

Nitrosation of amines[18] and indoles by the nitrousacidium ion.

Substrate	T°C.	pK_a	$\overleftarrow{k}_3$ x.10^{-2}	$\overleftarrow{k}_3'$ x.10^{-2}
			$l^2 mol^{-2} min^{-1}$	
2-Cl-aniline.	0.0	2.6		105.0
4-NO_2-aniline .	0.0	0.99		97.0
2-NO_2-aniline.	0.0	-0.28		87.0
2,4-dinitroaniline.	0.0	-4.5		2.2
1,2-dimethylindole	3.0	0.3	320.0	
2-methylindole.	3.0	-0.28	300.0	
2-phenylindole.	3.0	-1.85	390.0	
2-methyl-5-nitroindole	0.5	-3.58	150.0	
5-cyanoindole	0.5	-6.0	12.4	
1-methyl-5-nitroindole	0.5	-6.6	7.0	
5-nitroindole,	0.5	-7.4	2.7	

It has been postulated[66] that the observed insensitivity of the magnitude of the coefficient $\overleftarrow{k}_3$ to the basicity of the amine may arise from a diffusion controlled mechanism, in which the nitrousacidium ion reacts on encounter with an amine molecule. This hypothesis is attractive, since it has been demonstrated[67] that the nitrosation of certain amines by nitrosyl chloride proceeds at a rate closely approaching the rate of encounter of the reactants in solution , despite nitrosyl chloride being a weaker electrophile, presumably, than either the nitrousacidium ion or the nitrosonium ion.

The similarity in the results of the amine and indole nitrosations , recorded in Table (3.24) above, supports the notion of a diffusion controlled reaction, particularly as the insensitivity of $\overleftarrow{k}_3$ to basicity is even more marked than the analogous behaviour of $\overleftarrow{k}_3'$. It is interesting to note ,however, that the pK_a of the indole molecule does not adequately reflect the absolute reactivity of the indole to the nitrousacidium ion . 2-methyl-5-nitroindole, for instance, is over fifty times as reactive towards this reagent as is 2,4-dinitroaniline, of similar basicity. Thus the unexpectedly high reactivity of the indoles towards nitrous anhydride is also paralleled in reaction through the nitrousacidium ion.

In contrast to the more basic indoles, the rate of nitrosation of the four less basic indoles studied is a function of the basicity of the indole substrate, as was shown in FIGURE (3.5). This behaviour will be discussed at a later stage in this CHAPTER.

(iii). Nitrosyl chloride. The values of $\bar{k}_4$ (eq.3.45), which represent reaction through nitrosyl chloride, are recorded in TABLE (3.25). for the series of indoles.

TABLE (3.25).

Nitrosation of indoles by nitrosyl chloride.

Indole	pK_a	$T^\circ C.$	$\bar{k}_4$ (eq.3.45) x.10^{-7} $l.^3 mol.^{-3} min.^{-1}$
1,2-dimethyl.	+0.3	3.0	3.67
2-phenyl .	-1.85	3.0	2.85
2-methyl-5-nitro.	-3.58	0.5	1.10
5-cyano.	-6.0	0.5	<0.0001
1-methyl-5-nitro.	-6.6	0.5	<0.0001
5-nitro	-7.4	0.5	<0.0001

The apparent lack of selectivity of this reagent with the most basic indoles can be interpreted as arising from the operation of a diffusion controlled process. This conclusion is confirmed by calculation of the molecular rate-coefficients for reaction of nitrosyl chloride with the free indole. Since the equilibrium constant for the formation of nitrosyl chloride is known[68], ($K_{NOCl} = \frac{[NOCl]}{[HNO_2].[HCl]}$ the molecular rate-coefficients defined by equation (3.46) can be calculated from the data of TABLE (3.25).

$$\text{rate} = k_{NOCl}.[\text{indole base}].[NOCl] \quad --- \quad (3.46)$$

It is evident that the values of k_{NOCl} listed in TABLE (3.26) are of the order of magnitude expected for a diffusion controlled reaction at 3.0°C., ($k_{enc.} = 3.10^{11}$ $l.mol.^{-1}min.^{-1}$ at 3.0°C. calculated from the Debye equation[47],) if due allowance is made for the temperature dependence of the concentration of NOCl.

TABLE (3.26).

Nitrosation of indoles by nitrosyl chloride.

Values of k_{NOCl}, the molecular rate-coefficient .

Indole	pK_a	T°C.	k_{NOCl} (eq.3.46) $l,mol.^{-1}min.^{-1}$
1,2-dimethyl.	+0.3	3.0	$1.78x.10^{10}$
2-phenyl.	-1.85	3.0	$1.38x.10^{10}$
2-methyl-5-nitro.	-3.58	0.5	$5.32x.10^{9}$

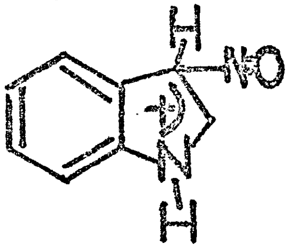
(K_{NOCl} = $2.06x.10^{-5}$ $l.mol.^{-1}$ at 25.0°C.[68]).

This observation of an encounter-controlled reaction of indoles more basic than 2-methyl-5-nitroindole is surprising in view of their relatively weakly basic nature compared to the amines, but it is in accord with the results discussed earlier, for the nitrousacidium ion and nitrous anhydride.

The apparent lack of appreciable chloride ion catalysis with the less basic indoles is both surprising , and inconsistent with the comparable results for the other indoles. It seems unlikely, if the more basic indoles react on encounter with nitrosyl chloride over a pK_a range of four units, that a further reduction in the basicity of 2.5 units would bring about a reduction of $10^6\%$ in the rate of reaction. Also, it is difficult to account for this difference in terms of either an alternative path for nitrosation , or structural effects. It is more probable that a change in the rate-determining step , on a common reaction path , occurs for the less basic indoles. Evidence for such a change comes from the studies of the nitrosation of deuteriated substrates, reported earlier, in which the more basic indole, 1,2-dimethylindole, involved little stretching of the carbon-hydrogen bond in the transition state, whereas the less basic 5-cyanoindole showed an appreciable isotope effect , consistent with a rate-determining fission of the bond at the 3-position.

One conclusion , therefore, is that the

indole substrates more basic than 2-methyl-5-nitroindole (pK_a = -3.58), react with the nitrousacidium ion and nitrosyl chloride in a rate-limiting initial nitrosation ,which is diffusion controlled, and the ensueing proton loss is fast but that the rate-limiting step in nitrosation of indoles less basic than 2-methyl-5-nitroindole is not the initial addition of the electrophilic reagent, but a subsequent carbon/hydrogen bond fission. This hypothesis, of course, accounts for the lack of detectable specific chloride ion catalysis in the nitrosation of the less basic indoles, since the chloride ion , being a poor base, cannot be reasonably accomodated in the transition state of this reaction,involving proton loss to the solvent from a positively charged Wheland intermediate , presumably that shown below,(ii).



(ii).

(iv). The change in the rate-determining step.

On introducing electron withdrawing groups into an aromatic molecule, the Free energy of both the Wheland intermediate and a positively charged transition state will normally be raised. However, the Free energy of the transition state for the nitrosation of the more basic indoles by the nitrousacidium ion , or by nitrosyl chloride, does not appear to be of kinetic significance, as the reactions are diffusion controlled, and hence the effect of a nitro group, conjugated to the reactio site, does not appreciably alter the rate of the initial nitrosation step. The observation of a change in the rate-determining step , however, implies that electron withdrawing groups exert a much greater influence on the rate of proton loss, and this process becomes consequently progressively slower, on reducing the indole basicity, until the initial nitrosation is no longer rate-controlling, giving way to the step involving carbon/hydrogen bond fission.

This behaviour is illustrated in FIGURE (3.6), in which the energy requirements for the nitrosation of both 1,2-dimethylindole and 5-nitroindole are drawn schematically.

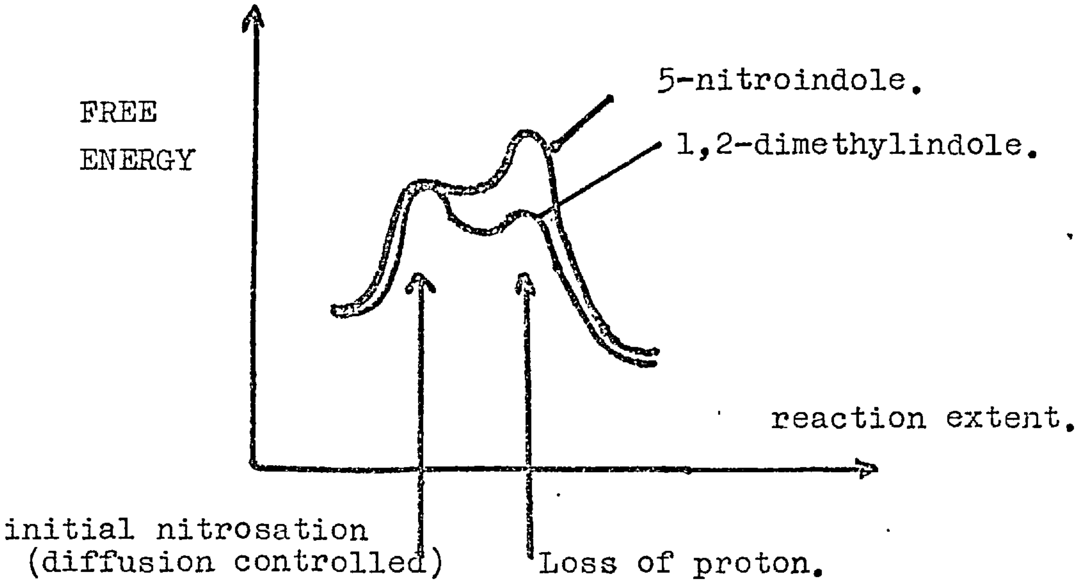
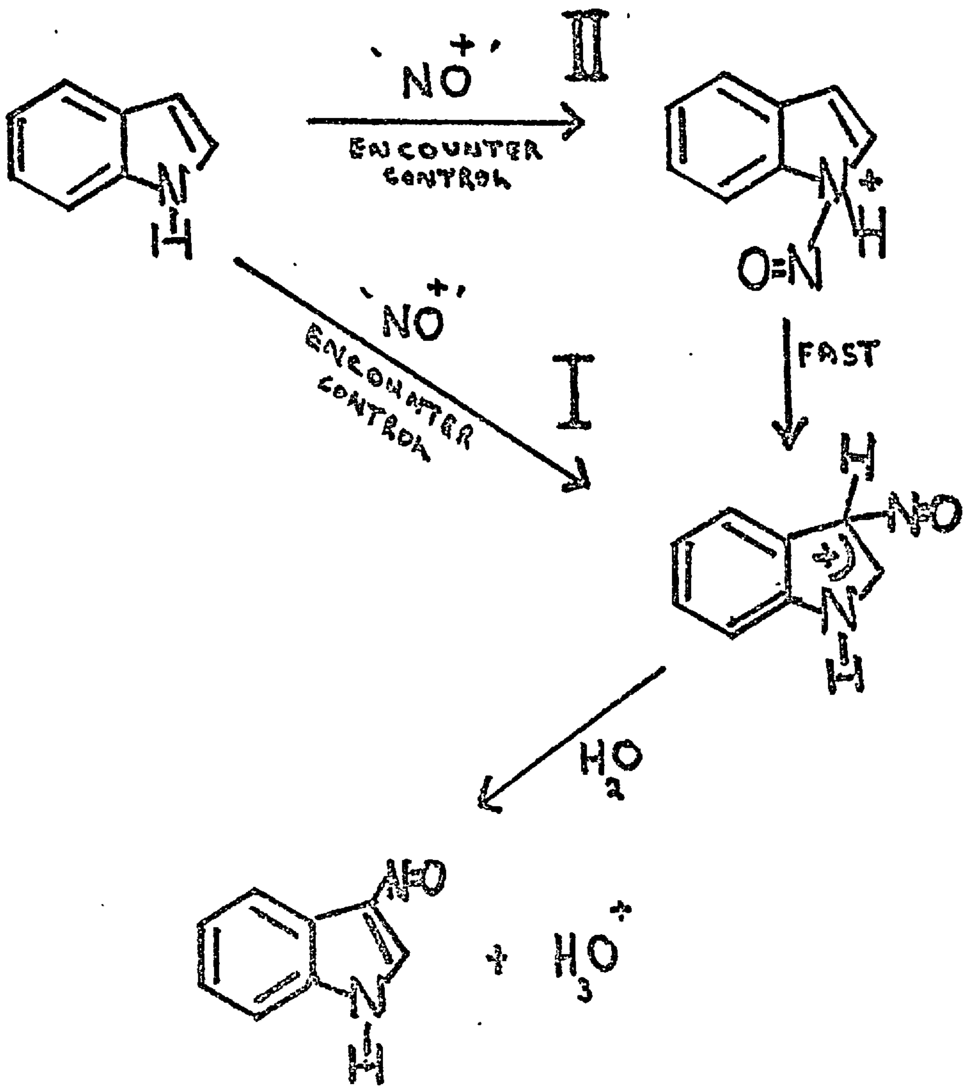


FIGURE (3.6).

(v). The detailed mechanism .

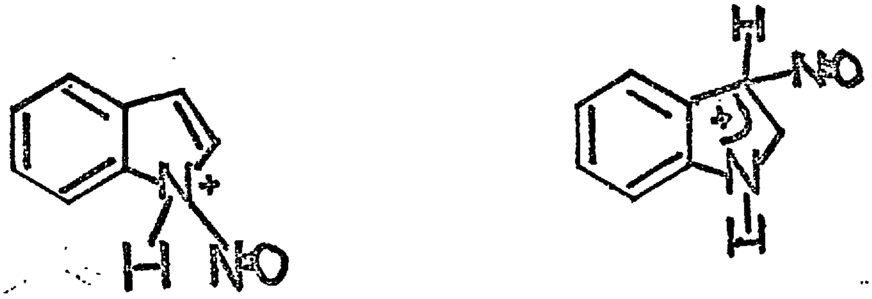
The observed results of the study of the nitrosation of indoles can be accomodated by the reaction Schemes I and II, shown below in FIGURE (3.7).



In both schemes, proton loss from the intermediate becomes rate-determining on reducing the basicity of the indole, as was discussed above. In Scheme I , however, the rate-limiting step for the most basic indoles is the diffusion controlled nitrosation of the 3-position, whereas , in Scheme II, the most basic indoles involve a rate-determining, diffusion - controlled nitrosation of the hetero-atom, followed by a fast intramolecular transfer of the nitroso group from nitrogen to carbon prior to, or synchronous with, fast proton transfer.

It is difficult to separate these two schemes on the basis of the available data; it has been stressed, however, that the observed reactivity of the most basic indoles towards the various nitrosating agents is far in excess of that expected on the grounds of the measured basicity of the 3-position . This anomaly can be accounted for in Scheme II, since the basicity of the hetero-atom must be much higher than that of the 3-position in an individual molecule. Unfortunately, it is not possible to measure the basicity of the hetero-atom by conventional methods, since the thermodynamically favoured firm of the protonated indole involves protonation at the 3-position[58]. Nevertheless, that the nitrogen is very reactive toward electrophilic attack can be demonstrated by considering the rates of protodedeuteriation at positions 1 and 3 in indoles. All indoles exchange the deuterium at position 1 "instantly" in pure water or dilute acid, whereas the loss of the deuteron at position 3 is a much slower process, requiring added acid to catalyse the rate in a measurable rate of reaction.[70]

Furthermore, the proposed rapid intramolecular transfer of the nitroso group can be rationalised in terms of the intermediates (iii) and (iv) , shown in FIGURE (3.8).



(iii) (iv)

FIGURE (3.8).

Intermediate (iii) is more readily formed because of the greater basicity of the nitrogen atom, but quickly rearranges to intermediate (iv), because this has a greater stability by virtue of the possibilities of delocalisation of the positive charge produced.

From these arguments, the observed data is more neatly accomodated by Scheme II, although Scheme I should not be too hastily discarded on the grounds of correlations of reactivity with basicity across two different classes of base, the aromatic amines and the indoles, especially when there is no certainty that the rate-determining step in diazotisation is necessarily that assumed by previous workers.[71, 72].

(J). A SUMMARY OF THE CONCLUSIONS OF THE STUDY OF NITROSATION OF INDOLES IN DILUTE PERCHLORIC ACID.

The principal kinetic forms identified in the diazotisation of the aromatic amines have also been identified in the C-nitrosation of indoles, and consequently, the same series of nitrosating agents are concluded to be operative in C-nitrosation as in diazotisation at these acidities.

Moreover, the initial attack by the electrophile approaches a diffusion-controlled process, when the species concerned is the nitrousacidium ion or nitrosyl chloride. However, the initial attack by the electrophile is rate-controlling only for the most basic substrates ; the less basic indoles involve a proton transfer from the 3-position in the slow step. This change in the rate-determining step is explained in terms of the relative sensitivity of the relevant transition states to the degree of positive charge dveloped in the reaction.

The mechanism of the nitrosation of indoles may incorporate an unusual nitrogen-to-carbon transfer of the fragment NO^+, in a fast step.

CHAPTER IV.

ACID CATALYSED NITROSATION IN MODERATELY CONCENTRATED SOLVENT ACID.

The experiments reported in this Chapter were primarily aimed at identifying the effective nitrosating species in moderately concentrated acid, and, in particular, to determine whether any distinction could be made between reaction by the nitrousacidium and the nitrosonium ions under these conditions.

As was discussed in Chapter I, previous attempts to identify the reactive nitrous species by rate/acidity correlations have led to discordant conclusions. It was thought desirable to re-examine some of this data, particularly the nitrosation of phenol in perchloric acid, because of the possibility of alternative mechanisms from those considered earlier, and the likelihood of experimental error arising from the reaction conditions. Morrison and Turney[36] examined the nitrosation of phenol in aqueous perchloric acid at 0.6° C from ca. 1.0 M to 6.0 M. They worked exclusively with equal concentrations of nitrous acid and phenol, and no experiments were reported to determine the order of reaction under the experimental conditions. The rates were assumed to follow equation (4.1) and the consistency of the rate coefficients throughout each kinetic run justified this assumption.

$$\text{rate} = k_2.(\text{phenol}).(HNO_2) \qquad \text{---} \quad (4.1).$$

Their reaction rates were determined by estimating the amount of unreacted nitrous acid, and no corrections were made for spontaneous decomposition of the reagent. It is clear from their results that reaction half-lives in many cases were of the order of several hours. When compared with the known rate of decomposition of nitrous acid under similar conditions[73], (1% to 2% per hour), it is clear that some error is introduced by neglecting to correct for spontaneous decomposition of the nitrous acid. Furthermore, with the reactant concentrations employed by Morrison and Turney, red coloured products are observed, which probably arise from the formation of indophenols, formed by further reaction of nitrous acid with <u>para</u> nitrosophenol. These possible sources of error have been minimised in the present work by reducing the initial nitrous acid concentration and increasing the initial phenol concentration for individual kinetic runs. Thus, pseudo first order kinetics were observed. These conditions minimise possible errors both by reducing the half-life of the reaction, and by inhibiting the indophenol formation by a concentration effect.

In addition to phenol, the nitrosation of anisole, 1,3,5-trimethoxybenzene, 1,2-dimethylindole, and 2-methylindole were also studied in moderately concentrated acidic solutions.

(A). NITROSATION OF PHENOL IN AQUEOUS $HClO_4$ AT 0.7°C.

The reaction of phenol with nitrous acid to produce para nitrosophenol has been investigated over an acidity range from 10^{-3} M. to 10.4 M. perchloric acid. The reaction is governed by equation (4.2), where $\bar{k}_2$ is a function of the solvent acidity.

$$\text{rate} = \bar{k}_2.(\text{phenol}).(HNO_2) \qquad \text{---} \quad (4.2).$$

When the initial concentration of phenol is much greater than the initial nitrous acid concentration, the rate-law simplifies to equation (4.3).

$$\text{rate} = \bar{k}_1.(HNO_2) \qquad \text{---} \quad (4.3).$$

The validity of these equations was checked briefly in the present investigation. The first order dependence of $\bar{k}_2$ on the phenol concentration is evident from the data listed in TABLE (4.1). Although the order in nitrous acid concentration was not checked specifically, rate constants calculated from equation (4.3) were reasonably constant up to 95% reaction.

TABLE (4.1).

Nitrosation of phenol in aqueous perchloric acid at 0.7°C.

(reactant) = initial stoich values.

Run	$(HClO_4)$ (M.)	(Phenol) ($x.10^3$ M)	(HNO_2) ($x.10^4$ M)	$\bar{k}_1$(eq. 4.3) ($min.^{-1}$) $X.10^3$	$\bar{k}_2$(eq. 4.2) ($l\ mols^{-1}\ min^{-1}$)
165	$1.0\ 10^{-2}$	30.9	1.1	2.2	0.071
167	$1.0\ 10^{-2}$	123.0	1.1	9.25	0.075
337	$1.0\ 10^{-1}$	103.0	1.0	8.65	0.084
85	$1.0\ 10^{-1}$	51.3	1.0	4.16	0.081
168	$1.0\ 10^{-1}$	30.9	1.0	2.38	0.077
101	1.70	51.9	2.5	9.45	0.181
80	1.72	51.3	1.0	9.65	0.189
88	1.72	51.3	1.0	9.85	0.192
87	3.99	2.57	1.0	3.96	1.54
336	3.95	9.80	1.0	14.6	1.48
90	3.98	51.3	1.0	76.0	1.47

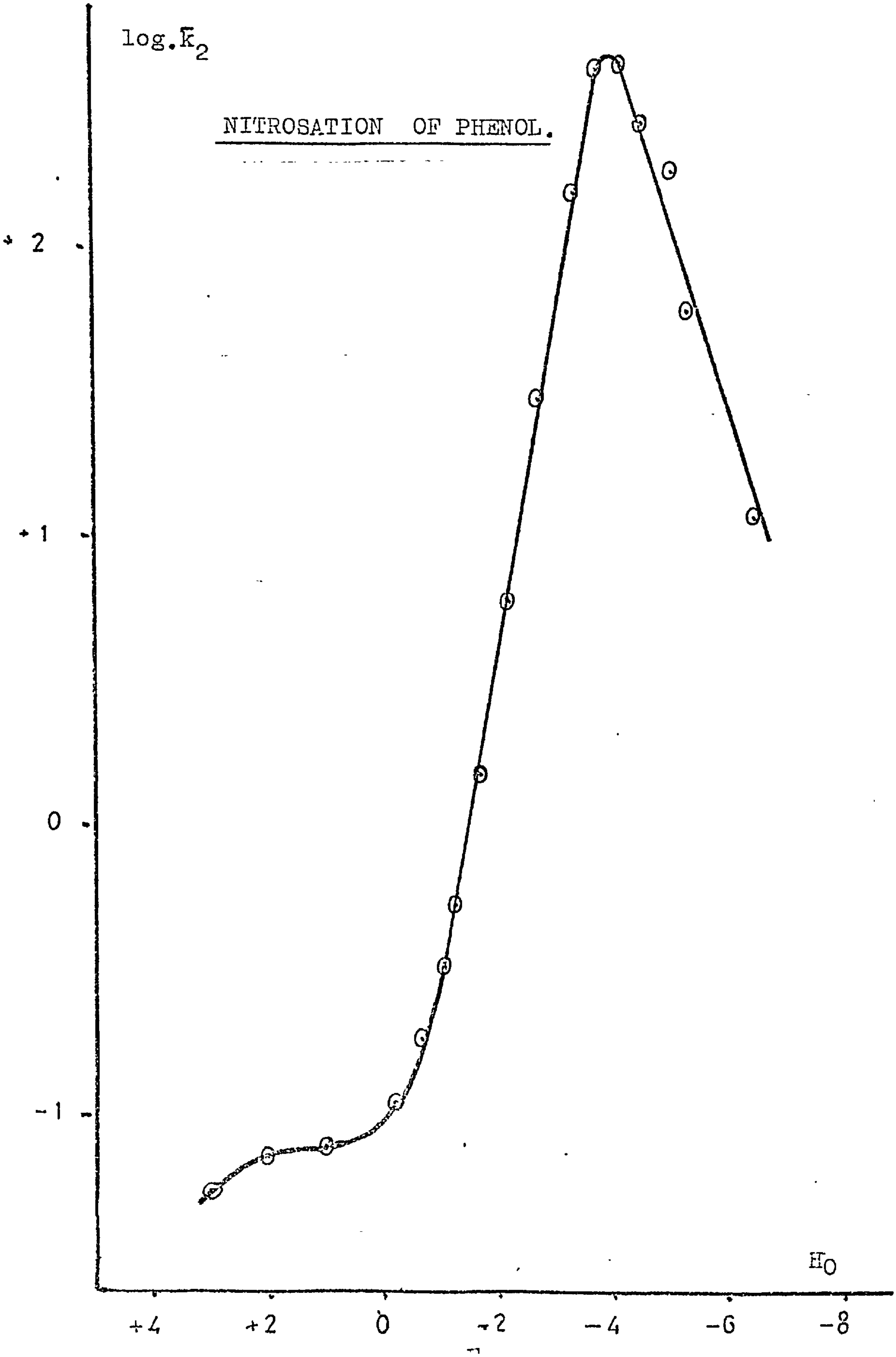
The influence of acidity on the coefficient $\bar{k}_2$ is recorded in TABLE (4.2), which also includes values of the H_o acidity function. These results are also presented graphically in FIGURE (4.1), where log. $\bar{k}_2$ is plotted against $-H_o$.

TABLE (4.2).

Nitrosation of phenol.

Variation of $\bar{k}_2$ (eq. 4.2) with acidity.

Run	$(HClO_4)$ (M.)	$-H_o$	$\bar{k}_2$(eq. 4.2) (l mols^{-1} min^{-1})
166	1.0×10^{-3}	-3.0	0.054
165,167	1.0×10^{-2}	-2.0	0.073
337,85,168	1.0×10^{-1}	-0.9	0.080
81	0.99	+0.20	0.125
80,88,101	1.71	0.66	0.185
78	2.50	1.03	0.326
79	3.02	1.26	0.532
336	3.95	1.70	1.48
90	3.98	1.73	1.47
87	3.99	1.74	1.54
86	4.92	2.22	5.96
113	5.80	2.73	28.3
120	6.74	3.36	152.0
121	7.32	3.77	395.0
122	7.87	4.18	430.0
94	8.28	4.58	275.0
124	8.90	5.05	123.0
96,119	9.40	5.35	61.0


log.k_2
NITROSATION OF PHENOL.
+ 2
+ 1
0
- 1
H_0
+ 4
+ 2
0
- 2
- 4
- 6
- 8

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As far as the acidity dependence is concerned, three distinct regions can be recognised from the data in FIGURE (4.1) :-

(i). At very low acidities, ($<$ 0.1M. $HClO_4$), the $\bar{k}_2$ value is virtually independent of acidity. Similar behaviour has been observed by Schmid and his coworkers in the nitrosation of phenol in dilute hydrochloric acid, and it is interesting to note that the value of $\bar{k}_2$ obtained by Schmid[37] is identical to the value obtained in the present work, within the limits of experimental error. This demonstrates the absence of specific chloride ion catalysis in this reaction.

(ii). From 0.1M to 7.5M $HClO_4$, the value of $\bar{k}_2$ increases rapidly with acidity. This sort of acidity dependence forms the basis of Morrison and Turney's conclusions, set out in Chapter I; however, the values of $\bar{k}_2$ which they obtained range from three hundred percent higher to one hundred percent lower than the values listed in TABLE (4.2), the differences presumably being due completely to the side reactions present in their work, as discussed above and in Chapter VII. Morrison and Turney also declare that the nitrosation of phenol follows the acidity function H_o, whereas a graph of their data would show that a plot of log. $\bar{k}_2$ against $-H_o$ shows considerable scatter of points. Reference to FIGURE (4.1), however, will indicate that the gradient of the linear section of the graph of log. $\bar{k}_2$ against $-H_o$ is in fact about 1.3, very little scatter being observed in the experimental points.

(iii). At acidities greater than 7.5M. $HClO_4$, $\bar{k}_2$ decreases with increasing acidity, and the slope of log. $\bar{k}_2$ versus $-H_0$ is about -0.6.

The observation of these three distinct regions must imply <u>either</u> reaction <u>via</u> different pathways, <u>or</u> changes in the rate-determining step, or must reveal the existence of acid/base pre-equilibria prior to the transition state. Thus before discussing the implications of the observed acidity dependence, further evidence on the nature of the rate-determining step was obtained from the studies of 4-(^{2}H)-phenol.

(i). The rate-determining step.

Nitrosation of 4-(^{2}H)-phenol in $HClO_4$ at 0.7°C.

Rate measurements were made under comparable conditions to those for phenol itself, great care being taken that no significant isotopic exchange occurred before nitrosation. This was checked by analysing for percentage ring dedeuteriation by infra-red spectroscopy before and after individual runs. Ring exchange was found to be negligible below 5.0M $HClO_4$. Values of $\bar{k}_2^D$ for the deuteriated species are listed in TABLE (4.3). For the purposes of comparison, the values of $\bar{k}_2^H$ for phenol are given, and these have been interpolated from the data of FIGURE (4.1).

TABLE (4.3).

Nitrosation of phenol and 4-(^{2}H)-phenol at 0.7°C.

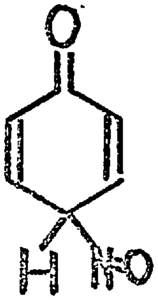
Run	($HClO_4$) (M.)	$-H_o$	k_2^H ($l.mols^{-1}$ min^{-1})	k_2^D ($l.mols^{-1}$ min^{-1})	k_2^H/k_2^D
116	1.05 x. 10^{-1}	-	0.081	0.021	3.9
118	1.67	0.74	0.181	0.043	4.2
117	2.25	0.98	0.262	0.064	4.1
115	3.86	1.72	1.30	0.39	3.3
114	4.13	1.85	1.85	0.52	3.6
106	4.87	2.23	5.25	1.60	3.4
107	5.89	2.82	33.0	9.4	3.6
					mean = 3.8

It is evident that the ratio $\bar{k}_2^H/\bar{k}_2^D$ is significantly greater than unity over a wide range of concentrations of acid. Also, bearing in mind that C-nitrosation at the para position only accounts for about 95% of the products of reaction, it is evident that the observed value of the ratio is in fact a minimum value. Thus, nitrosation of phenol involves as large a primary isotope effect as iodination of phenol, in which the k^H/k^D ratio is reported to be 4.0 .

The rate-determining step in both the acid-catalysed and uncatalysed paths therefore probably involves breaking of the carbon-hydrogen bond, rather than the initial attack of the electrophile.

(ii). The acid-independent path.

From pH3.0 to pH1.0, an acidity difference of 10^2 in the solvent, the value of $\bar{k}_2$ (equation 4.2) increases by only ca. 20%. In view of the observation of a large primary isotope effect in this reaction, one possible conclusion is that the transition state is essentially similar to a dienone intermediate (V) which loses the ring-hydrogen in the slow step.



(V).

This explanation is very attractive, especially since it accounts neatly for Schmid's similar results[37], without recourse to any unlikely mechanism involving molecular nitrous acid.

Since the rate-determining step involves loss of a proton to the solvent, great care must be taken in the definition of the origin of the intermediate (V). In theory, the dienone intermediate could be generated from either phenoxide ion or phenol, reacting with HNO_2 or NO^+ or H_2ONO^+ or N_2O_3. These eight possibilities may be reduced on careful consideration of two experimental findings :-

(1) In solvent HCl[37], equation (4.2) apparently defines the reaction rate, and $\bar{k}_2$ is independent of both acidity and concentration of chloride ion.

(2) $\bar{k}_2 = 0.08$ l.mol^{-1}min^{-1} at 0.5°C.

Reaction between the phenate ion and molecular nitrous acid would violate (1); also phenate ion and either NO^+ or H_2ONO^+ can be discounted on the evidence of the diffusion controlled reactions of Chapter III, since the observed rate, shown in (2) above, greatly exceeds the value calculated on the basis of encounter-controlled reaction between phenate ion and either of the two nitrous species.

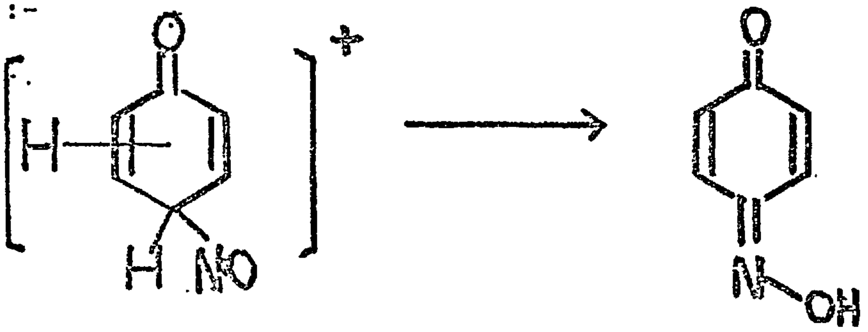
Reaction of N_2O_3 can also be disregarded, since the observed half-life of reaction under particular conditions has been observed to be much less than the known half-life of formation of this species under the same conditions.

Rejecting the attack of molecular phenol on molecular nitrous acid leaves only the conclusion that molecular phenol reacts with either the nitrosonium ion or the nitrousacidium ion, in a fast pre-equilibrium, to yield the intermediate neutral dienone, (V). Further definition of the precursors of this intermediate cannot be successfully attempted in the present state of knowledge.

(iii). The acid-dependent paths.

The incursion of an acid-catalysed path in acidities greater than 1.0M. $HClO_4$, with no change in the rate-determining step, suggests that the dienone intermediate (V) is being protonated prior to, or concurrent with, the release of the proton from the reaction site.

Thus :-



The site of protonation is not immediately clear, and consequently further information on this transition state was sought by the aid of solvent isotope effects.

Solvent isotope effects in the nitrosation of 4-(^{2}H)-phenol.

Reactions were carried out in H_2SO_4 and D_2SO_4 solutions of similar acidity, care being taken that the experimental conditions involved no detectable isotopic exchange in the ring hydrogen.

Solvent isotope effects on the ground state pre-equilibria can be taken into account, regardless of the active electrophile being the nitrousacidium ion or the nitrosonium ion, since both reagents hold a higher concentration, by a factor of about 2.0, in D_2SO_4 than they do in H_2SO_4 at the same acidity. This observation is partly in contradiction with existing work[75], but, as is explained at a later point in this Chapter, the results of the present studies suggest that the previous attempts to measure the solvent isotope effect on the concentration of the nitrosonium ion are in error.

Thus, since the acidity of D_2SO_4 and H_2SO_4 are closely similar at the same molar concentrations[81], a comparison of the rate of nitrosation of phenol in H_2SO_4 and D_2SO_4 should yield some information on the role of water in the transition state. The results are listed in TABLE (4.4), in which $\bar{k}_2^+$ represents the value of $\bar{k}_2$, (equation 4.2), corrected for the solvent isotope effects on the pre-equilibria controlling the concentration of the nitrous reagent.

Table (4.4).

Nitrosation of phenol in D_2SO_4 and H_2SO_4.

T = 0.7°C.

Run	(D_2SO_4)	(H_2SO_4)	$\bar{k}_2$	$\bar{k}_2^+$	$(\bar{k}_2^+)^H/(\bar{k}_2^+)^D$
	M.	M.	l.mol^{-1}min^{-1}.		
143		0.263	0.099	0.099	2.9
144	0.263		0.075	0.034	
142		3.95	3.5	3.5	
141		4.37	6.0	6.0	2.0
145	4.32		6.06	3·03.	

The observation of sizeable isotope effects, in both the acid-catalysed and uncatalysed paths, suggests that in both cases water is acting as a proton donor in the transition-state, since the observed reduction in rate in the deuteriated solvent can be looked upon as a primary isotope effect on the oxygen-hydrogen bond of water.

Thus the mechanism of the nitrosation of phenol may be represented in one possible scheme, shown in FIGURE (4.2), although other possibilities, involving protonation of the keto function in the transition state, should not be ruled out at this stage.

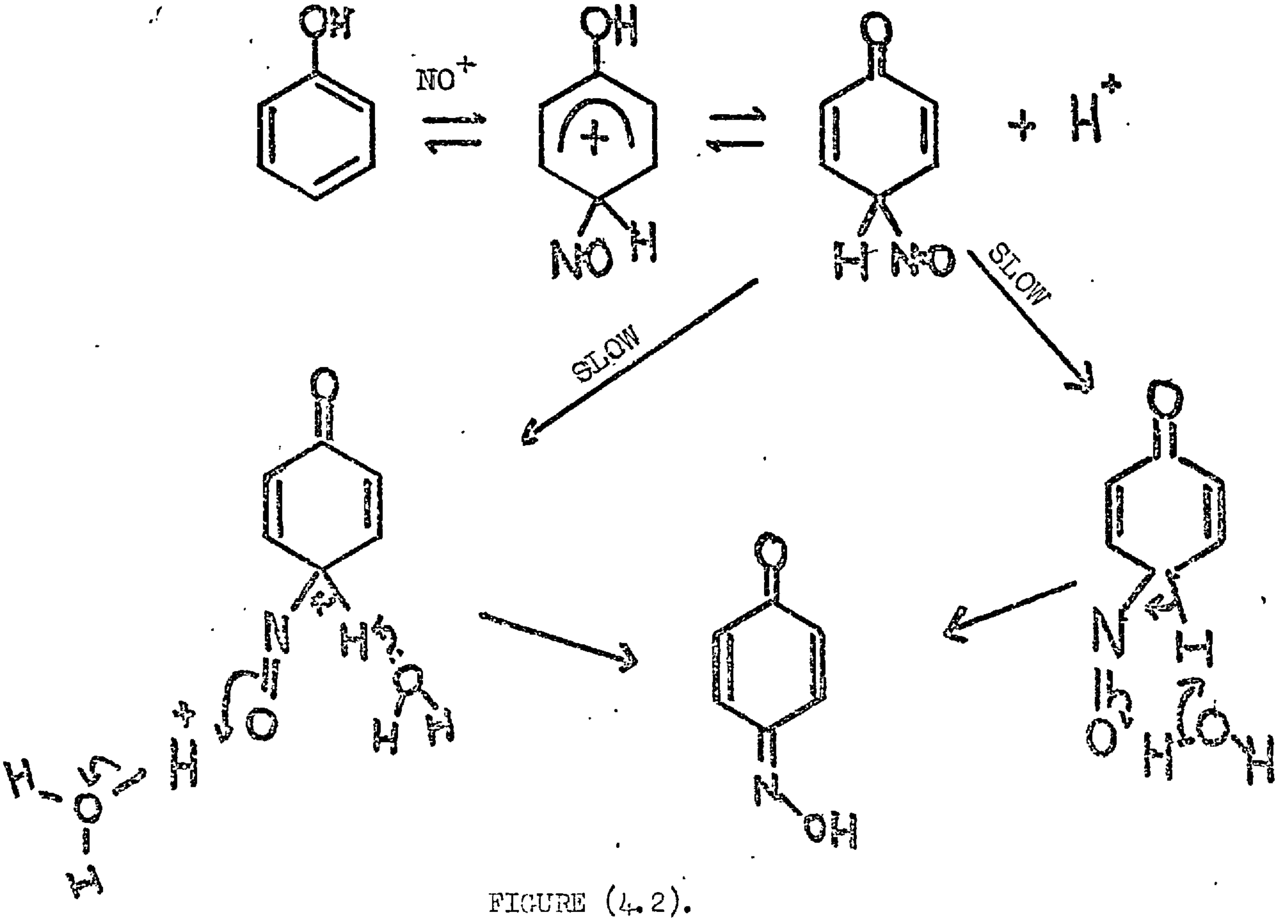
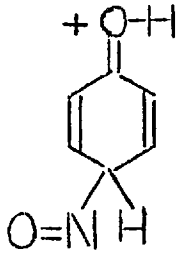
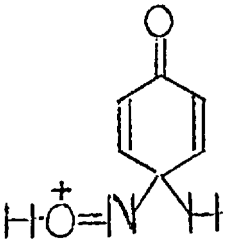


FIGURE (4.2).

If, however, the reaction scheme of FIGURE (4.2) is correct, then it is obvious that protonation on the nitroso function of the intermediate (V), leads to formation of the product of reaction, whereas protonation on the keto function leads to regeneration of the starting materials. Also, it is likely that the conjugate acid (VII) will be thermodynamically more stable than the tautomer (VIII),



(VII).



(VIII).

by virtue of the increased possibilities of delocalization of the positive charge in the case of (VII).

Thus the observed acidity dependence of FIGURE (4.1) could be explained by the effect of the solvent acidity on two factors influencing the rate of reaction :-

(1) the concentration of the nitrosonium ion, which has a pK_a of about -7.7 on an H_R scale,

(2) competition, between two basic sites on the dienone (V), of different basicity, for the solvent proton which will drive the reaction in one case to starting materials, in the other case to products.

To further elucidate this possibility, experiments were carried out on the nitrosation of anisole, which should not be able to undergo some of the postulated processes in the nitrosation of phenol.

(B). THE NITROSATION OF ANISOLE.

(i). The acid-catalysed path.

This reaction of anisole has been studied in aqueous perchloric acid at 0.7°C over a range of acidity from 4.0M. to 10.33M. The experiments were carried out with the ratio of (anisole)/(HNO_2) being greater than 10.0, under which conditions the observed rate followed equation (4.4). Moreover, a first order dependence of the rate on the anisole concentration was established by the experiments summarised in TABLE (4.5).

$$\text{rate} = \bar{k}_2.(\text{anisole}).(HNO_2) \qquad \text{--- (4.4).}$$

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TABLE (4.5).

Nitrosation of anisole in $HClO_4$ at 0.7°C.

Establishment of kinetic orders.

(reactant) = initial stoich values.

Run	($HClO_4$) (M.)	(anisole) (x. 10^4M.)	(HNO_2) (x. 10^4M.)	$\bar{k}_2$ (eq. 4.4) (l.mols^{-1} min^{-1})
151	5.96	29.4	1.1	4.24
340	5.96	38.0	1.1	4.30
170	6.01	26.4	1.1	4.41
174	6.03	13.2	1.1	4.45
175	6.05	13.2	1.3	4.78
344	10.22	9.25	0.48	32.4
345	10.22	6.65	0.48	35.8
150	10.33	4.40	0.14	30.9

As in the case of phenol, the nitrosation rate varies with acidity. This is demonstrated by the data of TABLE (4.6), which shows values of $\bar{k}_2$, (equation 4.4), as a function of both the concentration of $HClO_4$ and the H_o value.

TABLE (4.6).

Nitrosation of anisole at 0.7°C.

Variation of $\bar{k}_2$ (eq. 4.4) with acidity.

Run	($HClO_4$) (M.)	$-H_o$	$\bar{k}_2$ (1.mols^{-1} min^{-1})
234	4.96	2.31	0.21
152	5.32	2.52	0.68
169	5.52	2.63	1.11
151,340	5.96	2.85	4.27
170,174	6.02	2.90	4.43
175	6.05	2.91	4.78
154	6.46	3.18	16.7
148	6.84	3.43	43.0
155	7.40	3.84	124.0
149	7.84	4.15	173.0
162	8.00	4.25	180.0
156	8.50	4.70	129.0
147	8.72	4.88	102.0
157	9.41	5.55	71.0
344,345	10.22	6.32	34.1
150	10.33	6.40	30.9

A plot of $\log_{10}.\ \bar{k}_2$ versus $-H_o$ is given in FIGURE (4.3). The striking features of this curve, in comparison with the corresponding plot for phenol, are threefold :-

(a) there is no apparent evidence of a reaction path which is independent of the solvent acid concentration. This leads support to the hypothesis, postulated above, of a dienone intermediate in the nitrosation of phenol. Anisole, of course, cannot readily form a neutral sigma-bonded intermediate of this type. Unfortunately, however, it was not possible to measure the rate of anisole nitrosation at regions of lower acidity, (say pH 1.0) in order to justify this conclusion more fully, since the observed rate becomes virtually undetectable in acidities less than 3.0M. $HClO_4$.

(b) the curve of FIGURE (4.3) passes through a maximum at an H_o value of about -3.9, which is close to the acidity in which the corresponding curve for phenol nitrosation achieves its maximum value. This acidity is also very close to that at which the nitrosonium ion becomes the major nitrous species present in a solution of sodium nitrite in aqueous perchloric acid, suggesting that the nitrosonium ion is indeed the active nitrosating species in concentrated acid.

(c) the slopes of the linear portions of the curves of FIGURES (4.1) and (4.3) differ markedly in magnitude, over the range H_o -2 to -4, being 1.3 for phenol and 1.9 for anisole. Thus the reaction rate has a much greater dependence on the acidity in the case of anisole, but this could be an artefact of the possibility that the reaction

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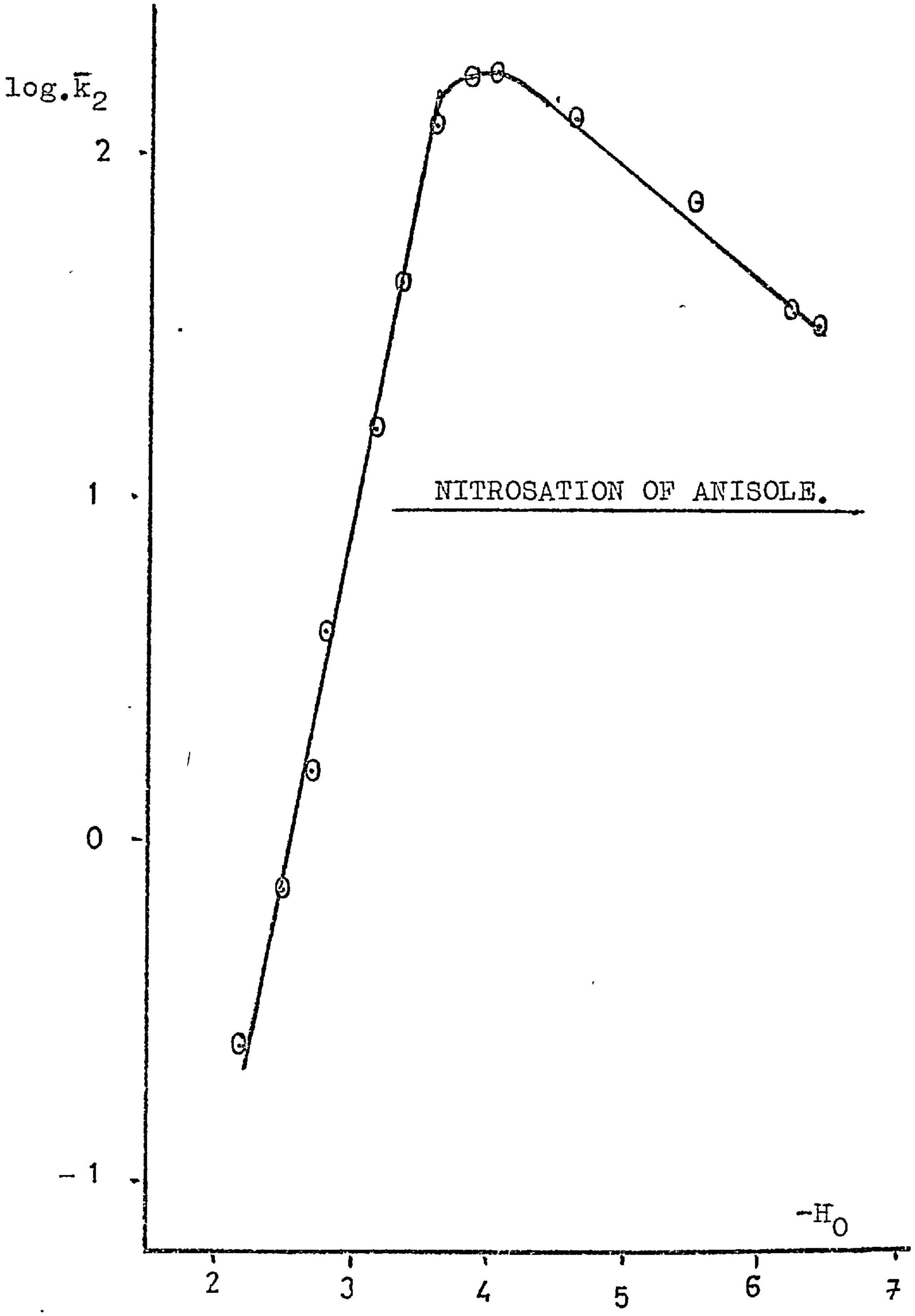


FIGURE (4.3).

involves a different rate-determining step in this case. Experiments with phenol showed that the proton loss from the Wheland intermediate is rate-limiting, and to establish whether this is a general feature of nitrosation reactions, (or a result of the formation of a dienone intermediate) evidence for a primary isotope effect was sought for the reaction of anisole.

(ii). Nitrosation of 4-(^{2}H)-anisole.

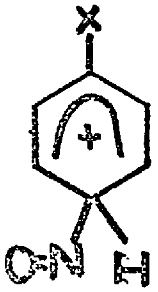
A direct comparison between the rates of nitrosation of anisole ($\bar{k}_2^H$) and 4-(^{2}H)-anisole($\bar{k}_2^D$) in aqueous $HClO_4$ was made at several acidities where the rate of nitrosation is much faster than the rate[56] of protodeuteriation. The values of $\bar{k}_2^H$ were interpolated, when necessary, from the data shown in FIGURE (4.3), to ensure identical acidity factors. The results are summarized in TABLE (4.7).

TABLE (4.7).

Nitrosation of anisole and 4-(^{2}H)-anisole at 0.7°C.

Run	($HClO_4$) (M.)	$\bar{k}_2^H$ (l. mols^{-1} min^{-1})	$\bar{k}_2^D$	k_2^H/k_2^D
172	5.53	1.23	0.404	3.0
159	5.94	3.98	1.74	2.4
161	6.88	47.8	16.4	2.9

The substantially reduced rate for the deuteriated substrate ($k_2^H/k_2^D = 2{\cdot}8$) is good evidence for a primary isotope effect. It would therefore seem that a feature of aromatic nitrosation is that breakdown of the Wheland intermediate, (IX), is normally the rate-controlling process.

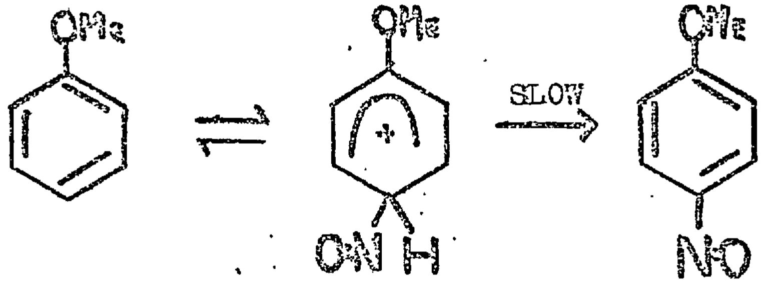


(IX).

(iii). <u>A comparison of the nitrosation of anisole and phenol.</u>

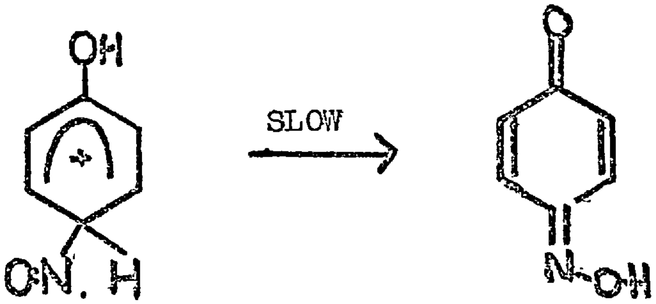
The marked difference in the acidity dependence of the nitrosation of anisole and phenol, particularly in the slopes of the acidity profile on both sides of the reaction maximum, is indeed consistent with the hypothesis, made earlier, in which the nitrosation of phenol involved a neutral intermediate (V), the breakdown of which by solvent acid, acting on two distinct sites, produced either starting materials or products by two discrete paths.

This process cannot take place in the nitrosation of anisole, since no neutral dienone structure can be readily formed, and reaction presumably occurs through the process shown below, with or without the assistance of the nitroso group.



Such a mechanism would in no way be anti-catalysed by increasing solvent acidity, except as a result of a reduction in the water activity. This probably accounts for the slight decrease in the reaction rate, for anisole, in the region of acidity 8.0M. to 10.5M. $HClO_4$, when the gradient of that section of the reaction profile, (FIGURE 4.3), is only $0.3.H_o$, as opposed to $0.6.H_o$ in the case of phenol.

An analogous path for the reaction of phenol, shown below, possibly contributes in addition to the scheme shown earlier in FIGURE (4.2),



but the arguments advanced in this Chapter suggest that this is not the major path in the acid-catalysed nitrosation of phenol. This conclusion is borne out by consideration of reactivity parameters in Chapter V, when the case of phenol is shown to be quite anomolous in comparison with the nitrosation of other mono-substituted benzenes.

(C). NITROSATION OF 1,3,5-TRIMETHOXYBENZENE.

The nitrosation of 1,3,5-trimethoxybenzene was briefly studied over an acidity range of 10^{-1}M. to 2.0M.$HclO_4$. The reaction, as expected, follows equation (4.5) at constant acidity.

$$\text{rate} = \bar{k}_2.(\text{trimethoxybenzene}).(\text{HNO}_2) \qquad \text{--- (4.5)}$$

The effect of added chloride ion on the reaction rate was also investigated, (TABLE 4.8). The small increase observed, (15% for 0.1 M. Cl^-) is more consistent with a kinetic salt effect than catalysis by chloride ion.

TABLE (4.8).

Nitrosation of 1,3,5-trimethoxybenzene in $HClO_4$ at 0.7°C.

Run	($HClO_4$) (M.)	(NaCl) (x. 10.M.)	$\bar{k}_2$ eq. (4.5) ($l.mols^{-1}\ min^{-1}$)
188	1.24×10^{-1}	0	5.9
201	1.17×10^{-1}	1.0	6.35
189	5.75×10^{-1}	0	56.6
186	1.0	0	151.0
202	1.09	1.0	236.0
187	1.94	0	910.0
190	1.96	0	910.0

This is, of course, the expected behaviour if, as in the case of anisole, breakdown of a Wheland intermediate is the rate-determining step.

Moreover, the values of $\bar{k}_2$ (equation 4.5) quoted in TABLE (4.8) show no incursion of a reaction path uncatalysed by acid. This serves to illustrate that the observation of an uncatalysed path in the nitrosation of phenol in similar solvent acidities is indeed associated with the acidity of the phenolic hydrogen in the reaction intermediate.

(D). NITROSATION OF 1,2-DIMETHYLINDOLE AND 2-METHYLINDOLE IN MODERATELY CONCENTRATED ACID.

The nitrosation of these two indoles, conducted in dilute acid solution, has been reported in the preceding Chapter. The foregoing results of the studies on the reactions of phenol and anisole, however, engendered interest in the nitrosation reaction of these extremely reactive aromatic compounds in more strongly acidic solutions.

The rate of reaction follows equation (4.6) at constant solvent acidity, in which the concentration

$$\text{rate} = \bar{k}_2.(\text{indole}).(HNO_2) \qquad \text{---} \ (4.6).$$

terms are the total, stoicheiometric values.

The observed values of $\bar{k}_2$ are recorded in TABLE (4.9) and TABLE (4.10), and shown in graphical form in FIGURE (4.4).

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TABLE (4.9).

Nitrosation of 1,2-dimethylindole in $HClO_4$ at 3.0°C.

Variation of $\bar{k}_2$ (eq. 4.8) with acidity.

Run	$(HClO_4)$ (M.)	$\bar{k}_2$ (eq. 4.6). ($l.mols^{-1}$ min^{-1}).
270	1.03×10^{-2}	253
183	4.8×10^{-2}	1510
182	1.35×10^{-1}	4350
275	2.4×10^{-1}	6090
272	3.6×10^{-1}	7630
181	1.19	7900
180	1.20	8150
185	2.38	7100
179	4.14	5140
184	4.77	2600
178	6.03	1390
273	6.90	940
158	7.91	179
164	8.22	58.0
163	9.04	3.14

TABLE (4.10).

Nitrosation of 2-methylindole in $HClO_4$ at 3.0°C.

Variation of $\bar{k}_2$ (eq. 4.6) with acidity.

Run	$(HClO_4)$ (M.)	$\bar{k}_2$ (eq. 4.6). ($l.mols^{-1}\ min^{-1}$)
137	2.45×10^{-1}	12,000
136	7.45×10^{-1}	28,500
134	1.21	50,000
135	1.21	51,500
139	1.99	57,000
126	3.50	87,500
128	4.10	31,000
127	5.07	17,000

The form of the curves of FIGURE (4.4) merit further discussion. The values of $\bar{k}_2$ reach maximum values on increasing the solvent acidity. This observation is concluded to be due to the removal of the neutral indole base by solvent protonation. Such a conclusion is strongly supported in particular by the sharp reduction in the rate of nitrosation of 1,2-dimethylindole on increasing the acidity in the

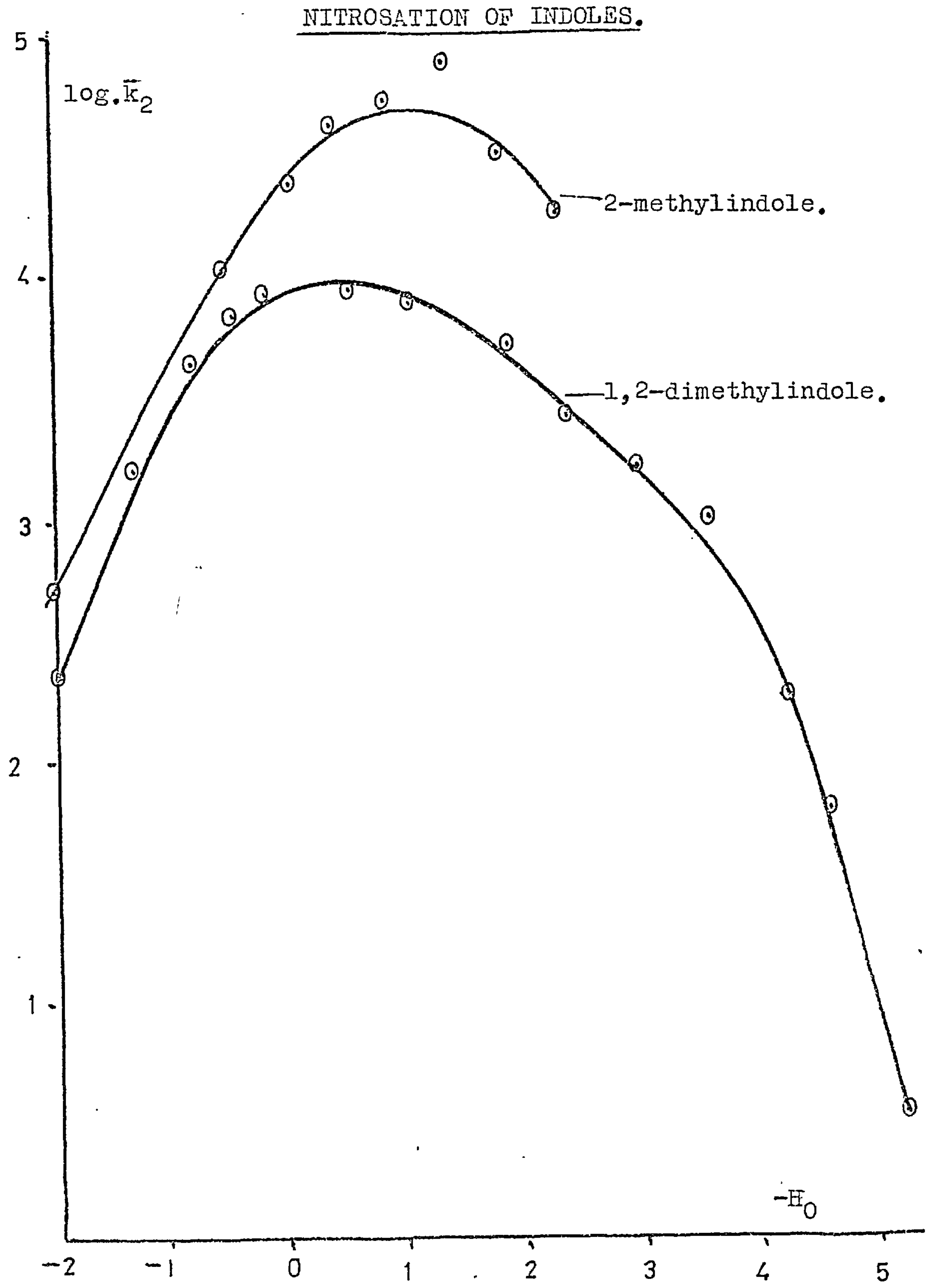

NITROSATION OF INDOLES.
5
4
3
2
1
log.$\overleftarrow{k}_2$
2-methylindole.
1,2-dimethylindole.
$-H_0$
-2
-1
0
1
2
3
4
5

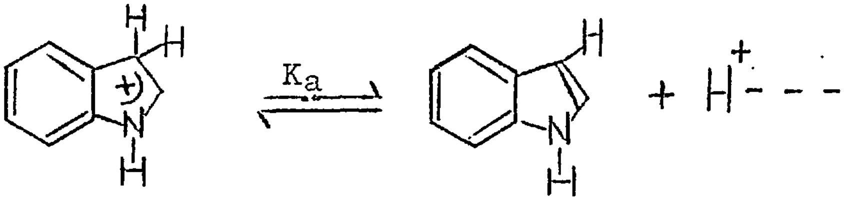
FIGURE (4.4).

range 8.0M. to 9.0M. $HClO_4$. Thus the indoles do not show that unusual feature of amine nitrosation, reaction via the conjugate acid.

Consequently, a new rate coefficient may be defined in terms of the molecular concentration of the free indole base, as recorded in equation (4.7)

$$\text{rate} = k_2 [\text{unprotonated indole}](\text{nitrous acid}). \qquad \text{---} (4.7).$$

The relative concentration of unprotonated indole, (equation 4.8), is governed by equation (4.9), in which h_I is a measured acidity function.



(INDH⁺). (IND). --- (4.8).

$$\frac{(\text{INDH})^+}{(\text{IND})} = \frac{h_I}{K_a} \qquad \text{---} (4.9).$$

Thus, combining equations (4.6), (4.7) and (4.9)

$$k_2 \text{ (eq. 4.7)} = \bar{k}_2 \text{ (eq. 4.6)} \times (1 + h_I/K_a) \qquad \text{---} (4.10).$$

Values of k_2 calculated according to equation (4.10) are recorded in TABLE (4.11) and TABLE (4.12).

TABLE (4.11).

Nitrosation of 1,2-dimethylindole in $HClO_4$ at 3.0°C.

Variation of k_2 (eq. 4.9) with acidity.

Run	$(HClO_4)$ (M.)	h_I	$\bar{k}_2$ (eq. 4.6) ($l.mols^{-1}\ min^{-1}$)	k_2 (eq. 4.7) ($l.mols^{-1}\ min^{-1}$)
270	$1.03 x. 10^{-2}$	$1.1 x. 10^{-2}$	253	258
183	$4.8 x. 10^{-2}$	$5.6 x. 10^{-2}$	1510	1680
182	$1.35 x. 10^{-1}$	$2.5 x. 10^{-1}$	4350	6520
275	$2.4 x. 10^{-1}$	$4.6 x. 10^{-1}$	6090	$1.17 x. 10^{4}$
272	$3.6 x. 10^{-1}$	$6.9 x. 10^{-1}$	7630	$1.82 x. 10^{4}$
181	1.19	5.75	7900	$9.9 x. 10^{4}$
180	1.20	5.9	8150	$1.04 x. 10^{5}$
185	2.38	47.8	7100	$6.15 x. 10^{6}$
179	4.14	$1.12 x. 10^{3}$	5140	$1.15 x. 10^{8}$
184	4.77	$3.31 x. 10^{3}$	2600	$1.72 x. 10^{8}$
178	6.03	$3.47 x. 10^{4}$	1390	$9.65 x. 10^{8}$
273	6.90	$1.5 x. 10^{5}$	940	$2.82 x. 10^{9}$
158	7.91	$1.0 x. 10^{6}$	179	$3.58 x. 10^{9}$
164	8.22	$1.6 x. 10^{6}$	58.0	$1.58 x. 10^{9}$
163	9.04	$1.0 x. 10^{7}$	3.14	$6.28 x. 10^{8}$

TABLE (4.12).

Nitrosation of 2-methylindole in $HClO_4$ at 3.0°C.

Variation of k_2 (eq. 4.9) with acidity.

Run	$(HClO_4)$ (M.)	h_I	10^{-3} x. $\bar{k}_2$ (eq. 4.6) ($l.mols^{-1}$ min^{-1})	k_2 (eq. 4.7) ($l.mols^{-1}min^{-1}$)
137	2.45 x. 10^{-1}	4.6 x. 10^{-1}	12.0	1.49 x. 10^{4}
136	7.45 x. 10^{-1}	2.4	28.5	6.43 x. 10^{4}
134	1.21	6.0	50.0	2.08 x. 10^{5}
135	1.21	6.0	51.5	2.14 x. 10^{5}
139	1.99	25.0	57.0	8.1 x. 10^{5}
126	3.50	347.0	87.5	1.6 x. 10^{7}
128	4.10	1050	31.0	1.7 x. 10^{7}
127	5.07	5620	17.0	5.0 x. 10^{7}

The rate-determining step.

The nitrosation of 1,2-dimethylindole at low acidities has been shown in Chapter III to involve a fast proton loss at the site of reaction. Experiments are now reported to determine if this is still true in reaction at higher acidities. Such experiments, however, necessitate the use of deuterosulphuric acid as solvent, since the protodedeuteriation of 1,2-dimethylindole is extremely fast[77] in acidic solutions. Consequently, careful account must be taken of the solvent isotope effects on both the nitrous acid pre-equilibria and the ground state pre-equilibrium of the protonation of the indole.

The pK_a (equation 4.8) of 1,2-dimethylindole-3-d in solvent D_2SO_4 has been measured and was reported earlier (TABLE 3.28) as $+0.85 \pm 0.1$, measured on an H_I scale of acidity. Since the analogous pK_a of 1,2-dimethylindole in H_2SO_4 is $+0.3$, the concentration of the conjugate base in moderately concentrated acid will be about 3.5 times less in the deuteroacid than in the proteoacid, at the same acidity measured by the H_I function.

The solvent isotope effect on the nitrous acid pre-equilibria, however, is less easy to estimate. It has been reported that the concentration of the nitrousacidium ion is greater[64] in deuteroacid by a factor of 2.2, but that the nitrosonium ion maintains the same concentration[75] in deutero and proteo acid of the same molarity.

However, in the present work, the solvent isotope effect on the concentration of the nitrosonium ion has been directly determined by a spectroscopic method, and it has been established that the concentration of this species is greater by a factor of about 2.0 in D_2SO_4 than in H_2SO_4 at the same solvent acidity.

Thus suitable correction can be made for the solvent isotope effects in the nitrosation reaction regardless of whether the nitrosating species is the nitrosonium or the nitrousacidium ion, and the magnitude of any primary isotope effect evaluated. The results are tabulated in

TABLE (4.13), in which the quoted kH/kD values are corrected for solvent isotope effects.

TABLE (4.13).

Nitrosation of 1,2-dimethylindole in H_2SO_4 and D_2SO_4 at 3.0°C.

Primary isotope effect.

Run	(H_2SO_4) (M.)	(D_2SO_4) (M.)	$-H_I$	$\bar{k}_2$ (eq. 4.8) ($l.mols^{-1}$ min^{-1})	k^H/k^D
333	2.97	-	1.84	7800	
334	4.95	-	3.16	2560	
331	6.32	-	4.10	1190	
335	6.45	-	4.15	1220	
353	-	5.78	3.71	1730	0.57
339	-	6.24	4.05	1230	0.61

Despite the magnitude of the assumption in these calculations, the observed kH/kD values of about 0.6 illustrate that the rate-controlling step does not involve breaking of the carbon hydrogen bond at the site of reaction in contrast to the reactions of phenol and anisole under similar acidity conditions.

(E). THE NITROSONIUM ION AS AN ELECTROPHILIC REAGENT.

The results of the nitrosation reactions studied in this Chapter are collected in FIGURE (4.5) in which log. k_2 (equation 4.11) is plotted against the solvent acidity measured by the H_o acidity function.

$$\text{rate} = k_2.(\text{Substrate}).(\text{nitrous acid}) \qquad \text{---} \ (4.11).$$

The obvious common feature of the reactions studied is the occurrence of a maximum in the profile at an acidity of $H_o = -3.6$, (Acid)~ 7.5M. This is close to the acidity at which the nitrosonium ion begins to be the major nitrous species present in solution. This strongly suggests that the nitrosonium ion is the active species in concentrated acid. Further evidence is suggested by the somewhat loose empirical calculation based on the slopes of the profiles of FIGURE (4.5), before and after the maximum.

Each reation apparently incorporates a factor which diminishes the rate on increasing acidity above 8.0M. solvent acid. This factor is believed to be due to the decreasing water activity, affecting the various transition states in the role of water as a base, (as in the case of anisole) and as a solvating molecule, (as in the case of 1,2-dimethylindole) or for some other reason, as in the case of phenol. If the extent of this factor is measured by the negative slope of the profile after the maximum, this can be extrapolated back to regions of lower acidity. Then the observed positive slope of the profile can be

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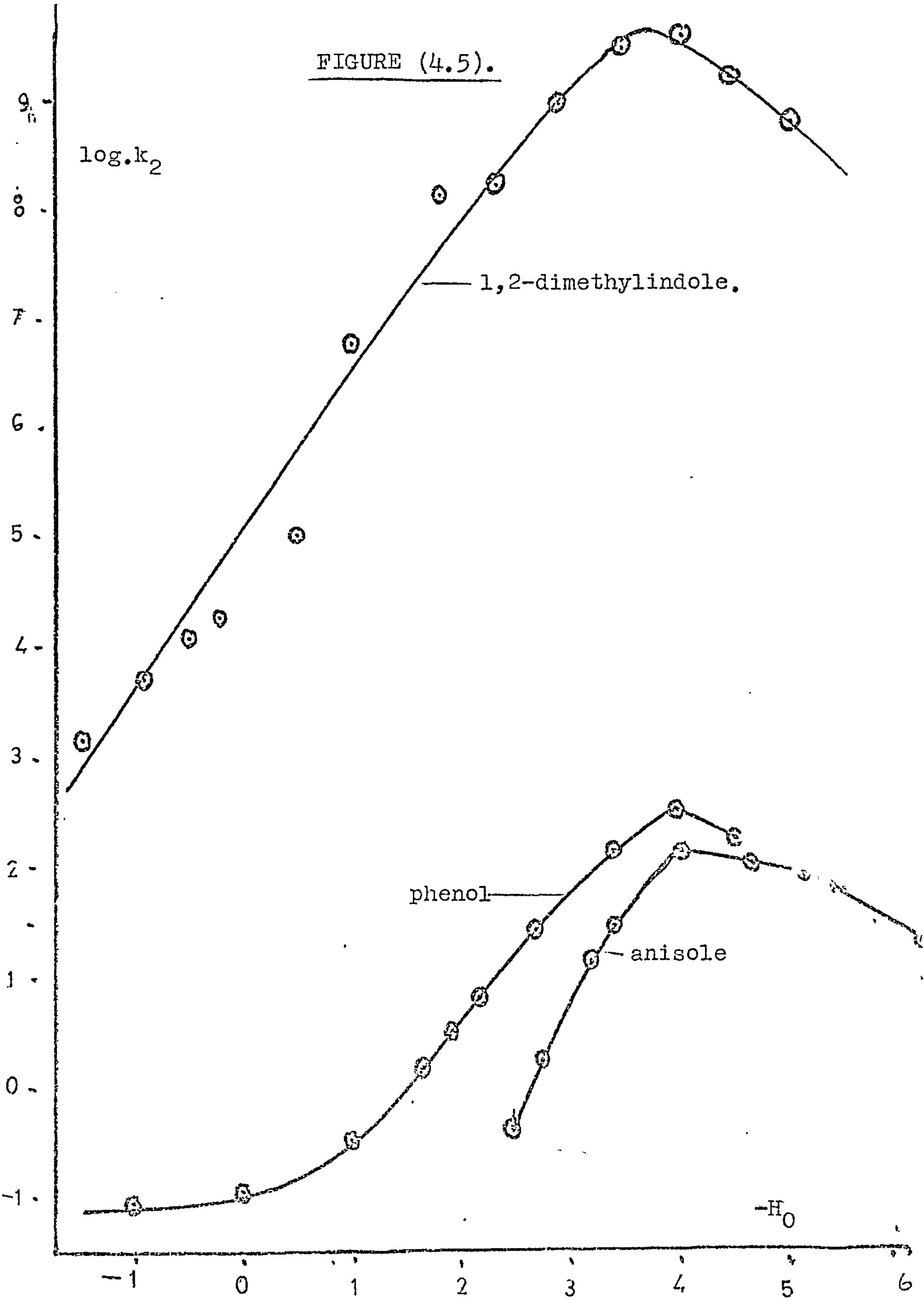
FIGURE (4.5).



regarded as a resultant of the 'true' degree of acid catalysis and the factor which is anti-catalysed by increasing acidity. Calculations of this sort, shown in TABLE (4.14), show that each of the three reactions studied shows a corrected acidity dependence corresponding to an H_o slope of ~ 2.0.

The concentration of the nitrosonium ion has been shown[17] to follow the acidity function H_R, which is numerically equal to about $2.0\ H_o$.

TABLE (4.14).

Substrate	Negative slope ($-H_o$)	Positive slope ($-H_o$)	Corrected acidity dependence ($-H_o$)
Phenol	-0.6	+1.3	1.9
Anisole	-0.3	+1.9	2.2
1,2-dimethylindole	-0.6	+1.4	2.0

Thus the nitrosonium ion can be deduced to be an agent in *C*-nitrosation reactions in concentrated mineral acid. This seemingly axiomatic conclusion has been overlooked by recent workers[78].

CHAPTER V.

NITROSATION OF SUBSTITUTED BENZENES BY THE NITROSONIUM ION.

The evidence presented in Chapter III suggests that nitrous species formed in acidic solution usually attack reactive carbon bases on encounter, and these results therefore give little information on the reactivity of nitrosating agents relative to other electrophiles. This difficulty can in principle be overcome by studying less reactive substrates, and the results of such an investigation are reported in this Chapter.

To minimise experimental and interpretive problems, this investigation was confined to a series of monosubstituted benzenes at 52.9°C. in aqueous perchloric acid, (10.4M.). At such high solvent acidities, the sole detectable nitrous species in solution is the nitrosonium ion, which apparently accounts for close to 100%[19] of the stoicheiometric "nitrous acid".

Hence the nature of the active reagent, and its concentration may be deduced with a fair amount of certainty at these acidities.

Furthermore, the rate of decomposition of nitrous acid is sharply reduced by increasing solvent acidity in the range 8.0M. to 11.0M. $HClO_4$, since the decomposition reaction involves[79] both the nitrosonium ion and molecular nitrous acid. Nevertheless, it was still only possible in the present work to study simple benzene derivatives more reactive than benzene itself, since the nitrosation reaction of the less reactive substrates was found to be slower than the observed rate of nitrous acid decomposition.

The observed rate of nitrosation, measured by the rate of disappearance of nitrous acid, is governed by equation (5.1).

$$\text{rate} = \bar{k}_2.(\text{Substrate}).(\text{HNO}_2) \qquad \text{---} \quad (5.1).$$

Since all the substrates used are unprotonated, and the nitrous acid is virtually completed converted to the nitrosonium ion at the acidity used, equation (5.1) can be rewritten in terms of molecular reactant concentrations, as equation (5.2).

$$\text{rate} = k_2^x.\left[\text{Substrate}\right].\left[\text{NO}^+\right]. \qquad \text{---} \quad (5.2).$$

Thus the observed rate coefficient k_2^x, (equation 5.2), approximates to the molecular coefficient for reaction between the nitrosonium ion, (NO^+) and the monosubstituted benzene,  . <u>Para</u> substituted products are formed predominantly, as discussed below in Chapter VII, page 168. For each substrate, therefore, the partial rate factor, (f_p^x), for the <u>para</u> position was calculated directly from the value of k_2^x (equation 5.2) relative to the corresponding rate coefficient, (k_2^H), for the nitrosation of any <u>one</u> position in benzene.

$$\text{Thus} \quad f_p^x = 6k_2^x/k_2^H \qquad \text{--- (5.3).}$$

(A). DIPHENYLETHER.

This reaction is complicated by further reaction of nitrous acid with phenol, which is formed by hydrolysis of the <u>para</u> nitrosodiphenyl ether formed in reaction, (FIGURE 5.1). The justification for such a reaction scheme is discussed in the experimental section, Chapter VII, page 170.

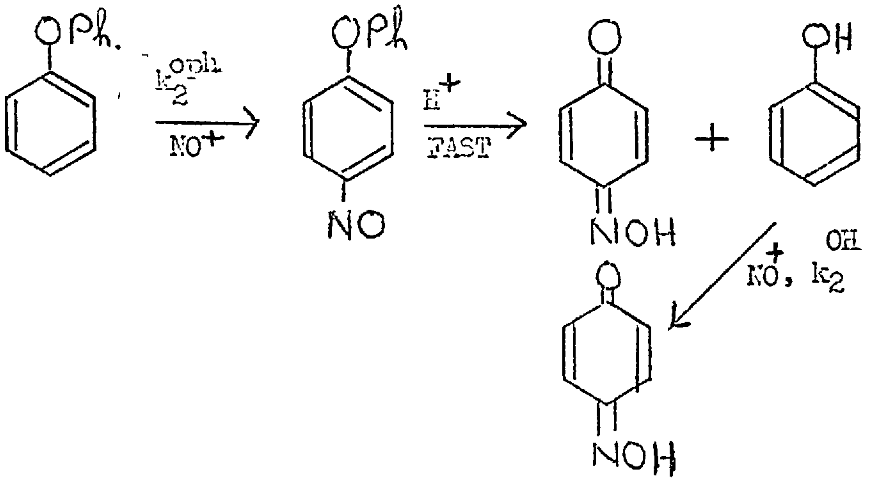


FIGURE (5.1).

Under initial conditions of a tenfold excess of diphenylether over the nitrosonium ion, and because $k_2^{oph} \ll k_2^{OH}$, the molecular rate coefficient, k_2^{oph}, is related to the observed second order rate coefficient defined by equation (5.1), by means of equation (5.4).

$$\bar{k}_2 = 2k_2^{oph} \qquad --- \quad (5.4).$$

Data for the nitrosation of diphenyl ether is shown in TABLE (5.1).

TABLE (5.1).

<u>Nitrosation of diphenylether in 10.4 M. $HClO_4$ at 52.9°C.</u>

(reactant) = initial stoich values.

$(HClO_4)$ = 10.40 M.

Run	(diphenylether) x.10^4 M.	(HNO_2) x.10^5 M.	$\bar{k}_2$ (eq. 5.1) l.moles^{-1} min^{-1}.	k_2^{oph} (eq. 5.4) l.moles^{-1} min^{-1}.
266	10.0	10.1	57.6	28.8
296	4.8	4.0	60.5	30.2
300	3.45	3.5	57.5	28.8
			mean =	29.2

(B). <u>TOLUENE AND BENZENE.</u>

These reactions are sufficiently slow that the rate of decomposition of nitrous acid has to be taken into account. The decomposition of nitrous acid approximately follows equation (5.5) at constant acidity.

$$- \frac{d.(HNO_2)}{dt.} = k'.(\text{nitrous acid}) \qquad --- \quad (5.5).$$

With excess aromatic substrate, the second order equation for nitrosation of the substrate, (equation 5.1), reduces to equation (5.6).

$$\text{rate} = \bar{k}_1.(HNO_2) \qquad --- \quad (5.6).$$

and thus the total rate of consumption of nitrous acid follows equation (5.7).

$$- \frac{d.(HNO_2)}{dt.} = (\bar{k}_1 + k').(HNO_2)$$

$$\equiv k_{obs}.(HNO_2). \qquad --- \quad (5.7).$$

Since the value k^1 for spontaneous nitrous acid decomposition has been measured independently under the experimental conditions, the coefficient k_1 (equation 5.6), and consequently the molecular coefficient for nitrosation of either toluene or benzene, k_2^x (equation 5.2), can be deduced from the observed first order rate constant, k_{obs}, equation (5.7).

The results for both benzene and toluene are recorded in TABLE (5.2).

TABLE (5.2).

Nitrosation of toluene and benzene at 52.9°C.

(HNO_2) = 1.0×10^{-4}M.

$(HClO_4)$ = 10.4M.

Run	(Substrate) x.10^4M.	K_{obs}(eq.5.7) min^{-1}x.10^3	k'(eq.5.5) min^{-1}x.10^3	$\bar{k}_1$(eq.5.6) min^{-1}x.10^3	k_2^x(eq.5.2) l.$mol^{-1}min^{-1}$
TOLUENE					
359	0.0	1.25	1.25	-	-
304	160.0	7.45	1.25	6.20	3.9 x.10^{-1}
260	40.0	2.92	1.25	1.67	4.2 x.10^{-1}
298	20.0	2.07	1.25	0.82	4.1 x.10^{-1}
297	8.0	1.54	1.25	0.29	3.6 x.10^{-1}
				mean =	3.9 x.10^{-1}
BENZENE					
256	0.0	0.73	0.73	-	-
255	90.0	0.94	0.73	0.21	2.3 x.10^{-2}
261	90.0	0.95	0.73	0.22	2.5 x.10^{-2}
				mean =	2.4 x.10^{-2}

(c). A SUMMARY OF THE RESULTS.

The values of k^x_2, (equation 5.2), for each of the three substituted benzenes described above, as well as for phenol and anisole, are listed in TABLE (5.3), along with the partial rate factors for nitrosation in the para position, calculated according to equation (5.3). The relevant σ^+_{para} values, according to the Hammett equation, (equation 5.11), are also recorded in TABLE (5.3), with the corresponding calculated values of ρ, equation (5.11).

$$\log. f^{x}_{\underline{para}} = \sigma^{+}_{\underline{para}} . \rho \qquad --- \quad (5.11).$$

TABLE (5.3).

$T = 52.9^{\circ}C$ $\qquad$ $(HClO_4) = 10.4$ M.

Substrate	k^x_2 l.mol^{-1}min^{-1}	$f^x_{\underline{para}}$	$\sigma^+_{\underline{para}}$	ρ
Benzene	2.4×10^{-2}	1.0	0.0	-
Toluene	3.9×10^{-1}	97.6	-0.311	-6.4
Diphenylether	29.2	3.65×10^{3}	-0.5	-7.1
Anisole	820.	2.04×10^{5}	-0.778	-6.8
Phenol	655.0	1.62×10^{5}	-0.92	-5.67

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A graph of log. $f^{x}_{\underline{para}}$ against $\sigma^{+}_{\underline{para}}$ is shown in FIGURE (5.2).

(D). DISCUSSION.

(i). The Rate-Determining Step.

It has been shown in Chapter IV that for anisole and phenol, (the most reactive aromatic substrates studied in this Chapter,) fission of the carbon-hydrogen band is the rate-limiting step in nitrosation. This leads to the question whether these two compounds are special cases, or whether rate-determining proton loss is generally observed in the nitrosation of benzene and its derivatives. To elucidate this point, the relative rates of nitrosation of hexadenterobenzene and benzene itself were compared in a brief study, in which the rates of product formation, with identical reactant concentrations at 52.9°C, were measured using solvent sulphuric acid. Deuteriated sulphuric acid, (D_2SO_4) however, was used for the nitrosation of the deuteriated benzene. This should not appreciably affect the validity of the comparison, since the acidities of the deutero and proteo sulphuric acids are closely similar[81] at any given molarity. Further, under the chosen experimental conditions, the reaction rate is not appreciably dependent on the acid concentration. This is probably because the nitrosonium ion is the only nitrous species present to any extent at these acidities. Thus solvent isotope effects operating on the ground state pre-equilibria are considered to be negligible.

In practice, the absorbance of products was measured at λ 3000 Å on samples of the reaction mixture which had been diluted by a factor of four with pure water. The results are collected in TABLE (5.4).

TABLE (5.4).

Nitrosation of Benzene and Benzene-d_6 at 52.9°C.

(reactant) = initial stoich values.

Benzene. Run 364. (benzene) = 1.0×10^{-2} M. (HNO_2) = 1.0×10^{-3} M.
(H_2SO_4) = 12.25M.

t (minutes)	Abs. λ 3000 Å	$\Delta(\text{Abs.})^H/\Delta t$
5	0.10	
35	0.16	1.2×10^{-3} min^{-1}
210	0.35	

Benzene-d_6 Run 363. (benzene-D_6) = 1.0×10^{-2} M. (DNO_2) = 1.0×10^{-3} M.
(D_2SO_4) = 12.45M.

t (minutes)	Abs. 3000 Å	$\Delta(\text{Abs.})^D/\Delta t$
5	0.14	
35	0.15	2.7×10^{-4} min^{-1}.
190	0.19	

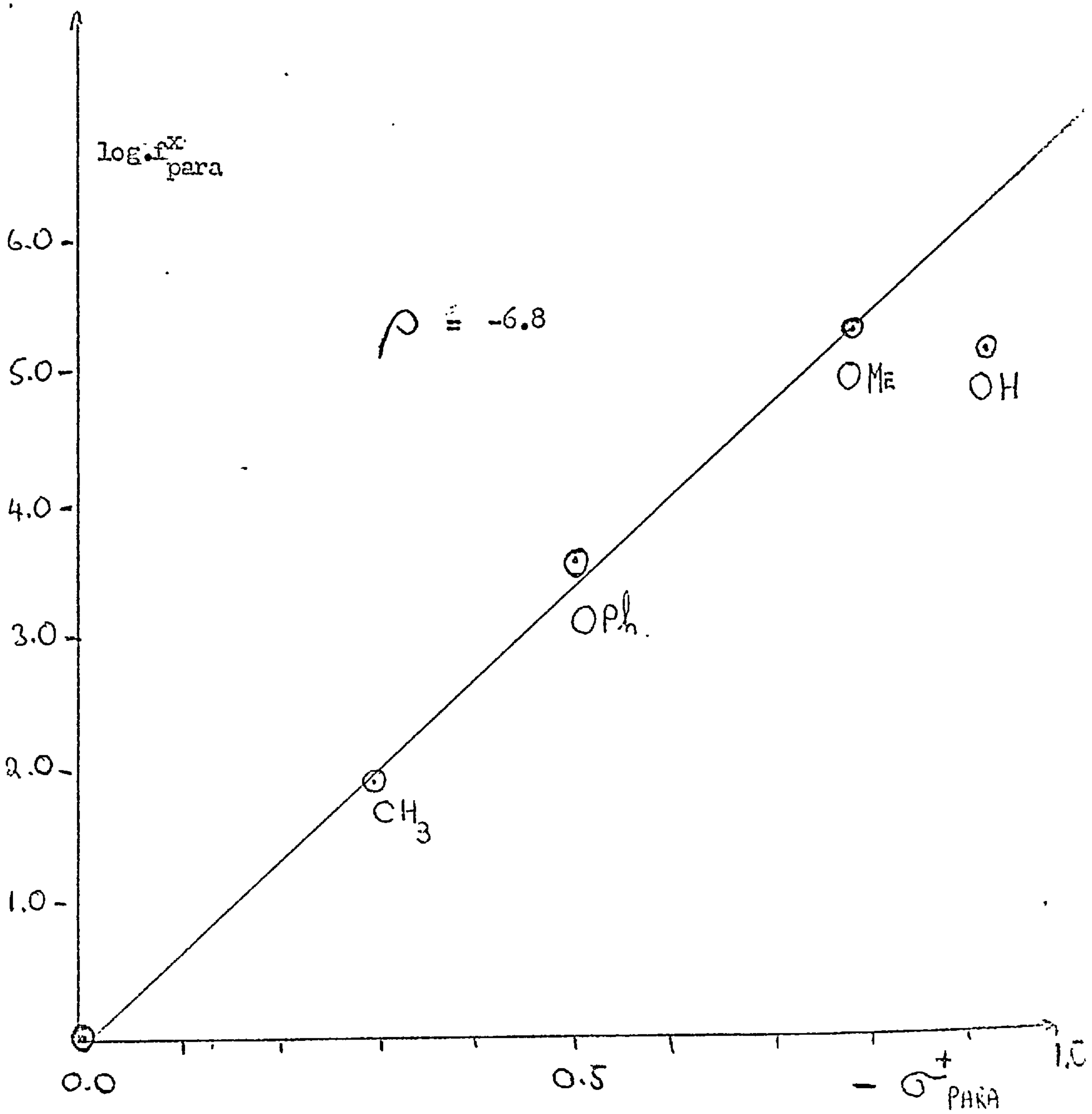

log.f^{x}_{para}
6.0
5.0
4.0
3.0
2.0
1.0
0.0
0.5
1.0
ρ = -6.8
OMe
OH
OPh.
CH_3
$-\sigma^{+}_{PARA}$

FIGURE (5.2).

The ratio of the initial rates should be directly proportional to the ratio of the second order molecular rate-coefficients, k_2^x, for the proteo and deutero substrates, since all other conditions are constant. This then leads to the conclusion that :-

$$\left(\frac{\Delta\,\text{Absorbance}}{\Delta\,\text{time}}\right)^{H} \Big/ \left(\frac{\Delta\,\text{Absorbance}}{\Delta\,\text{time}}\right)^{D} = k_2^H/k_2^D = 4.5$$

A substantial primary kinetic isotope effect is therefore indicated, and suggests that, as in the case of anisole and phenol, the rate-controlling step is the fission of the carbon/hydrogen bond from the intermediate shown in FIGURE (5.3).

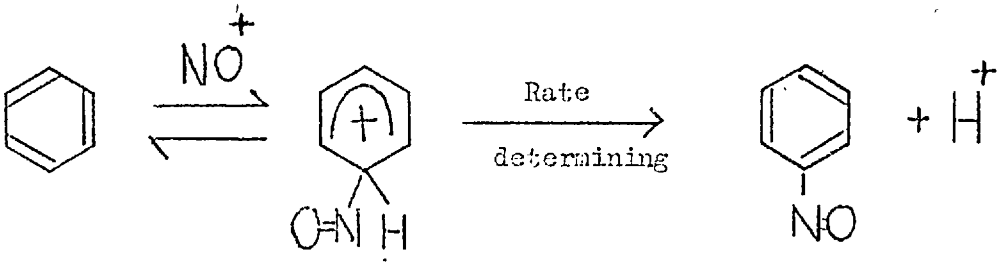


FIGURE (5.3).

(ii). The anomaly of Phenol.

Reference to FIGURE (5.2) will indicate that the value of log. f^{OH}_{para} does not conform to the value expected, based on the good linearity of the graph through the other four compounds studied. This deviation, which is well outside the calculated experimental error, can be explained in terms of a reaction, in the case of phenol, passing through a transition state involving protonation of the nitroso group, rather than the phenolic oxygen. Such a scheme was shown earlier (page 102, FIGURE 4.2) and can account for the marked differences in the observed results, already discussed, for the acid catalysed nitrosations of phenol and anisole.

On such an assumption, therefore, the σ^{+}_{para} value for the hydroxy group would be an inadequate parameter to describe this particular reaction of phenol, and consequently the anomalous deviation of this point from the graph of FIGURE (5.2) would be not unexpected.

(iii). The Reactivity of the Nitrosonium ion, as an Electrophilic Agent.

The results discussed above for anisole and benzene, point to proton loss from the intermediate as the rate-determining step for all four of the aromatic compounds studied. Thus the observed Hammett ρ value of -6.8 ± 0.5 refers to this process and does not reflect accurately the reactivity or selectivity of the nitrosonium ion, although the consistent observation of a primary isotope effect in itself can be argued[4] to reflect the action of a relatively weak electrophile.

CHAPTER VI.

A SUMMARY OF THE FEATURES OF C-NITROSATION.

In the discussion of the preceding three Chapters, the following observations have been made :-

(1) for the most reactive aromatic compounds, ($pK_a > -3.0$), nitrosation is a diffusion controlled process at low solvent acidities;

(2) for all less reactive aromatic substrates ($pK_a < -4.0$), the rate determining step of reaction is normally proton loss from the Wheland intermediate;

(3) the nitrosonium ion is an active electrophile in concentrated acid medium.

These observations lead logically to a consideration of the two outstanding questions in the study of electrophilic aromatic nitrosation :-

(a) What is the extent of competition between the nitrousacidium ion and the nitrosonium ion in reaction?

(b) In what ways, and for what reasons, does nitrosation by the nitrosonium ion idffer from the action of other electrophiles in general, and the analogous nitronium ion in particular?

These points are briefly discussed in this Chapter.

(A). THE IMPLICATIONS OF A DIFFUSION CONTROLLED REACTION.

(1) The observed Energies of Activation.

The nitrosation of the most basic amines[18] and indoles has been ascribed to a diffusion controlled mechanism, when the reagents nitrosyl chloride or the nitrousacidium ion are involved. Such reactions should involve very small free energies of activation, due largely[49] to the change of viscosity of the solvent with temperature. Nevertheless, any activation energies calculated from stoicheiometric rate coefficients will contain the temperature dependence of any ground state, fast, pre-equilibria. This can only be taken into account if the relevant thermodynamic information on the pre-equilibria is known. In the case of attack by the nitrousacidium ion, however, no direct evidence is available to enable any predictions to be made concerning the equilibrium which controls the concentration of this species in solution.

The reactions listed in TABLE (6.1), and governed by equation (6.1), are believed to proceed by a diffusion controlled mechanism, and hence the approximate effect of temperature on the ground state concentration of the nitrousacidium ion can be calculated.

$$\text{rate} = \bar{k}.(\text{Substrate}).(\text{HNO}_2). \qquad \text{---} \quad (6.1)$$

TABLE (6.1).

Nitrosation by the Nitrousacidium ion.

Activation Energies.

	$T^{o}C$	$\bar{k}$ (equation 6.1) $l.mols^{-1}\ min^{-1}$.	$(HClO_4)=10^{-2}M.$ E_A observed $k.cals.mole^{-1}$
1,2-dimethylindole	3.0	290	
	25.0	2580	16.5±2.0
2-methylindole	20.9	2880	
	17.4	2080	
	15.2	1690	
	11.2	1140	15.0±1.0
para-nitroaniline[82]			17.0±0.5

(All values of E_A include ~ 4k.cals.mole^{-1} due to viscosity change in the solvent with temperature.)

These approximate results imply an observed enthalpy of about 12 k.cals.mole^{-1} due to pre-equilibria processes governing the concentration of the nitrousacidium ion.

(ii) The concentration of the nitrousacidium ion in comparison to the nitrosonium ion, under identical conditions.

If the assumption that the nitrousacidium ion reacts on encounter with the more basic indoles is valid, then the proportional concentration of the nitrousacidium ion can be calculated at any acidity in dilute solutions of perchloric acid, since :-

$$\text{rate} = k_{\text{encounter}}.(\text{indole}).(H_2ONO^+). \qquad \text{---} \quad (6.2).$$

$$\equiv \bar{k}_2.(\text{indole}).(HNO_2). \qquad \text{---} \quad (6.3).$$

Thus, substituting values for the appropriate rate constants :-

$$(H_2ONO_2{}^+)/(HNO_2) = \frac{\bar{k}_2}{k_{\text{encounter}}} = \frac{3000^{\ddagger}}{6 \text{ x.} 10^{11}} \quad \frac{\text{l.mol}^{-1}\text{min}^{-1}}{\text{l.mol}^{-1}\text{min}^{-1}}.$$

$$= \underline{\underline{5 \text{ x.} 10^{-9}}}$$

for a solution of nitrous acid in 10^{-2}M. $HClO_4$ at 25°C. This can be compared with the value of the proportional concentration of the nitrosonium ion under the same conditions, calculated from equation (6.4).

(‡ - average value of $\bar{k}_2$ taken from Arrhenius plots of nitrosation of 1,2-dimethylindole and 2-methylindole, see TABLE 6.1).

$$pK_a = H_R + \log. \frac{(NO^+)}{(HNO_2)} \qquad --- \quad (6.4).$$

$$\log. \frac{(NO^+)}{(HNO_2)} = -7.7 - 2.0$$

$$= -9.7$$

$$\frac{(NO^+)}{(HNO_2)} = \underline{5 \times .10^{-9}} \text{ at } 25^\circ C \text{ in } 10^{-2} M.\ HClO_4.$$

The conclusion reached by such a comparison is that the nitrousacidium ion has a closely similar concentration to that of the nitrosonium ion, calculated from known parameters, in dilute solutions of mineral acid.

Since the existing evidence[26,27] is quite convincing for the nitrousacidium ion being the only active, positively charged electrophile in very dilute acidic solutions, the possible interpretations of the above conclusion are listed below.

(a) That the nitrosonium ion is a much less reactive electrophilic reagent than the nitrousacidium ion. This is unlikely, as is shown by studies of the analogous nitration of aromatic systems, in which the nitronium ion was found to be the predominant nitrating species in aqueous mineral acid and organic solvents.

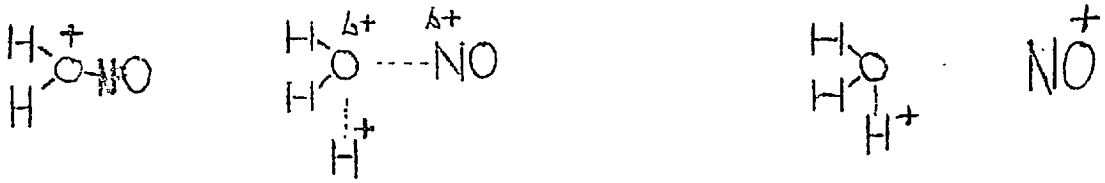
(b) That the nitrous species, detectable by its ultraviolet absorption[15], observed in concentrated solutions of $HClO_4$ and H_2SO_4

is not the nitrosonium ion, but the nitrousacidium ion. This postulate also is unlikely, on the grounds that the observed species has been studied both as an indicator type[17] and in terms of its Raman spectrum[85], and both results suggest that the species is the nitrosonium ion.

(c) That neither the nitrosonium ion nor the nitrousacidium ion react with any indole or amine substrate at collision frequency, or at a frequency even remotely approaching encounter, although the nitrosations by nitrosyl chloride are diffusion controlled, as shown by the calculations of Schmid[67]. Also, the nitrousacidium ion, for some reason other than diffusion control, shows little selectivity in the nitrosation of indoles and amines of varying basicity.

These conclusions are untenable, since they suppose that the neutral electrophile (NOCl) is more reactive than the positively charged electrophile, H_2ONO^+, and that a weak electrophile should show no selectivity in reaction with substrates of varying basicity.

(d) That the nitrosonium ion does not follow the Henderson equation, (equation 6.4), when it is carried through the dilute acid conditions; i.e., the nitrosonium ion is incapable of maintaining a discreet existence in a solvent of high water activity and low solvent acidity. This conclusion is possibly near the truth. Perhaps the covalent bond between oxygen and nitrogen in the nitrousacidium ion in very dilute acid (FIGURE 6.1), becomes progressively weaker as the solvent acidity is increased, until the water molecule has, in effect, more solvent character than covalent character.



dilute acid intermediate acid conc. acid

FIGURE (6.1).

This concept, that a solution of nitrous acid in aqueous mineral acid does not contain equilibrium controlled concentrations of both the nitrosonium ion and the nitrousacidium ion, but only one positively charged species of intermediate nature, is not completely new[86]. However, it seems that the concentration of this species is governed by the Henderson equation, (equation 6.4), using the thermodynamic pK_a of the nitrosonium ion, and, unexpectedly, the H_R acidity function. In dilute acid, this species would effectively be the nitrousacidium ion; in concentrated acid, the nitrosonium ion.

(B). NITROSATION AND NITRATION.

The general reaction scheme for nitrosation by the nitrosonium ion and nitration via the nitronium ion is shown in FIGURE (6.2), in which X^+ represents either of the two species.

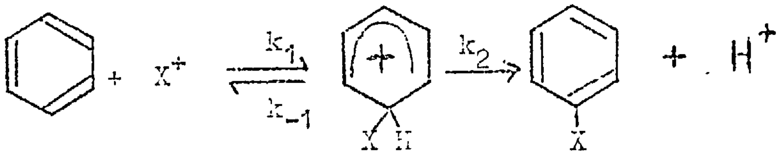


FIGURE (6.2).

In nitration, k_1 is often sufficiently large to allow the formation of the nitronium ion to become rate controlling, and k_2 is almost without exception very much greater than k_{-1}.

In nitrosation, by the nitrosonium ion, however, k_2 is always rate determining in part, at least, as is shown by the consistent observation of a substantial primary isotope effect throughout this present study. Also, however, the presence of a Wheland intermediate in nitrosation has not been detected, directly, despite numerous attempts to observe this spectrally in the present work, and in the studies of Ibue-Rasa[38].

These observations are in accord with two possible conclusions :-

(a) that the nitrosation process involves a synchronous attack of the nitrosonium ion and fission of the carbon-hydrogen bond at the site of reaction. Such a mechanism would be extremely unusual in an electrophilic substitution reaction. The observation recorded in Chapter IV moreover, that the nitrosation of phenol can proceed through a dienone intermediate with sufficient stability to present a kinetic form independent of the solvent acidity, would seem to rule out the possibility of a synchronous reaction in the general case.

(b) that $k_{-1} \gg k_2$ in nitrosation, the reverse being true for nitration. It seems unlikely that proton loss from the positively charged intermediate should be assisted directly by the nitro group and not by the nitroso group, since the nitroso group is actually much more basic than the nitro group, being able to form oximes, or 'isonitroso' compounds very readily. Consequently, the differences between nitration and nitrosation processes must lie in the relative magnitudes of k_{-1}, i.e., k_{-1} for nitration $\ll$ k_{-1} for nitrosation.

Regardless of the interpretation of this difference in magnitude of the coefficient k_{-1}, it is clear that the relative true reactivities of the nitrosonium and nitronium ions cannot be deduced simply from the relative rates of nitrosation and nitration reaction under equivalent conditions of reactant concentrations. Hence the conclusion, generally held, that the nitrosonium ion is a very selective and unreactive electrophile indeed, is not necessarily valid.

PART III

EXPERIMENTAL

CHAPTER VII.

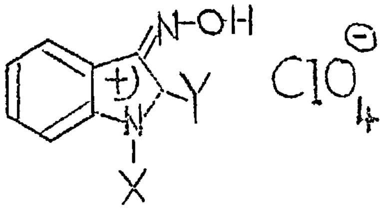
THE EXPERIMENTAL DETAILS.

(A). THE KINETIC METHODS.

The reaction rates were normally followed either by estimating the amount of product formed by spectrophotometric means or by determining the amount of unreacted nitrous acid by the method of Shinn[87]. Details of these methods are given below.

(i) Continuous Spectrophotometric Monitoring.

(a) For the kinetic studies of 2-methylindole, 1,2-dimethylindole and 2-phenylindole, the reaction was followed by monitoring the ultra-violet spectrum of the nitrosation product (X) at one of the suitable predetermined wavelengths given in TABLE (7.1).



(X).

The measurements of absorbed light were taken in either 1.0 cm. or 10.0 cm. silica cells maintained at constant temperature by circulation of water from a temperature-controlled bath. The cell faces were continuously swept with nitrogen gas to prevent condensation of atmospheric moisture on the cell windows in the case of the low temperature reactions.

The reaction solution was prepared in a volumetric flask. The required amount of an aqueous stock solution of the indole was run into the clean flask containing the calculated quantity of aqueous mineral acid. This solution was shaken and cooled for thirty minutes by immersion in the thermostatting bath. Reaction was initiated by adding, via a pipette, a quantity of thermally adjusted aqueous stock solution of sodium nitrite. The volumetric flask was shaken to ensure mixing, quickly made up to the graduation mark with a small amount of distilled water, and shaken again.

A sample of the reaction solution was then transferred with a dropping pipette to the spectrophotometer cell, which had been previously set, clean, dry and already at constant temperature, in the light beam of a Unicam SP700 recording spectrophotometer. The reaction was followed until no further change in the absorbance of the reaction solution was apparent. In all cases, this final value of the absorbance was checked with the calculated value based on 100% reaction, and these agreed to within 2%. Careful account was always taken of absorbance due to all species in solution. The temperature of the cell contents was measured after the run, and also at various intervals on a blank kinetic run. Finally, the acidity of each kinetic run was determined by titration of the reaction solution by standardised sodium hydroxide, using methyl red indicator.

(b) Spectrophotometric Estimation of the Nitrosation Product.

The ultra-violet absorption spectra of the conjugate acid (X) of the various 3-nitrosoindole products have not been reported previously. Details of the absorption maxima are given in TABLE (7.1).

TABLE (7.1).

Absorption Spectra of various nitrosoindoles.

Solvent : Aqueous perchloric acid.

	λ max. Å	log. ϵ	λmax. Å	log. ϵ	λmax. Å	log. ϵ	(H^+) (M).
X = H)	2490	4.21	2630	4.17	3470	3.76	2.6
y = me)	2490	4.21	2630	4.17	3470	3.76	10^{-2}
X = H)	2720	4.49					10^{-2}
y = Ph)	2720	4.49					10^{-1}
X = me)	2500	4.13	2670	4.18	3450	3.77	10^{-2}
y = me)					3450	3.77	1.0
					3450	3.77	6.5

In every case, the absorption of these species obeys the Beer-Lambert law of equation (7.1).

$$\log.(I_o/I) = \epsilon.c.l. \qquad \text{--- (7.1).}$$

where :- I_o/I represents the ratio of incident to transmitted light,

c represents the concentration of the absorbing species in gm.mols.l^{-1},

l. refers to the thickness of the cell, in centimetres, and ϵ is the molar extinction coefficient of the absorbing species.

(C). ABSORPTION DUE TO NITROUS ACID AND UNREACTED INDOLE.

The absorption due to the relevant nitrous species and unreacted indole were small in comparison to the absorption due to the nitroso product. This is illustrated by the estinction coefficients listed in TABLE (7.2).

TABLE (7.2).

Background Absorption of light in kinetic runs.

	λ (Å)	ϵ (NO^+)	ϵ (HNO_2)	ϵ (indole)	ϵ (product
2-methylindole	3470	100	43	10	5700
1,2-dimethylindole	3470	100	43	10	5850
2-phenylindole	2710		25	7500	31,500

Nevertheless, full and correct account was always taken of these background absorbances in the kinetic analyses.

(d) Side Reactions.

(i) Decomposition of Nitrous Acid.

Under the conditions employed, significant nitrous acid decomposition was detected only in the few runs performed at solvent acidities greater than 6.0M.$HClO_4$, when only about 90% of the nitrous acid initially added was observed to form products. The nitrous acid loss is greatest during initial shaking[19], and does not therefore seriously interfere with the kinetic analysis of product formation.

(ii) Stability of the Reaction Products.

The stability of each of the nitroso compounds under discussion was established both in the presence of an excess of unreacted indole, and also in an excess of mineral acid. The 3 nitroso compound from 2-methylindole, however, was observed to react further with excess nitrous acid. Consequently, all experiments with this compound were undertaken with an initial excess of indole, and at acidities less than 4.0M.$HClO_4$. The corresponding nitroso products of 2-phenylindole and 1,2-dimethylindole are both stable to an excess of nitrous acid.

(e) Typical Kinetic Runs.

Two typical kinetic experiments using the technique described above are shown in TABLE (7.3) and TABLE (7.4).

TABLE (7.3).

Nitrosation of 1,2-dimethylindole followed by production of product.

Run 275.

($HClO_4$) = 2.4 x. 10^{-1}

Initial Stoich.(indole) = 2.08 x.10^{-5}M.
Initial Stoich.(HNO_2) = 1.08 x.10^{-5}M.

temp. = 3.0°C.

100% reaction corresponds to an optical density at 3450 Å of 0.632 in a 10.0 cm. cell.

t (min)	O.D.	(HNO_2) x.10^6M.	(indole) x.10^6M.	% reaction	$\bar{k}_2$ l.mols^{-1}mi
1.75	0.164	7.97	17.97	25.9	6190
2.50	0.201	7.33	17.33	31.8	6360
3.25	0.231	6.81	16.81	36.5	6160
4.0	0.258	6.35	16.35	40.8	6100
5.5	0.307	5.51	15.51	48.6	
7.0	0.351	4.74	14.74	55.6	
8.5	0.383	4.21	14.21	60.2	
10.0	0.407	3.78	13.78	64.2	
13.0	0.457	2.91	12.91	72.3	
16.0	0.493	2.30	12.30	77.8	
19.0	0.523	1.78	11.78	82.7	
25.0	0.550	1.31	11.31	87.0	
∞	0.635	0	10.00	100.0	

TABLE (7.4).

Nitrosation of 1,2-dimethylindole followed by product formation.

Run 164.

$(HClO_4) = 8.22M.$ Initial Stoich.(indole) $= 1.2 \times 10^{-3}M.$

Initial Stoich.$(HNO_2) = 8.0 \times 10^{-5}M.$

temp. = 3.0°C. 100% reaction corresponds to an optical density at 3450 Å of 0.463 in a 1.0 cm. cell.

t (min)	O.D.	$(HNO_2) \times 10^5 M.$	% reaction	$\bar{k}_1 \times 10^2$ min^{-1}.
8.0	0.125	5.19	27.0	7.44
6.0	0.187	4.13	40.3	7.56
9.0	0.235	3.31	50.8	7.25
12.0	0.271	2.70	58.6	7.12
15.0	0.299	2.22	64.6	7.00
18.0	0.327	1.74	70.6	7.19
21.0	0.345	1.43	74.6	7.09
27.0	0.373	1.07	80.6	7.03
33.0	0.392	0.71	84.7	7.00
∞	0.429	0.0	92.9	

(iii) The Kinetic Method employing Analysis for Unreacted Nitrous Acid.

The direct spectrophotometric measurement of product formation is only satisfactory in the case of compounds forming stable products. This condition was fulfilled for the three indoles discussed above, presumably because the reactive nitroso group is stabilized by formation of an oxime structure. Nitroso compounds, however, which do not readily form oximes in acidic media are generally unstable, being prone to further oxidation and coupling reactions. Consequently, a different kinetic method was used for the study of reactions producing these relatively unstable compounds, in which aliquots of the reaction mixture were analysed for nitrous acid by a modification[88] of the method first used by Shinn[87].

(a) Determination of Nitrous acid by Shinn's Method.

This method involves the conversion of nitrous acid to a stable aromatic diazonium ion, which is then coupled with a suitable naphthol to produce an azo dye solution, the optical density of which is directly proportional to the original concentration of nitrous acid.

The following reagent solutions were used in this analysis :-

(i) Sulphanilamide (1.25 gm.) in 250 ml. of 5.0M. HCl.

(ii) N-1-naphthylethylenediamine di-hydrochloride (0.25 gm.) in 250 ml. water.

In a typical determination, 3 ml. of the nitrous acid solution were run into ca 15 ml. of distilled water contained in a 25 ml. graduated flask. Then 2 mls. of the sulphanilamide solution were added and the stoppered flask shaken thoroughly. After three minutes or so, two ml. of the naphthylethylenediammine solution were added, the solution was made up to volume and then shaken. The azo dye requires about 15 minutes to develop fully, after which time the optical density of the solution was measured at λ 5460 Å in a cell of suitable path length, using a reference cell containing only a similar dilution of the stock solutions in water. The light absorption by the dye was found to be directly proportional to the concentration of the nitrous acid sampled, as is demonstrated in FIGURE (7.1). The graph of optical density at 5460 Å against nitrous acid concentration is linear and passes through the origin. FIGURE (7.1) refers to a cell path length of 1.0 cm. and similar behaviour was found using a cell path length of 10.0 cm.

Thus :-

$$\log.(I_o/I) = \epsilon_{azo}.(\text{azo dye}).l. \qquad \text{--- (7.2).}$$

$$\propto \epsilon_{azo}.(\text{HNO}_2).l. \qquad \text{--- (7.3).}$$

where the symbols have their usual significance.
At 18°C., $\epsilon_{azo} = 5.4\ 10^4\ \text{l.mol}^{-1}\text{cm.}^{-1}$.

(b) <u>The Kinetic Method.</u>

In a typical kinetic experiment, the required amount of solvent acid was added to water contained in a 50 ml. graduated flask, and the solution was then immersed in a temperature controlled bath. A small quantity, generally 5 ml., of an aqueous stock

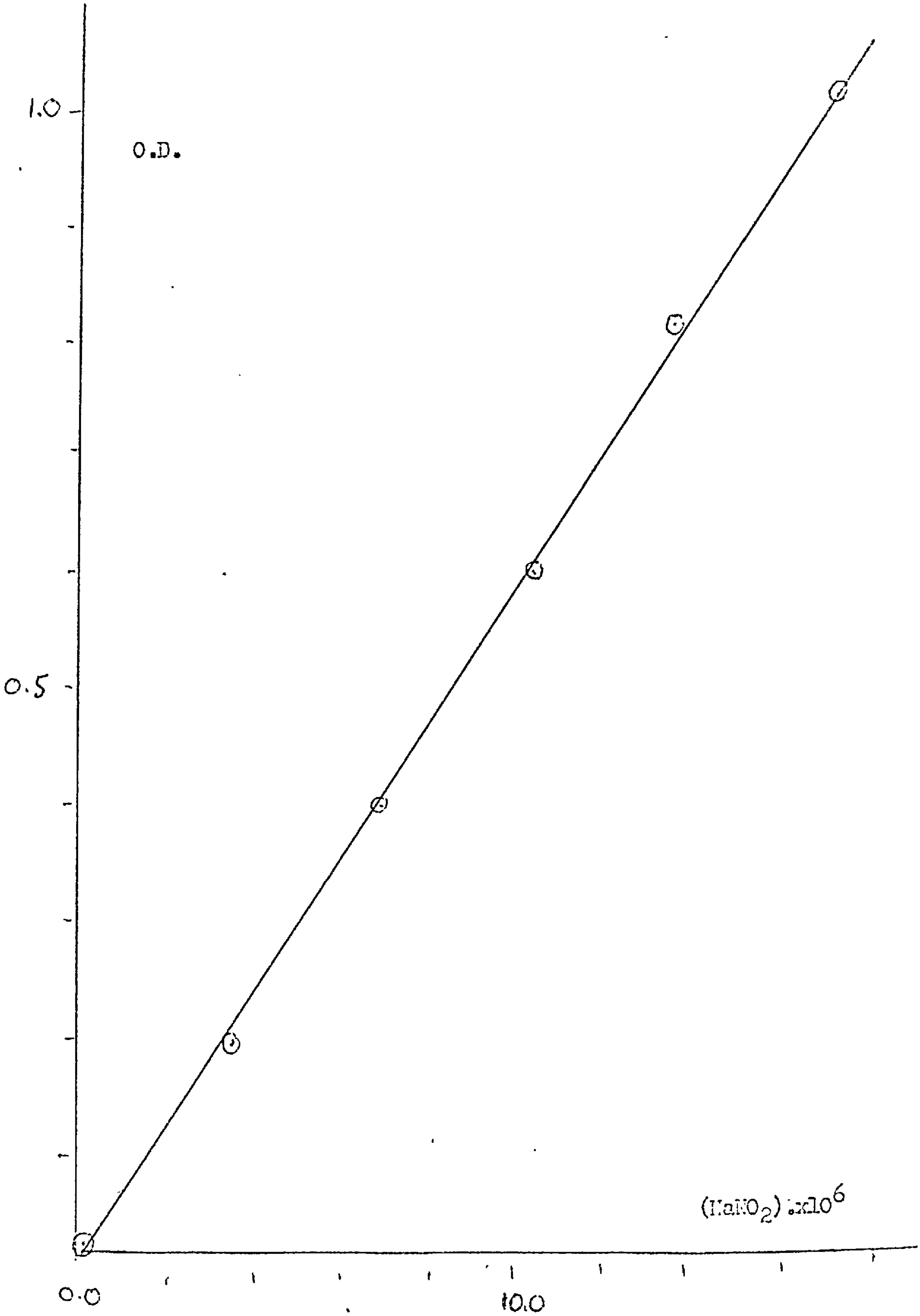


FIGURE (7.1).

solution of the aromatic substrate was introduced to the flask via a pipette and the solution shaken to mix. The reaction was brought about by the addition of a known quantity, generally 3 ml., of an aqueous stock solution of sodium nitrite. The volume of solution was adjusted with distilled water, shaken thoroughly and then reimmersed in the thermostatting bath, Aliquots were taken with a pipette at timed intervals and analysed for nitrous acid by the Shinn's method described above.

The gross acidity of the reaction solution was determined by titration against standardised sodium hydroxide using methyl red as indicator.

(c) Sources of Error.

(i) Side Reactions.

Side reactions which may introduce considerable error are the decomposition of nitrous acid, and subsequent reactions of the product with nitrous acid. For example, it has been shown[28] that aromatic C-nitroso compounds can react with an excess of nitrous acid to produce a diazonium ion, which may then couple with an activated aromatic substrate to produce an azo derivative. However, these sources of error have been minimised by employing very low initial concentrations of nitrous acid (ca 5.10^{-6} to 10^{-4} mol.l^{-1}) in individual runs) with a tenfold or greater excess of aromatic substrate. The proportional rate of nitrous acid decomposition is known[73] to decrease with decreasing concentration of nitrous acid, and the rate of any subsequent uptake of nitrous acid by the products of reaction will be minimised by the low concentration of both the nitroso compound and nitrous acid.

(ii) Error in the Shinn's analysis.

Apart from normal volumetric errors, the following are possible sources of error in this analytical procedure.

(1) Absorption by either the aromatic substrate or products of reaction at 5460 Å.

(2) Reaction of the aromatic substrate or the products of reaction with either sulphanilamide or the naphthol to produce a new species absorbing at 5460 Å.

(3) Reaction of the diazonium ion, (formed from sulphanilamide), with either the aromatic substrate or the reaction products before the introduction of the coupling agent.

Of these three possibilities, serious interference was detected only from the last, and that only in the case of the nitrosation of 1,2-dimethylindole. This compound was evidently reactive enough to couple with the diazonium ion, producing a new azo dye, λ 4300 Å, ϵ 28,200.).

(4) Incomplete quenching of reaction. In the kinetic procedure, a 3 ml. sample of the reaction solution was usually added to 15 ml. of distilled water prior to the analysis for nitrous acid. The resulting reduction in the acidity of the reaction mixture generally quenches the reaction. When, however, the nitrosation process was <u>accelerated</u> by a reduction in the solvent acidity,

as in the case of 1,2-dimethylindole and 2-methylindole in moderately concentrated acid, the alternative kinetic method involving direct spectrophotometric observation of the reaction products, described previously, was used instead.

(5) Stability of the Azo dye. The intensity of the dye, once fully developed, showed negligible change over a period of two hours at room temperature, regardless of the acidity of the solution being measured. All optical measurements were therefore taken within 90 minutes of the original coupling. The molar extinction coefficient of the azo dye showed a slight dependence on the acidity of the medium in which it was measured, being a few percent greater in stronger acid. This is unimportant under the pseudo first order conditions of the kinetic runs, since the observed optical density need only be directly proportional to the concentration of nitrous acid sampled.

Samples from kinetic runs at high acidities ($HClO_4 > 5M.$) required a longer time, (up to forty minutes) for the full colour development of the azo dye. These observations are in accordance with previous findings[89].

(d) Typical Kinetic Runs.

Two examples of typical kinetic experiments studied by analysis for unreacted nitrous acid are shown in TABLE (7.5) and TABLE (7.6). These runs are representative of the various conditions under which the reactions were studied. In particular, the reaction half-lives were always short, (usually of the order of 30 minutes,) in comparison with the rates of decomposition of nitrous acid under the same conditions, which have been listed in TABLE (7.7).

TABLE (7.5).

Nitrosation of phenol, followed by Shinn's method.

Run 79.

$(HClO_4)$ = 3.02M. Initial Stoich (phenol) = 5.13 10^{-2}M.

Initial Stoich (HNO_2) = 8.5 10^{-5}M.

temp. = 0.7°C.

100% reaction corresponds to an optical density at 5460 Å of 0.00 in 1.0 cm. cell.

time (minutes)	O.D. 5460 Å	(HNO_2) x.10^5M.	% reaction	$\bar{k}_1$ x. 10^2 (min.$^{-1}$)
2.0	0.506	7.97	6.3	
8.0	0.432	6.80	20.0	2.79
15.0	0.360	5.67	33.3	2.71
22.0	0.303	4.81	43.4	2.59
29.5	0.240	3.78	55.6	2.74
37.5	0.195	3.07	63.9	2.72
51.0	0.130	2.05	75.9	2.79
84.0	0.056	0.88	89.7	2.65
	0.00	0.0	100.0	

TABLE (7.6).

Nitrosation of Anisole followed by Shinn's method.

Run 157.

$(HClO_4)$ = 9.41M. Initial Stoich (Anisole) = 4.71 10^{-4}M.

Initial Stoich (HNO_2) = 1.10 10^{-5}M.

temp. = 0.7°C.

100% reaction corresponds to an optical density at 5460 Å of 0.00 in 10.0 Cm cell.

time (minutes)	O.D.	(HNO_2) x.10^6M.	% reaction	$\bar{k}_1$ x.10^2 (min.$^{-1}$)
3.5	0.642	10.10	8.2	
10.5	0.507	8.00	27.3	3.05
18.5	0.369	5.71	48.1	3.55
31.0	0.242	3.81	65.4	3.42
47.5	0.142	2.23	79.7	3.35
68.0	0.077	1.21	89.0	3.25
	0.00	0.0	100.0	

TABLE (7.7).

Rates of decomposition of nitrous acid in aqueous perchloric acid at 0.7°C.

Run	($HClO_4$) (M.)	(HNO_2) x.10^5M.	$t_{\frac{1}{2}}$ (hours)
290	10^{-1}	1.0	118
176	6.0	1.0	50
160	7.8	1.0	25
83	10^{-1}	10.0	200
82	3.0	10.0	40
84	5.0	10.0	15
153	5.4	10.0	20
173	6.0	10.0	12
77	10^{-1}	100.0	40
76	1.0	100.0	30
75	2.5	100.0	10

(iii) Kinetic Method employing Sealed Ampoules.

(a) The usefulness of the two foregoing methods is limited to kinetic runs of half lives shorter than 150 minutes at 0°C., mainly by virtue of the decomposition rate of nitrous acid, shown in TABLE (7.7). Thus, to study the nitrosation of less reactive substrates, a method was employed by which nitrous acid decomposition was reduced to about three percent per hour for an initial concentration of 10^{-4}M. nitrous acid at 52.9°C. This was achieved by studying the kinetics of solutions of perchloric acid at such an acidity that the nitrous acid is almost totally in the form of the nitrosonium ion. Since the decomposition of nitrous acid probably proceeds by attack of the nitrosonium ion on unionized nitrous acid, solutions of nitrous acid in very concentrated ($\sim$10.0M.$HClO_4$) acid should be more stable. To further diminish decomposition of the nitrous acid, and also to prevent loss of volatile reactants at the high temperature employed, these experiments were carried out in sealed ampoules. These experimental conditions greatly increase the range of accurate rate measurements, half-lives of up to 12 hours at 52.9°C. being possible.

The ampoules were prepared by constricting the neck of clean test-tubes of 'Pyrex' glass. Ampoules made in this way have a volume of approximately 11 or 12 ml. In a typical run having a half-life of greater than three hours, a weighed amount of aromatic substrate was contained in a 100 ml. graduated flask, along with 5 ml. water, and the required amount ($\simeq$ 85 ml.) of 72% $HClO_4$. The warm solution was shaken to complete solution of the aromatic substrate. The flask was then cooled in an ice-bath for 15 minutes, then 10 ml. of an aqueous stock solution of sodium nitrite of known concentration was introduced by pipette, the contents thoroughly mixed and the volume adjusted with distilled water. A sample of the solution was wuickly analysed for the stoicheiometric concentration of the substrate by measurement of ultra violet absorption. Aliquots (10 ml.) of the reaction mixture were introduced into each ampoule, which was then sealed with 'Parafilm' and quickly cooled in liquid nitrogen. The remaining solution was analysed spectrophotometrically once more, to establish that a constant concentration of reactants had been introduced into each tube.

The ampoules were then sealed with a blow-torch and brought to 0°C by suspension in an ice-bath for 10 minutes. Following this, the tubes were simultaneously immersed totally, by means of copper wire holders, in a temperature-controlled bath maintained at 52.9°C. After a further period of 10 minutes, each tube was shaken for 10 seconds and examined carefully to ensure complete solution of the aromatic compound.

Kinetic points were taken at noted times by removal of an ampoule from the bath, immediate washing of the glass with cold running tap-water, and followed by thorough drying with a paper towel. The ampoule was then placed in a clean dry 500 ml. bolt-necked reagent bottle, and broken by shaking the stoppered bottle. A sample (3 ml.) of the liquid was removed by pipette and analysed for nitrous acid by Shinn's method. The ultra violet spectrum of the remaining liquid was examined to estimate the nature and concentration of the reaction products.

The gross acidity of the run was checked by titration of a sample of the solution from two different ampoules against standardised sodium hydroxide, using methyl red indicator.

From an initial nine tubes, an average of two tubes cracked on immersion in liquid nitrogen, and these were, of course, discarded.

(b) Side Reactions.

(i) Decomposition of Nitrous acid.

The rate of the decomposition reaction in sealed tubes was found to approximate to a first order process over the first 75% of decomposition, according to equation (7.4).

$$- \frac{d(HNO_2)}{dt.} = k^1.(HNO_2) \qquad \text{--- (7.4).}$$

This relationship is not exact. When the concentration of the aromatic substrate is in constant excess over the initial concentration of nitrous acid, the rate of loss of nitrous acid to form products will follow the rate law of equation (7.5).

$$- \frac{d(HNO_2)}{dt.} = \bar{k}_1.(HNO_2) \qquad \text{--- (7.5).}$$

Thus the total observed rate of loss of nitrous acid can be expressed as in equation (7.6), as the sum of equation (7.4) and (7.5).

$$-\frac{d(HNO_2)}{dt.}.(\text{observed}) = (\bar{k}_1 + k^1).(HNO_2)$$

$$= k_{obs}(HNO_2) \qquad \text{--- (7.6).}$$

Thus the pseudo first order rate coefficient $(\bar{k}_1)$ for reaction between the substrate and nitrous acid can then be calculated directly from the observed rate of disappearance of nitrous acid.

(ii) Further reaction of the reaction products.

Under the experimental conditions of relatively high temperature and acidity, the nitroso compounds formed initially appear to undergo further reactions. The rate coefficients for nitrosation, however, calculated from the rate of disappearance of one of the reactants, nitrous acid, will be meaningful if no further nitrous acid is consumed in these subsequent reactions. This condition was always met, as is discussed below in connection with the general analysis of the reaction products.

(3). PRECISION OF THE MEASURED RATE COEFFICIENTS.

The second order rate coefficients defined by equation (7.7) for kinetic runs performed on phenol, anisole and the various indoles were reproducible to better than 3%. Rate coefficients for the reactions of benzene and toluene are subject to much higher error because of uncertainties in the rate of decomposition of nitrous acid. The error in these rate coefficients is of the order of ± 20%.

A stoichoiometric second order rate constant $(\bar{k}_2)$ has generally been calculated by graphical means from the experimental measurements, using the integrated form of equation (7.7).

$$-\frac{d(HIO_2)}{dt.} = \bar{k}_2(\text{substrate}).(HIO_2) \qquad \text{--- (7.7).}$$

The integration was carried out from the time of mixing of reactants.

The expressions used in the present work are given below, in which :-

a. and b. refer to the initial concentrations of reagents, measured in mols.l.$^{-1}$,

x. refers to the instantaneous concentration of a stable reaction product, measured in mols.l.$^{-1}$,

and t. refers to the time in minutes since initiation of reaction.

(i) Pseudo First Order Reaction.

One reagent in constant excess :-

$$\bar{k}_2 = \frac{2.303}{(t-t_0).b}.\log.\left(\frac{a}{a-x}\right) \qquad \text{--- (7.8).}$$

A graph of log.(a-x) against time is linear.

(ii) Second Order Reaction.

(a) Unequal concentrations of reactants :-

$$\bar{k}_2 = \frac{2.303}{(t-t_0).(a-b)}.\log.\frac{b.(a-x)}{a\ (b-x)} \qquad \text{--- (7.9).}$$

A graph of log.$\frac{(a-x)}{(b-x)}$ against time is linear.

(b) Equal concentration of reactants :-

$$\bar{k}_2 = \frac{1}{(t-t_0).a} \cdot \frac{X}{(a-x)} \qquad \text{--- (7.10).}$$

A graph of $\frac{1}{(a-x)}$ against time is linear.

The values of the rate coefficients $\bar{k}_2$ were obtained in each case from the gradients of the linear graphs.

(c). AN ANALYSIS OF THE PRODUCTS OF REACTION UNDER EXPERIMENTAL CONDITIONS.

(i). Nitrosation of Phenol.

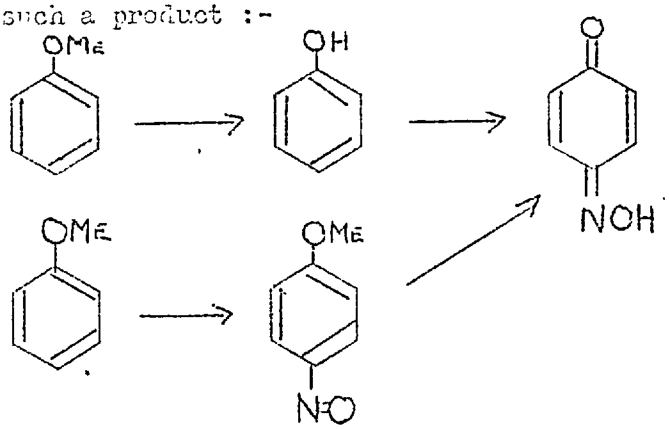
The product of the nitrosation of phenol in aqueous acid has been reported[90] to be > 95% *para* nitrosophenol, the remaining few percent being *ortho* nitrosophenol. The product of runs performed with phenol and 4-(H^2)phenol always corresponded to > 95% *para* nitrosophenol, based on the ultraviolet absorption spectrum[91]. No other products were detected spectrophotometrically.

(ii) Nitrosation of Anisole.

Under the conditions of the kinetic experiments, the product of this reaction also was always > 95% *para* nitrosophenol, no other product being observed spectrophotometrically. Two possible reaction schemes could yield such a product :-

Scheme 1

Scheme 2



The observations recorded below suggest that Scheme 2 is operative.

(a) A solution of anisole in 10.M.$HClO_4$, left overnight at 0°C., then made alkaline with sodium hydroxide to pH 12, showed no trace of phenoxide ion in the ultraviolet absorption spectrum.

(b) An authentic sample of <u>para</u> nitrosoanisole in aqueous solution reacted very readily under acidic or basic conditions to yield <u>para</u> nitrosophenol and no other detectable product. This observation is in agreement with those of other workers[92].

As is shown in TABLE (7.8), the rate of the acid catalysed hydrolysis of <u>para</u> nitrosoanisole was determined at one acidity and was also observed to be virtually instantaneous over the range of acidity employed in the kinetic studies of the nitrosation of anisole.

TABLE (7.8).

<u>Hydrolysis of p-nitrosoanisole at 0.7°C.</u>

<u>Variation of rate with acidity.</u>

$(HClO_4)$ (M.)	$t_{\frac{1}{2}}$ (hydrolysis)
10^{-1}	32 minutes
2.0	10 seconds
5.0	< 1 second
8.0	< 1 second
12.0	< 1 second

(c) The acidity profile of the rate of nitrosation of phenol and anisole are markedly different, as shown earlier in FIGURE (4.4). In particular, the observed rate of nitrosation of anisole in acidities greater than 10M.$HClO_4$ is faster than the corresponding rate for the reaction of phenol with nitrous acid.

These arguments exclude any reaction path in which anisole is converted to phenol prior to reaction with nitrous acid. The evidence is consistent, however, with the formation of para nitrosoanisole, which then hydrolyses extremely rapidly to para nitrosophenol.

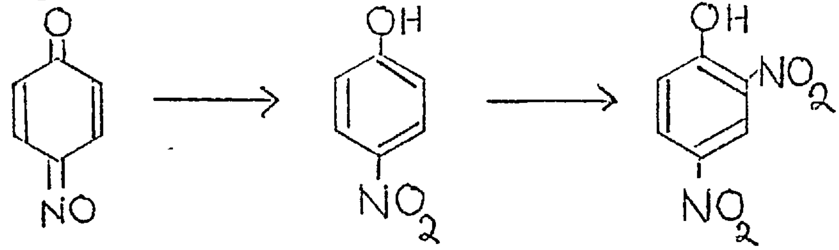
(iii) Nitrosation of Diphenylether.

The following observations were made in connection with the reaction between diphenylether and nitrous acid in 10.4M.$HClO_4$, at 52.9°C.

(a) A solution of diphenylether in 10.4M.$HClO_4$ left overnight at 52.9°C. showed no detectable hydrolysis to phenol on examination of the solution ultraviolet spectrum.

(b) When the initial concentration of diphenylether was in excess of the initial stoicheiometric nitrous acid, the sole product formed was para nitrosophenol, identified by its ultraviolet spectrum, and observed to correspond to greater than 95% reaction based on the initial nitrous acid.

(c) When the initial nitrous acid was in excess over the diphenylether, the ultimate product, against identified by ultraviolet spectral analysis, were established to be 2,4-dinitrophenol. The reaction sequence must be :-



since para nitrosophenol and para nitrophenol were also detected spectrally as transient intermediates. The final concentration of dinitrophenol corresponded to two mols. produced per mol. of initial diphenylether.

Also, treatment of a solution of an authentic sample of para nitrosophenol under the same conditions of acidity, nitrous acid concentration, and temperature, yielded 2,4-dinitrophenol, one mol. being produced per mol. of initial para nitrosophenol.

(d) The nitrosation was carried out under the following conditions :- Run 266.

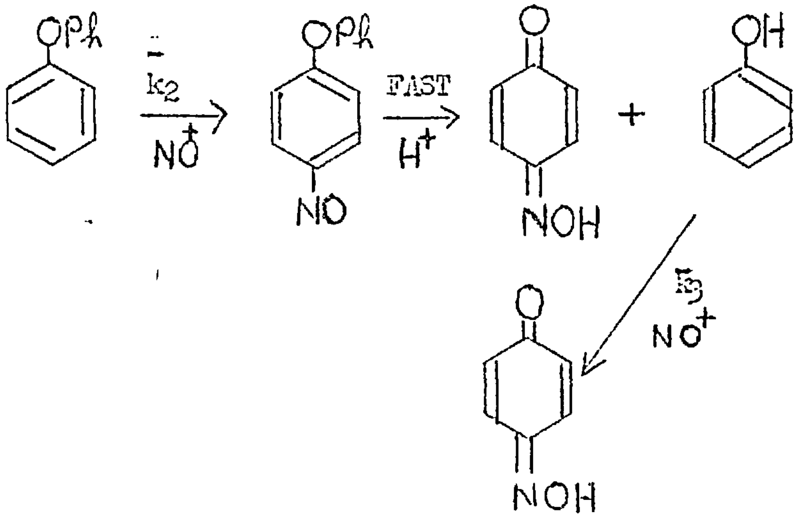
Temperature = 52.9°C. ($HClO_4$) = 10.4M.

(diphenylether) = $1.0.10^{-3}$ M.

(HNO_2) = $1.0.10^{-4}$M.

After fifteen minutes, approximately one half-life of reaction, a sample (5 mls.) of the reaction solution was run into cooled 4M NaOH (15 mls.). The basic solution was extracted with diethyl ether (10 mls.) to remove unreacted diphenylether. The ultraviolet spectrum of the alkaline aqueous layer showed the presence of a new band at 2550 Å (O.D. = 0.092), in addition to that expected for the product para nitrosophenol. Other samples taken after approximately 3 and 10 half-lives gave a similar absorption (O.D. = 0.092) for the band at 2350 Å. Assuming this absorption corresponds to that expected for phenol[93], (λ = 2350 Å, log ϵ = 4.04), the concentration of phenol produced during nitrosation under these conditions would be $3.4\ 10^{-5}$M.

One possible reaction scheme consistent with these observations is shown below, also above, in Chapter V.



Because of the high substrate concentrations of Run 266, the consumption of nitrous acid follows a first order rate law, equation (7.11).

$$-\frac{d\,(HNO_2)}{dt} = k_{obs}.(HNO_2) \qquad --- (7.11).$$

This will be equal, of course, to the sum of the reaction of both diphenyl ether and phenol with nitrous acid, expressed by equation (7.12).

$$-\frac{d(\mathrm{HNO_2})}{dt} = \bar{k}_2(\text{diphenyl ether}).(\mathrm{HNO_2}) + \bar{k}_3(\text{phenol}).(\mathrm{HNO_2}) \quad \text{---} \quad (7.12).$$

From equation (7.11) and (7.12) :-

$$\bar{k}_2.(\text{diphenylether}) + \bar{k}_3.(\text{phenol}) = k_{(\text{obs})} \quad \text{---} \quad (7.13).$$

Under the conditions of Run 266, the value of $\bar{k}_3$, determined independently, is greater than $k_{(\text{obs})}/(\text{diphenylether})$ by a factor of more than ten, as shown in TABLE (7.9). Hence $\bar{k}_3$ must obviously be greater than $\bar{k}_2$ by at least this factor.

TABLE (7.9).

Nitrosation of Phenol and diphenylether at 52.9°C.

Run	$(\mathrm{HClO_4})$ (M.)	$\bar{k}_3$ l.moles^{-1} min^{-1}	$k_{\text{obs}}/(\text{diphenylether})$ l.moles^{-1} min^{-1}.
299	10.4	655.0	-
266	10.4	-	57.6

This implies that the concentration of phenol under these conditions will be maintained at a low, approximately constant value, throughout reaction. Applying the steady state approximation to this reaction therefore, :-

$$+\ \frac{d(\text{phenol})}{dt} \quad = \quad -\ \frac{d(\text{phenol})}{dt}$$

$$\bar{k}_2.(\text{diphenylether}).(\text{HNO}_2) \quad = \quad \bar{k}_3.(\text{phenol}).(\text{HNO}_2) \qquad \text{---}\ (7.14).$$

$$(\text{phenol}) \quad = \quad \bar{k}_2/\bar{k}_3.(\text{diphenylether}) \qquad \text{---}\ (7.15).$$

From equation (7.15) and (7.13), :-

$$k_{obs} \quad = \quad 2\bar{k}_2.(\text{diphenylether}). \qquad \text{---}\ (7.16).$$

Thus for Run 266, $\bar{k}_2$ was calculated to be 28.8 $1.\text{mols}^{-1}\ \text{min}^{-1}$. Substituting the appropriate values of $\bar{k}_2$, $\bar{k}_3$ and (diphenylether) into equation (7.15), we may derive for the stated conditions of Run 266 :-

$$(\text{phenol}) \quad = \quad \frac{28.8}{655.0}\ .\ (10^{-3})$$

$$= \quad 4.3\ 10^{-5}\ \text{mol}.1^{-1}. \qquad \text{---}\ (7.17).$$

This is close to the experimentally observed value, mentioned above, ($3.4\ 10^{-5}\text{mol}.1^{-1}$) and illustrates the consistency of the observed results with the reaction scheme proposed, and offers justification for the kinetic approximation employed in the analysis of the experimental results.

(iv) Nitrosation of Toluene.

Toluene reacts at a measurable rate with nitrous acid in concentrated perchloric acid at 32.9°C, to produce a deep green coloured solution. The details of the ultraviolet absorption spectrum of this product are recorded in TABLE (7.10), the extinction coefficients values being only approximate, since they are based on the amount of nitrous acid consumed in reaction.

TABLE (7.10).

Absorption spectrum of product of Nitrosation of Toluene in aq. $HClO_4$.

$(HClO_4)$ (M.)	λ (Å)	log. ϵ.	λ (Å)	log. ϵ.
10.4	255	4.15	454	4.25
1.0	255	4.15	454	4.25

Identification of the product by the usual methods was not successful, since insufficient quantities were isolated. However, incidental evidence, summarised below, suggests that the product results from condensation of *para* nitrosotoluene with toluene itself.

Neither reaction between authentic *ortho* nitrosotoluene and either toluene nitrous acid or *para* nitrosotoluene, nor reaction between *para* nitrosotoluene and nitrous acid, produced (on the basis of the ultraviolet spectrum) the product observed in the toluene nitrosation. The required ultraviolet spectrum could be produced, however, by introducing a very dilute solution of *para* nitrosotoluene into a stirred solution of toluene in perchloric acid at 52.9°C. No nitrous acid is required for the conversion to the unknown product. With the rate of addition of *para* nitrosotoluene as low as 2.10^{-9} mols.min^{-1}, into a stirred volume of 20 mls. of 10^{-2}M. toluene in 10.4M.$HClO_4$, the extinction coefficient of the product at all wavelengths (based on the amount of *para* nitrosotoluene introduced) tallies with the values quoted in TABLE (7.10), which were calculated on the consumption of nitrous acid in the nitrosation reaction.

Thus it is likely that nitrosation of toluene results in the formation of the *para* isomer exclusively, but this reacts with further toluene under the kinetic conditions to produce a new unidentified product with no further uptake of nitrous acid. This course of reaction cannot be duplicated with a more concentrated solution of *para* nitrosotoluene, however, since higher concentrations of nitrosotoluene encourage another path[94], which is presumably second order in nitrosotoluene, since it involves a condensation of two molecules to form substituted hydroxylamines.

The nature of this unknown product is not pertinent to the present study, once it has been established that there is fast subsequent reaction not involving nitrous acid.

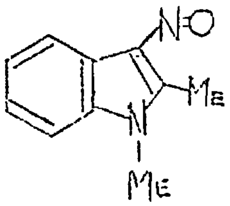
(V). Nitrosation of Benzene.

The reaction of benzene with nitrous acid in concentrated

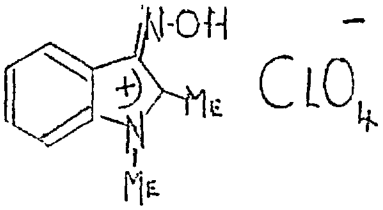
$HClO_4$ at 52.9°C results in the formation of nitrobenzene. This has been established by comparison of ultraviolet spectra of the product of reaction and of authentic nitrobenzene in both aqueous and organic solvents. Also, a comparative thin layer chromatography demonstrated that nitrobenzene was the sole detectable product. A solution of authentic nitrosobenzene in $HClO_4$, under the kinetic conditions of temperature and acidity, was observed to yield nitrobenzene after twelve hours, in the absence of either nitrous acid or benzene.

(VI). Nitrosation of 1,2-dimethylindole.

The ultraviolet spectrum of an authentic sample of (XI) in aqueous solution is recorded in TABLE (7.11). The pH dependent spectral change was observed to be fully reversible, indicating a protonation equilibrium and identifying the product followed in individual kinetic runs as the compound (XII).



(XI).



(XII).

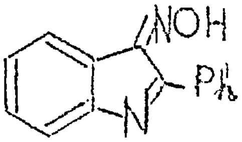
TABLE (7.11).

Absorption Spectra of 1,2-dimethyl-3-nitrosoindole.

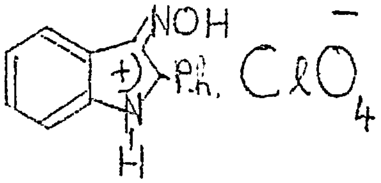
	$(HClO_4)$ (M.)	λ_{max} (Å)	log ε	λ_{max} (Å)	log ε	λ_{max} (Å)	log ε
Authentic	10^{-8}	2500	4.12	2850	4.06	3630	4.21
Sample	10^{-4}	2500	4.18	2670	4.18	3450	3.77
	1.0	2500	4.18	2670	4.18	3450	3.77
Kinetic	6.0	2500	4.18	2670	4.18	3450	3.77
Product	10^{-3}	2500	4.18	2670	4.18	3450	3.77

(VII). Nitrosation of 2-phenylindole.

The ultraviolet spectrum of an authentic sample of (XIII) in aqueous solution is recorded in TABLE (7.12). The pH dependent spectral change was observed to be fully reversible, indicating a similar acid/base equilibrium to that for 1,2-dimethylindole and identifying the product of nitrosation of 2-phenylindole, under the conditions of the kinetic study, as the compound (XIV).



(XIII).



(XIV).

K2

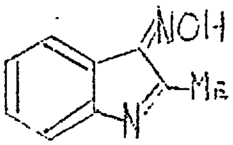
TABLE (7.12).

Absorption Spectra of 2-phenyl-3-nitrosoindole.

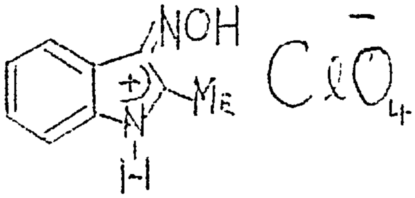
	$(HClO_4)$ (M.)	λ_{max} (Å)	log. ϵ
Authentic	10^{-8}	2460	4.58
Sample	10^{-3}	2720	4.49
	2.0	2720	4.49
Kinetic	10^{-2}	2720	4.49
Product	10^{-1}	2720	4.49

(VIII). Nitrosation of 2-methylindole.

The ultraviolet spectrum of the compound (XV) in aqueous solution is recorded in TABLE (7.13). The pH dependent spectral change is fully reversible, and the product of the nitrosation reaction under the experimental conditions of kinetic study is therefore identified as (XVI)



(XV).



(XVI).

TABLE (7.13).

Absorption spectra of 2-methyl-3-nitrosoindole.

	$(HClO_4)$ (M.)	λ_{max} (Å)	log.ε	λ_{max} (Å)	log.ε	λ_{max} (Å)	log.ε
Authentic Sample	10^{-8}	2480	4.23	2770	3.77	3580	3.80
	10^{-2}	2490	4.21	2630	4.17	3470	3.76
	4.4	2490	4.21	2630	4.17	3470	3.76
Kinetic Product	10^{-3}	2490	4.21	2630	4.17	3470	3.76
	2.6	2490	4.21	2630	4.17	3470	3.76

(IX). Nitrosation of the Other Indoles Studied.

The corresponding 3-nitroso derivatives of 2-methyl-5-nitroindole, 1-methyl-5-nitroindole, 5-cyanoindole, and 5-nitroindole could not be isolated in a pure state, despite repeated attempts. In dilute solution, however, the nitrosation reactions were observed to be uncomplicated by further reaction, as shown by the detection of good isosbestic points in the spectral analysis of the reaction, prior to undertaking kinetic measurements. By analogy with the more basic indoles, above, and with studies of other electrophilic substitution of the indole nucleus, it was assumed that nitrosation results in each case in a product substituted at the 3-position. These nitroso products would be less basic than those derived from the indoles already described, and probably exist in the kinetic solutions in their free base forms, which can undergo further coupling and polymerization reaction on attempted isolation.

The observation of a primary isotope effect as discussed in Chapter III, in the nitrosation of 5-cyanoindole labelled specifically at position 3, also suggests that nitrosation proceeds at the 3-position even for the deactivated indoles, irrespective of the stability of the ensuing nitroso compound.

(X). Nitrosation of 1,3,5-trimethoxybenzene.

The product of nitrosation of 1,3,5-trimethoxybenzene is assumed to be 3,5-dimethoxy-4-nitrosophenol, by analogy with similar studies on other aromatic ethers[95].

(D). PREPARATION AND PURIFICATION OF MATERIALS.

(i) SUBSTRATES

'Analar' grade phenol was fractionally distilled under reduced pressure, and was dried over P_2O_5 in a vacuum desiccator. F.P. 40.5°C. (lit.[96] 40.5°– 41.5°C.)

Reagent grade anisole was shaken with 4.0M. aqueous sodium hydroxide to remove traces of phenolic impurities, washed with water, separated and dried over anhydrous calcium sulphate, prior to fractional distillation under reduced pressure. $n_D^{20} = 1.5172$ (lit.[97] n_D^{20} 1.5179).

'Analar' benzene and toluene were fractionally distilled, large initial and final fractions being discarded.

Benzene $n_D^{20} = 1.5008$ (lit.[98] n_D^{20} 1.5011)

Toluene $n_D^{20} = 1.4955$ (lit.[99] n_D^{20} 1.4961).

Reagent grade 2-phenylindole was crystallized from glacial acetic acid, washed with water, dried in a vacuum desiccator, and sublimed to constant melting point. M.P. = 190°C. (lit.[100] 189^{0}0) The white, crystalline compound was kept under oxygen-free nitrogen, in the dark.

2-Methylindole, 1,2-dimethylindole, 5-nitroindole, 2-methyl-5-nitroindole and 5-cyanoindole were supplied by the Aldrich Chemical Company, and were sublimed under reduced pressure and dried in a vacuum desiccator prior to storage under nitrogen in the absence of light. All indoles were resublimed immediately before use, and aqueous stock solutions of the indoles were kept under nitrogen. Solutions of longer than three days standing were discarded.

Indole	1,2-dimethyl;	2-methyl;	2-methyl-5-nitro;	5-nitro;	5-cyano
M.P. (°C)	55	61	175	142	106
Lit. (°C)	55[101]	61[102]	175-6[103]	141[104]	107[105]

Reagent grade diphenylether was shaken with aqueous sodium hydroxide (3.0M), then washed well with water. Recrystallization from ethanol yielded white leaflets, M.P. 27.5°C. (lit.[106] = 27.5°C).

Phenol-4-(^{2}H) was prepared by an adaption of the procedure of Gilman[107]. This involved the addition of deuterium oxide to an ethereal solution the lithium complex prepared from *para* bromophenol and n-butyllithium. F.P. 39.5°C (lit.[96] 40.5° - 41.5°C for phenol).

The product was 86% pure with respect to the isotopic label in the *para* position, as determined by mass spectrometry, infrared spectroscopy, and N.M.R. analysis.

2,4,6-trideuteriophenol was prepared by the method of Gold and Wilson[108]. F.P. 39.5°C.

Anisole-4-(^{2}H) was kindly prepared by Mr. R. Iqbal from *para* bromoanisole by a grignard reaction. The product was 95% with respect to the isotopic label, as determined by mass spectrometry.

(n_D^{20} = 1.5180 lt.[97] value = 1.5179).

1-Methyl-5-nitroindole is a new compound. This was prepared by a similar method to that used for the preparation of other[109] 5-nitroindoles, and was purified by steam distillation, followed by recrystallisation from ligroin. M.P. 169°C. The assignment of the nitrogroup to the five position is substantiated by inspection of the N.M.R. spectrum.

Elemental analysis is recorded below.

	C %	H %	N %
Found	61.3	4.52	15.79
$C_9H_8N_2O_2$ requires	61.4	4.54	15.91

(ii) THE PREPARATION OF SOME PRODUCTS OF REACTIONS.

3-Nitroso-2-methylindole, and 3-nitroso-2-phenylindole were prepared by reaction of sodium nitrite on the appropriate indole in solvent glacial acetic acid at 0°C. 2-methyl-3-nitrosoindole was purified by successive vacuum sublimation. M.P. **198° (lit. 198-9° [110])** 3-nitroso-2-phenylindole was purified by washing the crude solid with hot ethanol, to leave a yellow amorphous solid M.P. 282°C. (lit.[111] 280°C).

1,2-Dimethyl-3-nitrosoindole was prepared in the following way: 1,2-dimethylindole (0.24 g., 1.68 m.mole) was dissolved in 50 mls. of 10.0M $HClO_4$, and the solution cooled to 0°C. An aqueous solution of sodium nitrite (0.12 g, 1.75 m.mole dissolved in 5 ml. H_2O) was added dropwise to the stirred, cooled, acid solution over a period of five minutes. The solution was stirred at 0°C for a further ten minutes, then poured into 200 mls. of water. The acidic solution was neutralized to pH. 8.0 by the addition of solid sodium bicarbonate, and extracted with ether, which was then dried, and the ether removed. The dark brown solid was sublimed under vacuum (100°C, 0.1 mm. Hg.) to yield a small amount of green crystalline 1,2-dimethyl-3-nitrosoindole. Thin layer chromatography failed to detect the presence of impurities. (M.P. 156-158°C, dec.). Yield 0.015 g., 5%.

Elemental analysis is recorded below.

	C %	H %	N %
Found	68.95	5.82	15.76
$C_{10}H_{10}N_2O$ requires	68.90	5.75	16.06

para nitrosoanisole[112], *para nitrosotoluene*, and *ortho nitrosotoluene*[113] were prepared by existing methods.

(iii) OTHER REAGENTS

'Analar' *sodium nitrite*, and *sodium chloride* were dried in a vacuum desiccator and used without further purification.

Both *perchloric* and *sulphuric* acids were B.D.H. 'Analar' reagents, and were used without further purification. Solutions were prepared by dilution with distilled water and the concentration of acid in each kinetic run was checked by titration with B.D.H. standard alkali solutions.

Deuteriosulphuric acid (D_2SO_4) was prepared by distilling freshly prepared, purified sulphur trioxide into deuterium oxide after the method described by Challis[114].

Deuterium oxide (99.7% deuteriated) was Koch-Light 'puriss' grade, carefully redistilled from a few crystals of potassium permanganate, and the conductivity of the distillate checked.

All other reagents used were of the best available grade.

BIBLIOGRAPHY

(1) P.B.D. De La Mare and J.H. Ridd, "Aromatic Substitution", (Butterworths.) (1959).

(2) R.O.C. Norman and R. Taylor, "Electrophilic Substitution in Benzenoid Compounds", (Elsevier), (1965).

(3) E. Berliner, "Progress in Physical Organic Chemistry", (Interscience), Vol. 2. 253 (1964).

(4) Idem. 306.

(5) Idem. 282-285.

(6) cf. P.B.D. De La Mare and J.H. Ridd, "Aromatic Substitution", Chapter 5, (1959).

(7) A.D. Ketley, P.B.D. De La Mare and C.A. Vernon, J. Chem. Soc., (1954) 1290.

(8) R.P. Bell and E. Gelles, J. Chem. Soc., (1951) 2734.

(9) J. Arotsky and M.C.R. Symons, Quart. Rev. (London), 16, (1962) 282.

(10) P.B.D. De La Mare and I.C. Hilton, J. Chem. Soc., (1962) 997.

(11) E. Grovenstein and D.C. Kilby, J. Amer. Chem. Soc., (1957) 79, 2792.

(12) C.R. de Fabrizio, Ann. Chim. (Rome)., 58, (12) 1435 (1968).

(13) E. Grovenstein and N.S. Aprahamian, J. Amer. Chem. Soc., 84 (1962) 212.

(14) K. Singer and P.A. Vamplew, J. Chem. Soc. (1956) 3971.

(15) Idem.

(16) N.C. Deno, H.E. Berkheimer, W.L. Evans and H.J. Peterson, J. Amer. Chem. Soc., 1959, 81 2344.

(17) Idem.

(18) J.H. Ridd, Quart. Rev., 15, 418 (1961).

(19) N.S. Bayliss and D.W. Watts, Austral. J. Chem., 9, 319, 1956.

(20) B.C. Challis and J.H. Ridd, Proc. Chem. Soc., 1961, 173.

(21) B.C. Challis and J.H. Ridd, Proc. Chem. Soc., 1960, 245.

(22) T.D.B. Morgan, G. Stedman and M.N. Hughes, J. Chem. Soc., (B) 1968, 344.

(23) H. Ladenheim and M.L. Bender, J. Amer. Chem. Soc., 1960 82 1895.

(24) M.N. Hughes and G. Stedman, J. Chem. Soc., 1964, 5840.

(25) B.C. Challis, and J.A. Challis, "Chemistry of the Carboxamide Group", (Ed. Zabicky) Wiley, 1970.

(26) C.A. Bunton, D.R. Llewellyn and G. Stedman, J. Chem. Soc., 1959, 568.

(27) E.D. Hughes, C.K. Ingold and J.H. Ridd, J. Chem. Soc., (1958) 65.

(28) J.M. Tedder, J. Chem. Soc., (1957) 4003.

(29) T. Suzawa, Z. Yasuoka, O. Manabe and H. Hiyama, Sci. and Ind., (Japan), 29, 7, 1955.

(30) H.H. Hodgson and E.A.C. Crouch., J. Chem. Soc., (1943) 221 and Preceding Papers.

(31) L. Blongcy, Helv. Chim. Acta., (1938) 21, 1579.

(32) F. Piozzi and M. Dubini, Gazz. Chim. Ital., 89, 638 (1959).

(33) T. Ajello, Ibid., 69, 646 (1939).

(34) cf. R.O.C. Norman and R. Taylor, "Electrophilic Substitution in Benzenoid Compounds", Chapter 3.

(35) E.L. Blackhall, E.D. Hughes and C.K. Ingold, J. Chem. Soc., 1952, 28.

(36) D.A. Morrison and T.A. Turney, J. Chem. Soc., 1960, 4827.

(37) H. Schmid, G. Muhr and P. Riedl, Monatsh. Chemie., 97 (3), 781 (1966).

(38) K.M. Ibne-Rasa, J. Amer. Chem. Soc., 84, 4962, 1962.

(39) S. Veibel, Chem. Ber., 63B, 1577, 1930.

(40) cf. E.D. Hughes, C.K. Ingold and J.H. Ridd, J. Chem. Soc., (1958) 95.

(41) Idem. 61.

(42) G. Stedman, J. Chem. Soc., (1959) 2949.

(44) cf. B.C. Challis, Thesis, Univ. of London, (1960).

(45) cf. R.O.C. Norman and R. Taylor, "Electrophilic Substitution in Benzenoid Compounds", 63.

(46) F. Long and M.A. Paul, Chem. Rev., (1957).

(47) P. Debye, Trans. Electrochem. Soc., 82, 265 (1942).

(48) cf. S.W. Benson, "The Foundations of Chemical Kinetics", McGraw-Hill Co., (1960) P. 497.

(49) cf. H. Schmid and Eggler, Monatsh, 88, 1110, 1957.

(50) cf. E.F. Caldin, "Fast Reactions in Solution", Blackwell, 1964.

(51) cf. E.S. Gould, "Mechanism and Structure in Organic Chemistry", P. 220.

(52) H.C. Brown and Y. Okamoto, J. Amer. Chem. Soc., 79, 1913 (1957).

(53) cf. J.E. Leffler and E. Grunwald, "Rates and Equilibria of Organic Reactions", (Wiley) 1963.

(54) P.B.D. De La Mare and J.T. Harvey, J. Chem. Soc., 1956, 36.

(55) cf. E. Berliner, "Progress in Physical Organic Chemistry", (Interscience), Vol. 2., 306, 1964.

(56) R. Iqbal, Personal Communication.

(57) cf. A.R. Katrizky, "Heterocyclic Chemistry", Methuen, 1960.

(58) R.L. Hinman and J. Lang, J. Amer. Chem. Soc., 86, 3796 (1964).

(59) cf. W.J. Moore, "Physical Chemistry", (Longmans) 542.

(60) E.D. Hughes, C.K. Ingold and J.H. Ridd, Nature, 1950 166 642.

(61) E.D. Hughes, C.K. Ingold and J.R. Ridd, J. Chem. Soc., 1958, 65.

(62) Idem. 59.

(63) cf. L. Melander, "Isotope Effects on Reaction Rates", 125 (1960) Ronald.

(64) B.C. Challis, Thesis, Univ. of London (1960).

(65) E.M. Millar, Thesis, Univ. of St. Andrews, (1969).

(66) J.H. Ridd, Quart. Rev., 15 432 (1961).

(67) H. Schmid and I. Fouad, Monatsh, 88, 631, 1957.

(68) H. Schmid and A. Maschka, Z. Physik. Chemie., B49 (1941) 171.

(69) E.M. Millar, Thesis, Univ. of St. Andrews (1969).

(70) E.M. Millar, Thesis, Univ. of St. Andrews (1969).

(71) E. Kalatzis and J.H. Ridd, J. Chem. Soc., 1966 B., 529.

(72) B.C. Challis, P. 69, Thesis, Univ. of London (1960).

(73) E.D. Hughes and J.H. Ridd, J. Chem. Soc., (1958) 82.

(74) H.A.J. Schoatissen, Rec. Trav. Chim., 40, 753 (1921).

(75) C.R. De Fabrizio, Thesis, Univ. of London.

(76) cf. J.H. Ridd, Quart. Rev., 15, 429 (1961).

(77) E.M. Millar, Thesis, Univ. of St. Andrews (1969).

(78) E. Kalatzis, J. Chem. Soc., (B) 1967, 277.

(79) N.S. Bayliss and D.W. Watts, Austral. J. Chem., 16, 927 (1963).

(80) J.E. Leffler and E. Grunwald, "Rates and Equilibria", (Wiley, 1963) P.204.

(81) E. Hogfeldt and J. Bigeleisen, J. Amer. Chem. Soc., 82, 15 (1960).

(82) B.C. Challis, P.57, Thesis, Univ. of London (1960).

(83) R.G. Coombes, R.B. Moodie and K. Schofield, J. Chem. Soc., (B), 1968, 800.

(84) J.G. Hoggett, R.B. Moodie and K. Schofield, J. Chem. Soc., (B), 1969 1.

(85) Angus and Leckie, Proc. Roy. Soc., 1935, A, 150, 615.

(86) B.C. Challis, Thesis, Univ. of London (1960).

(87) M.B. Shinn, Ind. Eng. Chem. (Anal. Ed.), 13, 33 (1941).

(88) Idem. 14, 312 (1942).

(89) B.C. Challis, Thesis, Univ. of London (1960).

(90) S. Veibel, Ber., 63(B), 1577, 1930.

(91) Organic Electronic Spectral Data. Vol 1. 78.

(92) A. Bayer and E. Knorr, Ber., 35, 3035.

(93) E.F.G. Herrington, and W. Kynaston, Trans. Faraday Soc., 53, 138 (1957).

(94) E. Bamberger and W. Ham, Ann., 382, 82.

(95) H.H. Hodgson and H. Clay, J. Chem. Soc., 1930, 1872.

(96) Dictionary of Organic Compounds.

(97) 47th "Handbook of Chemistry and Physics", C-168.

(98) Ibid C-146.

(99) Ibid C-571.

(100) W.E. Noland, K.R. Rush and L.R. Smith, J. Org. Chem., 31, 65 (1966).

(101) B.L. Van Duuren, J. Org. Chem., 26, 2954 (1961).

(102) 47th "Handbook of Chemistry and Physics", C-376.

(103) W.E. Noland, L.R. Smith and D.C. Johnson, J. Org. Chem., 28, 2262 (1963).

(104) J. Thesing, G. Semler and G. Mohr, Chem. Ber., 95, 2205 (1962).

(105) Idem.

(106) 47th "Handbook of Chemistry and Physics", C-317.

(107) H. Gilman and C.E. Arntzen, J. Amer. Chem. Soc., 69, 1537 (1947).

(108) C.K. Ingold, C.G. Raisin and C.L. Wilson, J. Chem. Soc., (1936) 1637.

(109) W.E. Noland, L.R. Smith and K.R. Rush, J. Org. Chem., 30, 3457, 1965.

(110) Idem.

(111) W.E. Noland, K.R. Rush and L.R. Smith, J. Org. Chem., 31, 65, 1966.

(112) A. Bayer and E. Knorr, Ber., 35, 3035.

(113) W.J. Mijs, E. Hoekstra, R.M. Ulmann and E. Havinga, Rec. Trav. Chim., 77, 746 (1958).

(114) B.C. Challis, P.183. Thesis, Univ. of London (1960).