THE MECHANISM OF AROMATIC NITROSATION AND RELATED REACTIONS.

by

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ABSTRACT.

The mechanistic aspects of certain electrophilic aromatic substitution reactions are reviewed, with particular regard to aromatic C-nitrosation. The kinetic principles of the investigation are then outlined.

An account of the nitrosation of azulene and 1-nitro--azulene in dilute aqueous acid is presented, in which nitrosyl chloride and the nitrousacidium ion are identified as active electrophiles. An A-S_E2 mechanism is proposed in which proton loss from the Wheland intermediate is rate-limiting for nitro--azulene, but for azulene the reaction is diffusion controlled.

An investigation of the o-nitrosation of a series of p-substituted phenols by the nitrosonium ion in aqueous perchloric acid is reported, which proceeds in an A-S_E2 mechanism *via* the formation of a dienone intermediate. A low ρ value of -6.2 obtained for the reaction reflects the sensitivity of the rate limiting step, which is proton loss from the intermediate, to electron supply.

A large primary deuterium isotope effect is reported for the nitrosation of benzene in concentrated sulphuric acid, which confirms that rate-limiting proton loss is characteristic of

C-nitrosation at high acidity, and is not related to the acidity of the leaving proton. Catalysis of the nitrosation of phenol and benzene by the anions of strong polybasic acids in concentrated solutions is reported as a further consequence of rate limiting proton transfer in these reactions.

An account of the nitrosation of phenol and 2-naphthol in very dilute acidic media is presented and conclusive evidence is reported for an A-S_E2 mechanism in which the rate-determining step can be either the formation of, or proton loss from, a steady state neutral dienone intermediate, the major deciding factor being the acidity of the medium. Thus the first 'fast' proton transfer for an aromatic C-nitrosation is reported.

Nitrosation in dilute aqueous buffer solutions is reported to be subject to only moderate intramolecular base catalysis in phenolic compounds with acetate and carboxylate functions neighbouring the site of substitution.

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PART I.

INTRODUCTION.

CHAPTER I.

THE HISTORICAL SURVEY.

(A). Electrophilic Aromatic Substitution.

Few organic processes have attracted more attention and interest than that of electrophilic aromatic substitution. In one direction they form the basis of a diverse and important chemical industry, and, in another, the investigation of their mechanism was a historical, yet continuing, factor in the development of electronic theories of organic chemistry. These reactions have been widely reviewed, but for general aspects reference is drawn to monographs by De la Mare and Ridd[1] and by Taylor and his colleagues[2,3]. No comprehensive coverage of even the recent literature is given in this introduction, but attention is focussed on mechanistic aspects, such as factors affecting the rate-determining step and the nature of the intermediates, that were emphasised in 1964 by the reviews of Zollinger[4] and Berliner[5]. The overall substitution process, for the general replacement of hydrogen, can be represented as a two stage process (equ.(1.1)), where ArH represents the aromatic substrate, E^+

an electron deficient reagent and $ArHE^+$ an intermediate.

$$ArH + E^+ \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} ArHE^+$$

$$ArHE^+ + B \xrightarrow{k_2} ArE + BH^+ \quad \ldots\ldots(1.1).$$

The process may be further complicated by preequilibrium formation of E^+. The mechanism described by equ.(1.1) is termed an S_E-2 process and, where acid catalysis is involved in generating the electrophile E^+ , an A-S_E2 process. This is believed to be the usual mechanism for aromatic substitution and no examples of an alternative S_E-3 mechanism, (equ.(1.2)), have been discovered.

$$ArH + E \xrightarrow{k_1} (E...Ar..H..B) \xrightarrow{k_2} ArE + BH^+ \quad ..(1.2).$$

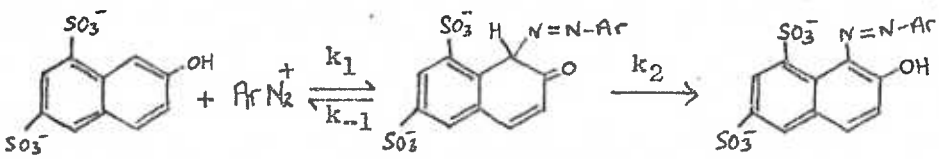
For the S_E-2 type mechanism, the observed overall rate for the reaction will be given by equ.(1.3), if the intermediate is assumed to be formed in small stationary concentrations . It

$$\text{Rate} = \frac{k_1 k_2 / k_{-1} \cdot [ArH][E^+][B]}{1 + k_2/k_{-1} \cdot [B]} \quad \ldots (1.3).$$

follows that if the intermediate returns more readily to reactants than to products (i.e. $k_{-1} \gg k_2$), the observed rate will be given by $k_1 k_2 / k_{-1} \cdot [ArH][E^+][B]$. Since this expression depends on k_2, the reaction will show a primary hydrogen isotope effect ($k_H/k_D > 1$) if deuteriated substrates are used : also the observed rate will depend on the base concentration, which will be linear

if $k_2[B]/k_{-1} \ll 1$. In contrast, if $k_2[B] \gg k_{-1}$, then the observed rate will be given by $k_1.[ArH][E^+]$ i.e. it is dependant on the first step only and no primary deuterium isotope effect or base catalysis will be observed. The validity of equ.(1.3) has been widely established , and several factors have been shown to influence the rates of the two steps of the S_E-2 mechanism.

Zollinger[6,7] was the first to show, from experiments of azo coupling, that structural effects in the intermediate were important in determining the rate-limiting step. Steric hindrance in the intermediate was shown to produce a primary deuterium isotope effect, as, for example, in the coupling of G-salt in the one position, and explained originally as arising from an



. . (1.4).

increase in the k_{-1} step (equ.(1.4)) . The acidifying effect of a range of electrophiles on the leaving proton was also observed to influence the magnitude of the primary deuterium isotope effect in azo coupling, the k_H/k_D ratioϕ decreasing with increasing acidity of the leaving proton. Catalysis of these reactions by base followed the non-linear dependance of equ.(1.3) and the primary deuterium isotope effect decreased with increasing base

concentration. Bulky bases were apparently less effective catalysts, indicating that steric effects were also important in the second step of equ.(1.1). More recent investigations by Snyckers and Zollinger[8] suggest this factor may have been previously underestimated : they have concluded that steric hindrance does not in fact accelerate k_{-1}, but inhibits the substitution reaction through steric effects operating in the second, k_2 step. They proposed a preffered asymmetric conformation of the σ -complex in the substitution of 8-substituted,2-naphthoate anions by the electrophile E, as illustrated in FIG.(1.1). The pseudo-axial

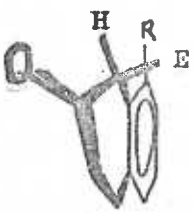
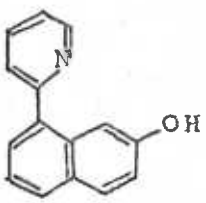


FIG.(1.1).

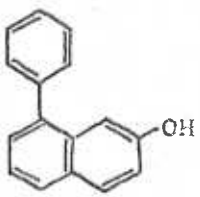
position of the electrophile decreases the steric interaction between this group and the peri-substituent, whilst the swinging into the aromatic plane of E in the second, proton removal,step is greatly hindered.

Studies of azo coupling also gave the first example of intra-molecular base catalysis in electrophilic aromatic substitution; the rate of diazonium ion attack at the 2-position of 1-hydroxynaphthalene-3-sulphonic acid was 15x faster than

coupling at the 4-position.[9] This difference was believed to arise from intramolecular base catalysis by the phenolic oxygen of proton loss from the σ-complex in the ortho-coupling reaction. Snyckers and Zollinger have also reported that coupling to 8-(2'-pyridyl)-2-naphthols, I , showed no primary deuterium isotope effect, whereas coupling to the 8-phenyl substituted compound, II , gave $k_H/k_D = 2.6$. This difference was also



I



II

interpreted as evidence of intramolecular base catalysis of the second step of the reaction by the neighbouring pyridyl function which increased k_2 suuficiently to bring about a change in the rate-determining step.

Deductions made from studies of azo coupling reactions have been extended to other kinds of electrophilic aromatic substitution . In most cases, these results are less complete and less convincing. Thus the occurrence of a primary deuterium isotope effect in aromatic sulphonation[10] has been attributed to the low acidity of the leaving proton. Also steric hindrance in

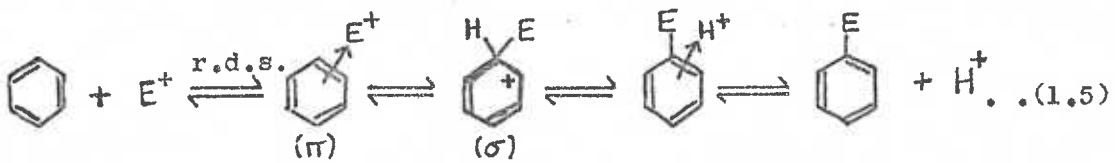
the intermediate , arising from the size of the electrophilic reagent, has been invoked to explain the range of behaviour observed for halogenation reactions. No primary deuterium isotope effect has yet been observed for aromatic chlorination, but is observed in almost every case of iodination[11]. Other factors may be important, however, such as the lower acidifying effect of the iodine electrophile on the leaving proton[12], the greater nucleo--philicity of the iodide anion which should increase k_{-1}[13], and the low strength of the C-I bond[14]. Aromatic bromination has been observed to show a kinetic deuterium isotope effect only in cases involving sterically crowded substrates[15]. There are two reported cases of aromatic nitration occurring with significant primary deuterium isotope effects : for the nitration of anthracene by nitronium tetrafluoroborate[16a] and for the nitration of 1-methyl,2,4,6-tri --tBu-benzene[16b]. The latter was explained in terms of steric repulsion in the intermediate which decreased k_2 with respect to k_{-1}.

Finally, mention should be made of special structural effects that so stabilise the intermediate that its concentration builds up to measurable proportions during the reaction and so violates the steady state equ.(1.2). Since in these cases k_{-1} is extremely small, a primary deuterium isotope effect arises from the rate-determining breakdown of this stable intermediate, as has been

observed in the bromination of G-salt[17] and in some halogenations of phenolic type substrates where the stable quinonoid intermediate was isolable[18].

In addition to the structural features of the intermediate outlined above , the reactivity of the aromatic substrate and especially the substituting entity may be important in determining the nature of the transition state and the timing of the carbon-hydrogen bond breaking in an aromatic substitution reaction. The first quantitative treatment of the importance of electrophilic reactivity in aromatic substitution was made by Brown and Nelson[19]. This led to the well known principles of the reactivity-selectivity relationships. A more theoretical version of the treatment was later independantly derived by Dewar[20]. The principles derived from both were that, in general, a reaction between a powerful electrophile and a highly activated substrate will have an 'early' transition state on the reaction coordinate and will not show a kinetic hydrogen isotope effect. Conversely, the non-reactive but selective reagents should have 'late' transition states (i.e. closely resembling the intermediate) and will be predisposed towards kinetic hydrogen isotope effects. Although these ideas have been generally accepted, little rigorous experimental proof is available.

The significance of π-complex formation in aromatic substitution reactions has often been questioned and raised, most significantly by Olah in the early 1960's[21]. In studies of aromatic substitution reactions involving strongly electrophilic reagents such as preformed nitronium salts in nitration in organic solvents, Olah and coworkers reported low substrate selectivities , but at the same time the normal high positional selectivities. Olah proposed that such reactions involved a rate-determining π-complex formation (determining substrate selectivity) followed by a σ--complex formation (deciding positional selectivity) in a non rate-controlling step, as shown in equ.(1.5). This concept,



.(1.5)

particularly as applied to the mechanism of nitration has been greatly critised[22,23] and the controversy surrounding this hypothesis continues[24,25]. Most recent studies by Ridd and coworkers[26] on the nitration of dibenzyl have strengthened the arguments which dismiss Olah's conclusions on the grounds that the competition method used determine relative reactivities can be misleading as a result of incomplete mixing of reagents. It has been widely suggested that such kinetic methods cannot be used for fast reactions[27].

Independant evidence of the extremely rapid reaction between benzene and nitronium ions has been provided by Coombes, Moodie and Schofield[28,29], who have concluded that the nitration in aqueous sulphuric acid of substrates more reactive than benzene are diffusion controlled . This introduced a new mechanistic criteria for electrophilic aromatic substitution in which the rate-limiting step is formation of a reactant encounter pair, the rate of which is controlled by the viscosity and temperature of the reaction medium . The evidence of a limiting encounter rate for nitration of aromatics in other solvents is less clear-cut, but the results of Schofield and coworkers [30] and Coombes[31] are sufficient to require an interpretation of this kind. Because of the early onset of diffusion control for the nitration reaction of aromatic substrates[32], the interpretations of selectivity - reactivity relationships are subject to great uncertainty.

Despite the shortage of available evidence, there are other examples of cases in which the reactivity-selectivity principles do not appear to predict kinetic observations adequately. The low ρ value of mercuration[33] should imply an early transition state with little C-H bond stretching , whereas in practice a primary deuterium isotope effect is always observed[34]. Similarly,

in comparison with nitration, reactions with low ρ values, such as Friedel-Crafts alkylation and mercuration, might be expected to show a low threshold to encounter control with reactive substrates, but this is not observed. It would appear that structural effects in the intermediate are often large enough, in some reactions, to override the effect of the timing of the transition state on the reaction coordinate and both effects must be fully considered before a complete description of the reaction mechanism can be given.

To summarise, it is evident that many factors are involved in making up a detailed description of the mechanism of any particular electrophilic aromatic substitution reaction and indeed of the nature of the transition state in general. Detailed information is necessary on the relationship between the occurrence of primary deuterium isotope effects and such factors as the electrophilicity of the substituting agent, special structural features in the intermediate, the factors affecting the formation of stationary and non-stationary intermediates and the occurrence of base catalysis. Extension of these investigations to a wider range of electrophilic substitution reactions is needed, Previous investigation has suggested that such information could be

obtained from the study of aromatic nitrosation reactions. These will be reviewed in the next section.

(B). Aromatic C - Nitrosation.

The reaction of nitrous acid with aromatic substrates is usually difficult in the absence of powerfully activating substituents such as -OH, -OR, and $-NR_2$. Often the nitroso product initially formed undergoes further transformation[35] and the nitrous acid is unstable in moderately acidic solutions at elevated temperatures[36]. This combination of adverse factors has limited the applicability of the reactions for synthetic methods and similarly discouraged detailed investigation, with the result that until recently[37], little was known about their mechanism. The only major application of direct nitrosation by nitrous acid has been in the preparation of nitroso-phenols[38,39,40], and nitroso-naphthols[41], and to a lesser extent, of some substituted nitroso-indoles[42,43]. The preparation and chemistry of C-nitroso compounds has been reviewed recently by Boyer[35].

Before discussing the mechanism of aromatic nitrosation, it is relevant to consider the forms of various electrophilic nitrosating agents generated by nitrous acid in aqueous solution. The bulk of this information has come from studies on the diazotisation of amines, and the findings in this field prior

to 1964 have been presented in an excellent review by Butler and Challis[44]. An aqueous acidic solution of nitrous acid can be considered to contain the potential nitrosating species shown in TABLE(1.1), and the predominance of any one agent will be favoured by the conditions shown. All the agents can be

TABLE(1.1).

Reagent	Formula	Conditions.
Nitrous acid	HNO_2	Low acidity, low nitrite concn.
Nitrous anhydride	N_2O_3	Low water activity, high nitrite concn.
Nitrosyl halide	NOCl etc.	High acidity, high halide ion concn.
Nitrousacidium ion	H_2ONO^+	High acidity.
Nitrosonium ion	NO^+	High acidity, low water activity.
Miscellaneous (X = acetate, phthalate, nitrate, or thiocyanate ion)	NO.X	High acidity, high X^- concn.

regarded as carriers of NO^+ and hence can be placed in an expected order of reactivity based on the basic strength of the moiety bound to this ion. This order of rectivity is shown below.

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

The effectiveness of a particular reagent, however, depends on its relative concentration as well as its specific reactivity. Thus the most reactive electrophile, NO^+, is not important at low acidities because its concentration is so low.

Nitrous acid , despite being the major component in dilute acid , is apparently unable to diazotize aromatic amines. However, all three species H_2ONO^+, NOCl and N_2O_3 have been shown conclusively to be active nitrosating agents in the diazotisation of amines at low acidities. At higher acidities , the nature of the effective reagent becomes less clear. Correlation of the rate of reaction with acidity functions, as discussed in Chapter 11, was thought to be a possible way of separating the roles of NO^+ and H_2ONO^+, but this method could not be applied to amine diazotisation at moderate solvent acidities because a new pathway was observed involving reaction of the amine via its conjugate acid[45]. In a study of the nitrosation of benzamide in moderately concentrated H_2SO_4, Ladenheim and Bender[46] assumed the reaction to involve a rate determining attack of the electrophile on the free amide and showed a correlation between the reaction rate and the h_R acidity function. They therefore concluded that the nitrosonium ion was the active nitrosating species. Hughes and Stedman[47],

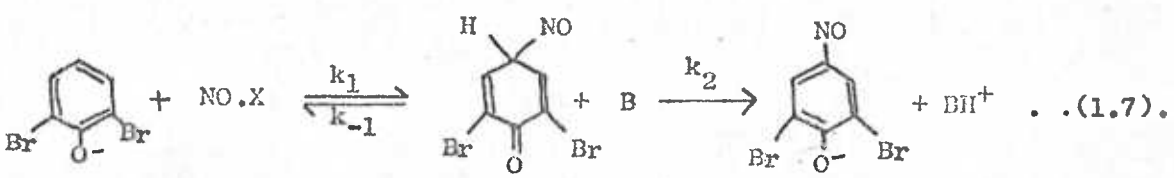
however, from results of studies on acetamide, concluded that the nitrosation of both acetamide and benzamide proceeded by reaction with H_2ONO^+ at moderate acidities. The possibility of an initial nitrosation at the amide oxygen followed by a potentially slow rearrangement of the fragment NO^+ to nitrogen was not considered, although this would alter the significance of the acidity function correlations. It is clear that firm predictions can be made as to the nitrosating agent effective in dilute acids , but not in concentrated acids.

The first detailed kinetic investigation of aromatic nitrosation was reported in 1955 by Suzawa and his coworkers[48]. They established that the nitrosation of phenol in dilute aqueous mineral acid followed equ.(1.6) and concluded that nitrous acid

$$\text{Rate} = \bar{k}_2 [\text{Phenol}][HNO_2] \quad \ldots\ldots (1.6).$$

reacted slowly with molecular phenol. Subsequently, Morrison and Turney[49] studied catalysis by perchloric acid on the same reaction and confirmed the validity of equ.(1.6) with a linear dependance of log $\bar{k}_2$ on the H_o acidity function (at least up to 6M $HClO_4$). This was interpreted to mean that reaction involved H_2ONO^+ rather than NO^+. The same conclusion was later reached by Schmid and his coworkers[50] from a study of the nitrosation of phenol in aqueous-sulphuric acid . Schmid's group also found that, at

constant ionic strength, the rate was independant of the hydrogen ion concentration in the range 10^{-5} to 10^{-1}M. H_2SO_4, which confirms the earlier findings of Suzawa and his colleagues. An interesting point is that all the mechanistic deductions based on these kinetic studies assumed that, in common with many other electro--philic substitutions, the attack of the nitrosating agent on the aromatic substrate was rate-limiting. However, previous to the work of Schmid and his coworkers, Ibne-Rasa[51] found a large primary isotope effect (k_H/k_D = 3.6) and base catalysis for the nitrosation of 2,6-dibromophenol in the 4-position. Accordingly, he proposed reaction <u>via</u> reversible formation of a neutral quinonoid intermediate (equ.(1.7)) from the interaction of either H_2ONO^+ or N_2O_3 with the phenolate anion, with proton loss from

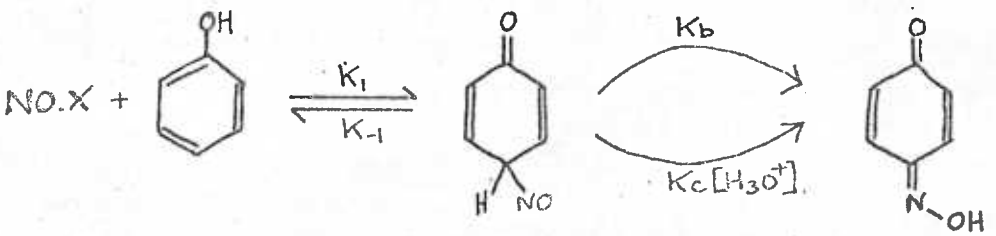


. .(1.7).

from the intermeadiate being rate determining.

In the light of Ibne-Rasa's findings, Challis and Lawson[52] carefully reinvestigated the nitrosation of phenol in aqueous $HClO_4$ from 10^{-3} to 10M and showed that the reaction proceeds with a large primary deuterium isotope effect at both low and high acidities. Since proton-loss from the intermediate is therefore rate-determining, the acidity dependance cannot be

diagnostic for the H_2ONO^+ reagent as previously assumed. They confirmed that the reaction rate was acid independant below 0.1M $HClO_4$ but increased rapidly with increasing acidity , reaching a maximum at about 8M $HClO_4$. These results suggest that the reaction proceeds <u>via</u> the formation of a neutral dienone intermediate (equ.(1.8)), rate determining proton loss from which is either spontaneous (low acidity) or acid catalysed



....(1.8).

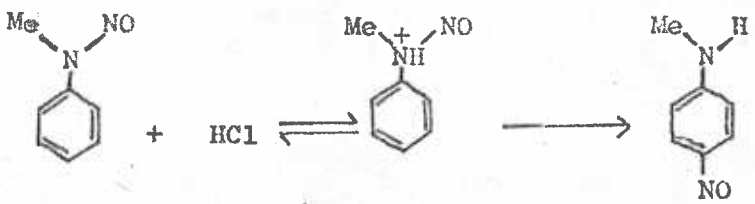
(high acidity), The rate maximum corresponded to the acidity at which nitrous acid is totally converted to the NO^+ species, which might imply that it is the electrophile at high acidities. Arelated investigation of the nitrosation of anisole in $HClO_4$ strongly supported many of these conclusions. Thus no acid independant reaction was observed for anisole, but the reaction rate was more strongly catalysed by acid than that for phenol. The slope of the log k_2 versus the H_R acidity function suggested that NO^+ was the effective nitrosating agent in $HClO_4$ $>$ 5M. This deduction is consistent with Ladenheim and Bender's findings

for the N-nitrosation of benzamide in moderately concentrated H_2SO_4. Challis and Lawson also investigated the kinetics of nitrosation of benzene, toluene, diphenylether and anisole in 10M $HClO_4$[37], and obtained a linear plot of the logarithm of the partial rate factors versus the Hammett substituent parameter σ^+_{para}. From this plot a ρ value of -6.9 was obtained and assigned to the NO^+ reagent in aromatic nitrosation. Since the reaction of anisole shows a primary deuterium isotope, it was concluded that the surprisingly low ρ value for the relatively unreactive NO^+ in fact reflected the sensitivity of proton loss to electron supply, and was therefore not true measure of the reactivity of the electrophile. However, since the rate-determining step for the reaction of substrates other than anisole was unproven, these mechanistic deductions could not be considered final.

In studies of the nitrosation of a series of substituted indoles in dilute $HClO_4$, Challis and Lawson showed NOCl and H_2ONO^+ to be the active electrophiles. The rate of nitrosation of species more basic than 2-methyl-5-nitro-indole ($pK_A = -3.58$) was found to be relatively insensitive to the basicity of the indole and no primary deuterium isotope effect was observed. They concluded that these substrates react at an encounter rate

and are thus diffusion controlled: the calulated molecular rate coefficient for reaction with NOCl approaches a value of 10^9 l.mole^{-1}sec^{-1}. Nitrosation of indoles less basic than 2-methyl-5-nitro-indole proceeded with a significant primary primary deuterium isotope effect, indicating rate-limiting proton loss from the Wheland intermediate. However, some doubt exists as to the generality of these conclusions with regard to aromatic C-nitrosation, since the possibility of an initial N-nitrosation followed by a fast transfer of NO^+ to the C-3 position of the indole cannot be ruled out.

Other reports of aromatic nitrosation have been incidental to investigations of other reactions. For example, Morgan and Williams[53] have recently reported a substantial primary deuterium isotope effect for the Fischer-Hepp re--arrangement of N-methyl-N-nitroso-aniline, in dilute acid , to the para-isomer (equ.(1.9)).



. . (1.9)

Also aspects of aromatic nitrosation were examined earlier in studies of the nitrous acid catalysed nitration reaction by Hughes, Ingold and their colleagues[54]. In a series of

extensive investigations of the mechanism of aromatic nitration, they formulated a'special' nitrous acid catalysed' mechanism involving prior C-nitrosation. The initially formed nitroso-product was rapidly oxidised by the solvent nitric acid to the corresponding nitro compound with concomitant regeneration of nitrous acid, Although information about the initial nitrosation reaction is inherent in their results, it is difficult to extract because of competition in concentrated acid from the general mechanism of nitration involving the NO_2^+ ion. However, Ingold and his colleagues concluded that the electrophiles operating in the nitrous acid catalysed nitration of 4- chloro--anisole by nitric acid in acetic acid were NO^+ and N_2O_4 . Reference has also been made to aromatic C-nitrosation in more recent discussions of anomalous resuts apparent in past work on aromatic nitration in various solvents. Schofield and coworkers[28] have recently shown that the nitration of many activated aromatic substrates in various solvents can be diffusion controlled and hence the reagent shows little substrate selectivity. For the nitration of very reactive substrates in acetic anhydride[55], they observed a concurrent alternative pathway for the reaction involving initial slow C-nitrosation followed by rapid oxidation of the initial nitroso product. Similar results have been found by Hancock and coworkers[56] who reported that nitration of

p-dimethoxybenzene by N_2O_4 in carbon tetrachloride appeared to proceed *via* an initial nitrosation reaction. Both groups of workers have proposed that such oxidative-nitrosation pathways may explain earlier contradictory evidence[57] that nitration of rective aromatic compounds under similar conditions is strongly dependant on their reactivity. Butler and Hendry[58] have observed a similar oxidative-nitrosation pathway for the nitration of thiophene derivatives in concentrated mineral acids.

A Summary.

There is evidence for the operation of the same electrophilic reagents in aromatic C-nitrosation in very dilute acid as in amine nitrosation, namely N_2O_3, H_2ONO^+, and NOCl. Although no conclusive evidence has been presented for the active species at intermediate acidities, it would appear that the nitrosating agent in mineral acid solutions $>$ 5M is the NO^+ species. The observation of a rate-limiting proton transfer from a dienone intermediate in the nitrosation of phenol explains previous discordances of conclusions from acidity function correlations. From the results of the limited number of reactions so far studied. it might be thought that rate-determining loss may be a general feature of aromatic C-nitrosation , except for the most

reactive compounds for which the reaction is diffusion controlled. This rate-limiting proton transfer may then explain the relatively low magnitude of the first ρ value found for nitrosation by the electrophile NO^+ which has generally been believed to be a very unreactive and selective reagent.

CHAPTER II.

THE KINETIC PRINCIPLES.

The kinetic study of nitrosation reactions in aqueous media is complicated, as discussed previously, by the presence of several potential reagents in equilibrium with each other. The outcome is that particular kinetic equations do not always have unique interpretations. Some options can be eliminated, however, by other considerations. The theoretical background to these considerations and their application to nitrosation, are discussed briefly below.

(A). Rate Expressions in the Kinetics of Nitrosation, and Acidity Function Correlations.

Rate-limiting formation of either molecular nitrous acid or H_2ONO^+ from their conjugate bases seems unlikely, since proton transfer to oxygen is generally rapid . Generation of N_2O_3[59] and NOCl[60], however, may be slow under the appropiate conditions. Likewise, the formation of NO^+ may be rate-limiting in principle, but such has not been observed to

date. Thus the expressions listed in Table(2.1) summarise the possible kinetic equations for nitrosation by various reagents, where all steps subsequent to the initial nitrosation are fast.

TABLE(2.1).

Rate Expressions for Nitrosation Reactions.

Reagent	Slow step	Rate law.
HNO_2	Attack	$v \propto [S][HNO_2]$.
N_2O_3	Formation	$v \propto [HNO_2]^2$.
	Attack	$v \propto [S][HNO_2]^2$.
NO.X	Formation	$v \propto [H^+][HNO_2][X]$.
	Attack	$v \propto [S][H^+][HNO_2][X]$.
NO^+	Formation	$v \propto [H^+][HNO_2]$.
	Attack	$v \propto [S][H^+][HNO_2]$.
H_2ONO^+	Attack	$v \propto [S][H^+][HNO_2]$.

'S' represents the substrate.
'X' " " a basic species.

It is evident from Table(2.1) that reactions involving rate-controlling attack by either the H_2ONO^+ or NO^+ on

the substrate give an identical rate law. In dilute acid solutions, the rate expression does not distinguish between these two reagents, but in concentrated acid solutions a distinction should, in principle, be possible by means of h_o and h_R acidity function correlations. The basis of the argumement is outlined briefly below.

The Bronsted rate expression for a rate controlling attack of H_2ONO^+ on a neutral substrate 'S' is given by equ.(2.1),

$$\text{rate} = k \cdot \frac{a_{H_2ONO^+} \cdot a_S}{f^{\neq}} \quad \ldots\ldots (2.1).$$

The protonation of HNO_2 to give H_2ONO^+ (equ.(2.2)) might

$$HNO_2 + H^+ \rightleftharpoons H_2ONO^+ \quad \ldots\ldots (2.2)$$

in common with other oxygen bases be expected to follow the h_o acidity function. Accordingly, the activity of the H_2ONO^+ ($a_{H_2ONO^+}$) is given by equ. (2.3), where $K_a = a_{HNO_2} \cdot a_{H^+} / a_{H_2ONO^+}$ and f_B and f_{BH^+} are the activity coefficients of the indicator base and conjugate acid for the h_o function

$$a_{H_2ONO^+} = \frac{a_{HNO_2} \cdot f_{BH^+} \cdot h_o}{K_a \cdot f_B} \quad \ldots (2.3).$$

Substituting in equ.(2.1) for $a_{H_2ONO^+}$ gives :-

$$\text{Rate} = \frac{k.\ a_S.a_{HNO_2}.\ h_o\ .\ f_{BH^+}}{K_a\ .\ f_B\ .\ f^{\neq}}$$

$$= \frac{k.[HNO_2][S].h_o\ .f_{HNO_2}.f_S.f_{BH^+}}{K_a \qquad\qquad f_B\ .\ f^{\neq}} \quad . .(2.4).$$

Provided that the activity coefficient ratio term is medium independent, and $[H_2ONO^+]$ is low, equ.(2.4) reduces to equ.(2.5)

$$\text{Rate} = k_3\ .\ [S][HNO_2]\ .h_o \qquad . . . (2.5).$$

Thus, for reaction of H_2ONO^+, the second order coefficient (k_2) defined by equ.(2.6), should be directly proportional to the h_o acidity function i.e.

$$\text{Rate} = k_2\ .[S]\ .[HNO_2] \qquad . . . . . (2.6).$$

$$\underline{k_2 \quad \propto \quad h_o}\ .$$

For rate controlling attack of NO^+ on the molecular substrate 'S', the corresponding Bronsted rate equation is given by equ.(2.7)

$$\text{rate} = \frac{k\ .\ a_{NO^+}\ .\ a_S}{f^{\neq}} \qquad . . . . . (2.7).$$

The equilibrium concentration of NO^+ (equ.(2.8)), however,

$$HNO_2 + H^+ \rightleftharpoons NO^+ + H_2O \quad \ldots (2.8)$$

is known to follow the h_R acidity function[61], and the value of a_{NO^+} is therefore given by equ.(2.9), where $K_{NO^+} = \frac{a_{HNO_2} a_{H^+}}{a_{H_2O} \cdot a_{NO^+}}$ and f_{R^+} and f_{ROH} are the activity coefficients of the indicator species.

$$a_{NO^+} = \frac{a_{HNO_2} \cdot h_R \cdot f_{R^+}}{K_{NO^+} \cdot f_{ROH}} \quad \ldots (2.9)$$

Substituting for a_{NO^+} into equ.(2.7) gives equ.(2.10)

$$\text{rate} = \frac{k_o \, a_{HNO_2} \cdot a_S \cdot h_R}{K_{NO^+}} \cdot \frac{f_{R^+}}{f_{ROH} \cdot f^{\neq}}$$

$$= \frac{k_o [HNO_2][S] \cdot h_R \cdot f_{R^+} \cdot f_{HNO_2} \cdot f_S}{K_{NO^+} \cdot f_{ROH} \cdot f^{\neq}} \quad \ldots (2.10).$$

Assuming that the activity coefficient ratio term is medium independent, equ.(2.10) reduces to

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

Thus the observed second order rate coefficient (k_2) for this reaction is linearly related to the h_R acidity function i.e.

$$k_2 \propto h_R \quad \ldots . (2.12).$$

As the function is more strongly dependant on stoicheiometric solvent acidity than h_o, correlation of the second order rate coefficients with these functions, in principle, distinguishes between the H_2ONO^+ and NO^+ reagents.

(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[62].

$$k_{en} = \frac{8NkT}{3000} \times \frac{1}{4\eta} \cdot \left(2 + \frac{R_2}{R_1} + \frac{R_1}{R_2}\right) \quad \ldots (2.13)$$

where,

N = Avogadro's number,

k = Boltzmann's constant,

η = specific viscosity of solvent,

R_1, R_2 = molecular diameters of reacting particles.

The rates of encounter-controlled reactions are thus inversely proportional to the viscositiy of the solvent, and are characterised by a low activation energy[63] which arises mainly from the change in viscosity of the medium with temperature. The reactivity of the participants is largely unimportant in determining the rate of reaction, which for water at 25°C leads to a maximum bimolecular rate coefficient of the order of 10^{10} $l.mole^{-1}.sec^{-1}$.[64]

(C). Concerning Kinetics in Buffer Solutions.

1. Salt Effects.

In buffer solutions it is necessary to consider the importance of salt effects on the reaction rates.

(i). Primary Salt Effects. These arise from the effect of the medium on the activity coefficients (f) of the reactants and the activated complex. For the bimolecular process,

$$A + B \rightleftharpoons M^{\ddagger}$$

the dependence of the observed second order coefficient (k) on that for infinite dilution (k_o) is given by equ.(2.14)

$$k = \frac{k_o \cdot f_A \cdot f_B}{f^*} \quad \ldots \quad (2.14).$$

For very dilute solutions ($< 0.01M$), the Debye-Huckel theorey predicts that when one or more of the reactants are ions, the rate coefficients are related by equ.(2.15)

$$\ln k = \ln k_o + \frac{2 z_A z_A \cdot \alpha\sqrt{\mu}}{1 + \beta a\sqrt{\mu}} \quad \ldots \quad (2.15).$$

Thus if one of the reactants is a neutral molecule, no effect of ionic strength should be apparent. However at $\mu > 0.1$, the activity coefficients of both an ion[65] and a neutral molecule[66]. have been shown to be proportional to the first power of the ionic strength. The more general equation is thus equ.(2.16) in which k' is largely

$$\ln k = \ln k_o + k'\mu \quad \ldots \quad (2.16)$$

empirical and can be positive or negative.

In these investigations, the practice has been to first determine the influence of ionic strength on the reaction rate and then either to make an empirical correction for this effect or to study the reaction in a medium of

constant ionic strength.

(ii). Secondary Salt Effects.

Secondary salt effects arise from the influence of the ionic strength on the dissociation of the buffer acid. The hydrogen ion concentration depends upon the ionic strength according to eq.(2.17)

$$\log [H^+] = \log K_{HA} + \log \frac{[HA]}{[A^-]} - 2\alpha\sqrt{\mu} \quad \ldots.(2.17).$$

In the present investigation, empirical corrections have generally been made for this effect, having first determined the influence of acidity on the reaction rate at constant ionic strength.

2. General Base Catalysis in Electrophilic Substitution.

For an S_E-2 reaction involving a steady state intermediate,

$$ArH + E^+ \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} ArHE^+$$

$$ArHE^+ + B_i \xrightarrow{k_{2i}} ArE + B_iH^+$$

the reaction rate is given by equ.(2.18), where B_i

represents the general base catalyst,

$$\text{rate} = [E^+][ArH] \cdot \sum^{i} \frac{k_1 k_{2i} [B_i]}{k_{-1} + k_{2i}[B_i]} \quad \ldots (2.18)^{67}$$

The usual second order experimental coefficient (equ.(2.19))

$$\text{rate} = k^{o} \cdot [ArH][E^+] \quad \ldots\ldots\ldots (2.19)$$

is then given by equ.(2.20),

$$k^{o} = \sum^{i} \frac{k_1 k_{2i} [B_i]}{k_{-1} + k_{2i}[B_i]} \quad \ldots (2.20).$$

Base catalysis will only be observed when $k_{-1} \gg k_{2i}[B_i]$. In the particular case where $k_{-1} > k_{2i}[B_i]$, equ.(2.20) reduces to

$$k^{o} = \sum^{i} \frac{k_1 k_{2i} [B_i]}{k_{-1}} \quad \ldots\ldots (2.21)$$

and k^{o} shows a first order dependence on $[B_i]$.

For the usual experimental conditions of aqueous solutions with a single buffer, equ.(2.21) can be simplified to equ. (2.22), where k_w^{o} and k_{4i}^{o} are the experimental second

$$k^{o} = k_{w}^{o} + k_{4i}^{o}[B_i] \quad \ldots \quad (2.22)$$

and third order coefficients for catalysis by H_2O and base B_i, respectively.

The catalytic coefficients k_{2i} in equ.(2.21) will be related to the basic strength of B_i by the Bronsted equation[68] (2.23),

$$k_{2i} = G \cdot K_i^{\beta} \quad \ldots \ldots (2.23)$$

where G and β are constants, and K_i is the base dissociation constant of B_i .

From equ.(2.21) and (2.22),

$$k_{4i}^{o} = \frac{k_1 k_{2i}}{k_{-1}}$$

and therefore,

$$k_{4i}^{o} = G' \cdot K_i^{\beta} \quad \ldots \ldots \quad (2.24).$$

Thus the Bronsted β for the S_E-2 reaction can be calculated from equ.(2.24) employing the experimentally observed relationship of equ.(2.22), provided that $k_{-1} \gg k_{2i}[B_i]$.

Values of the Bronsted β for any base catalysed reaction are usually such that $0 < \beta < 1$. The β-value

gives a measure of the degree of proton transfer in the transition state: thus for ρ = 0.5, the transition state is symmetrical and the primary hydrogen isotope effect will be large[69].

(D). The Hammett $\sigma^+ - \rho$ Relationship.

It is well known that substituent effects for aromatic electrophilic substitution can be correlated by a modified form[70] of the Hammett relationship (equ.(2.25)),

$$\log.\left(\frac{k^x}{k^H}\right) = \sigma_x^+ . \rho \quad \ldots\ldots (2.25),$$

where :

k^x is the rate coefficient for reaction of the substituted benzene,

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

ρ is the reaction constant, and

σ^+ is the substituent constant.

Several ρ -values for electrophilic substitution reactions have been determined[33]. All are negative, 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. For example, bromination in perchloric acid has a ρ of -5.78[71], while the less reactive diazonium ion in azo coupling reactions has been predicted to have a ρ of about -12[72].

(E). Conventions Used in the Present Work.

Two types of rate coefficient are employed;

(i). In most part, the rate coefficient is denoted by k and is the proportionality constant of a rate equation, defined as it arises in the text, containing the actual concentrations of the specified species denoted by the use of square brackets e.g. $[HNO_2]$. Experimental rate coefficients are in the form k_1 , k_2 etc. whereas calculated molecular rate coefficients are specified as in k_{NOCl}, k_{NO^+} etc.

(ii). When confusion may arise because of the prescence of reactants in dissociated and undissociated forms of acid--base preequlibria, as in Chapter 6 in the pH region , a second rate coefficient $\bar{k}$ is used, which is the proportionality constant of a rate equation containing the total stoicheiometric (analytical) concentrations of the reactants, which are denoted by the use of round brackets e.g. rate = $\bar{k}$ (X)(Y). The real rate coefficients k, defined by rate = $k[X][Y]$ can then be calculated after correcting for the dissociation of X and Y. At constant acidity, the ratio of the actual to the stoicheiometric concentration of each reactant is constant throughout a kinetic run. Thus the kinetic form of the run is independent of the type of rate coefficient calculated.

PART II.

DISCUSSION OF EXPERIMENTAL RESULTS.

CHAPTER III.

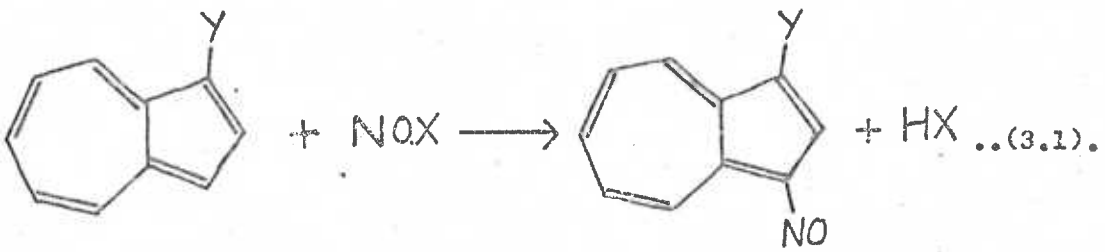
AROMATIC C-NITROSATION IN DILUTE MINERAL ACID.

Previous studies on the nitrosation of indoles[37] in dilute acid indicated that NOCl, N_2O_3 and H_2ONO^+ are effective agents in C-nitrosation, and that NOCl and H_2ONO^+ react on encounter with the most basic indoles. The less basic substrates involved a rate-determining proton loss from the Wheland intermediate.

To test the generality of these conclusions and to examine, in particular, whether the amine N-atom of the indole nucleus was involved in C-nitrosation, the kinetics of nitrosation of azulene and 1-nitroazulene in dilute perchloric acid have been investigated, compounds which have a reactivity similar to that of the indole series. The azulene molecule is known to undergo electrophilic substitutions[73], including nitrosation,[74,75] with ease at the 1- or equivalent 3- position and the basicity of the parent molecule and several of its derivatives have

been extensively investigated[76].

The overall reaction is shown in equ.(3.1),



..(3.1).

(A). The Nitrosation of Azulene in Dilute Acid.

The rate of nitrosation of azulene in dilute $HClO_4$ follows equ.(3.2) at constant acidity, with a first order

$$\text{rate} = k_2.[\text{azulene}][HNO_2] \quad \ldots . \quad (3.2)$$

dependance on both nitrous acid and azulene concentrations. The constancy of the values of k_2 determined using varying initial concentrations of reactants justifies the adoption of equ.(3.2). This evidence is presented in TABLE (3.1) for two representative acidities.

TABLE (3.1).

Nitrosation of azulene at 2.0°C.

Run	$10^3.[HClO_4]$ M.	$10^5.[Azulene]$ M.	$10^5.[HNO_2]$ M.	k_2 $l.mole^{-1}.sec^{-1}$
10	2.50	4.00	11.3	9.3
11	2.50	2.00	5.6	9.0
12	2.50	2.00	8.0	9.6
13	12.0	4.00	5.6	45.2
14	12.0	4.00	11.3	45.3
15	12.0	2.00	5.6	46.1

The k_2 values in TABLE (3.1) were calculated from the analysis of individual runs employing the normal logarithmic function for the integrated form of equ.(3.2), shown in equ.(3.3),

$$k_2.(t - t_o) = \frac{2.303}{a - b}.\log_{10}\left[\frac{b\,(a - x)}{a\,(b - x)}\right] \quad . \; . \; .(3.3)$$

where the symbols have their usual significance. This equation is particularly sensitive to the validity of equ.(3.2), especially if the initial concentrations of reactants are in the order of 2:1, which is the case in these studies.

The second order rate coefficient for the nitrosation of azulene has a first-order dependence on acidity from 10^{-3}M to 10^{-2}M $[HClO_4]$. This evidence is presented in TABLE (3.2).

TABLE (3.2).

Nitrosation of azulene at 2.0°C, in $HClO_4$.

Acidity dependence of k_2 (equ.(3.2)).

Run	$10^3[HClO_4]$ M	k_2 $l.mole^{-1}.sec^{-1}$	$k_3 = \frac{k_2}{H^+}$ $l^2.mole^{-2}.sec^{-1}$
11 - 13	2.5	9.3	3710
20	3.8	14.7	3870
21	7.3	28.5	3900
22	12.0	45.5	3800
		mean =	3820

Thus the full kinetic equation for the nitrosation of azulene in dilute $HClO_4 < 0.1M$, in the absence of any other nucleo-phile is given by equ.(3.4),

$$\text{rate} = k_3 [\text{azulene}] [HNO_2] [H^+] \quad . \quad . \quad . \quad (3.4).$$

Catalysis by Chloride Ion.

Addition of sodium chloride strongly accelerates the rate of nitrosation of azulene and the rate coefficient k_2, at constant acidity, has a linear dependence on the concentration of chloride ion , as illustrated by TABLE (3.3) and the plot of these data shown in FIGURE (3.1).

TABLE (3.3).

Nitrosation of azulene at 2.0°C.

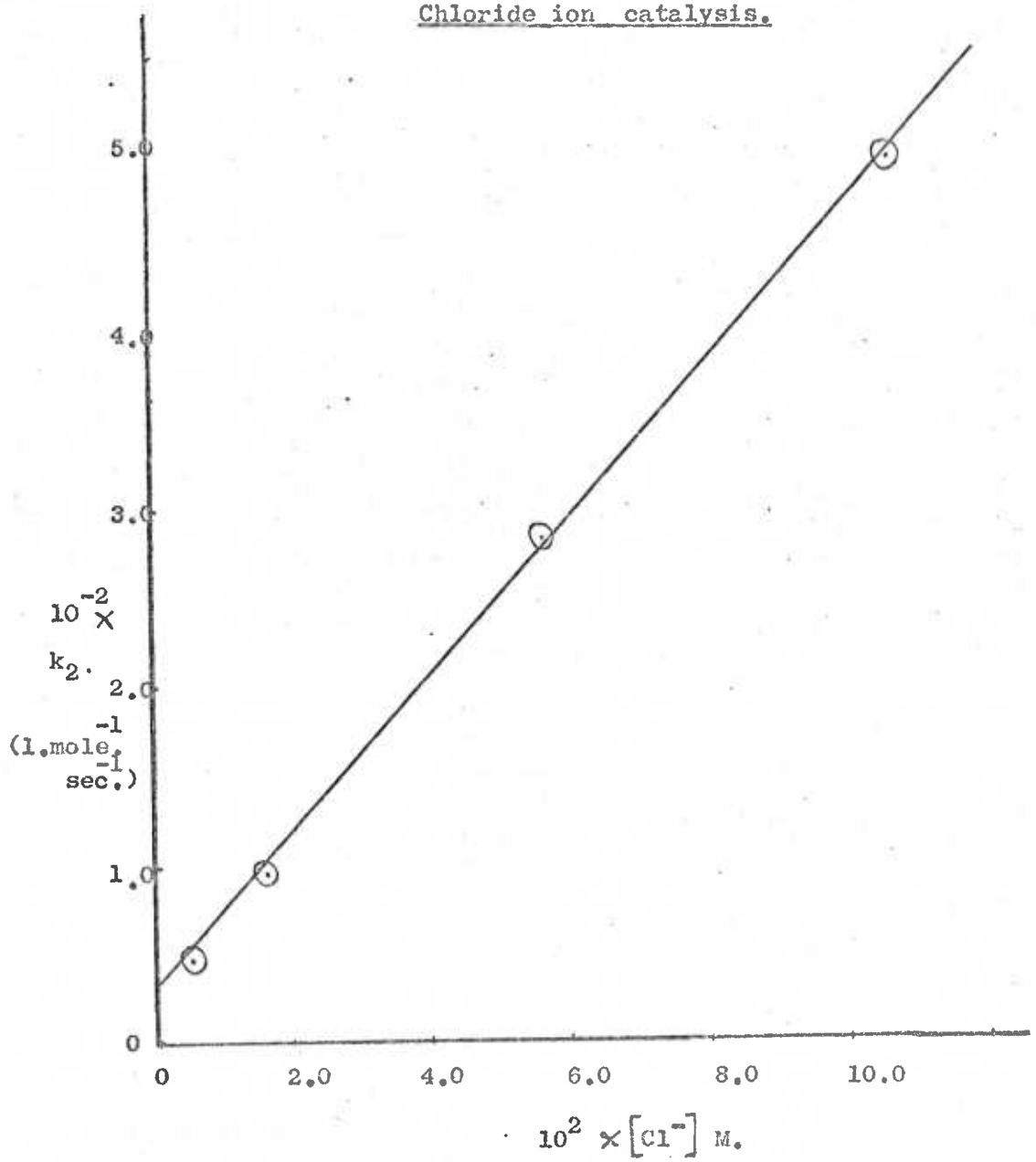
Chloride-ion catalysis at constant $[HClO_4] = 5.0.\ 10^{-3}$M.

Run	$10^2[Cl^-]$ M.	k_2 $l.mole^{-1}.sec^{-1}$
16	0.5	41.8
17	1.5	90.4
18	5.5	279
19	10.5	512

FIGURE (3.1).

Nitrosation of azulene at 2.0°C:

Chloride ion catalysis.



The intercept of FIGURE (3.1) gives a value of k_2 = 18 $l.mole^{-1}.sec^{-1}$. The value of $k_3[H^+]$ for 5.0×10^{-3}M $HClO_4$, interpolated from the data of TABLE (3.2), is k_2 = 19 $l.mole^{-1}.sec^{-1}$, and the correlation of these two values indicates that k_2 can be expressed as in equ.(3.5),

$$k_2 = k_3.[H^+] + k_4.[H^+][Cl^-] \quad \ldots (3.5).$$

The form of equ.(3.5) is rigorously proved by the results of a study of the variation of k_2 with acidity in HCl. In HCl, equ.(3.5) becomes equivalent to equ.(3.6)

$$k_2 = k_3.[H^+] + k_4.[H^+]^2 \quad \ldots . (3.6)$$

and thus a plot of $k_2/[H^+]$ versus $[H^+]$ should be linear according to equ.(3.7)

$$\frac{k_2}{[H^+]} = k_3 + k_4.[H^+] \quad \ldots . (3.7).$$

The data for the nitrosation of azulene in HCl are shown in TABLE (3.4), and the plot of these data according to equ.(3.7) is shown in FIGURE (3.2).

FIGURE (3.2).

Nitrosation of azulene in HCl at 2.0°C;

plot of $k_2/[H^+]$ vs $[H^+]$ (equ.(3.7)).

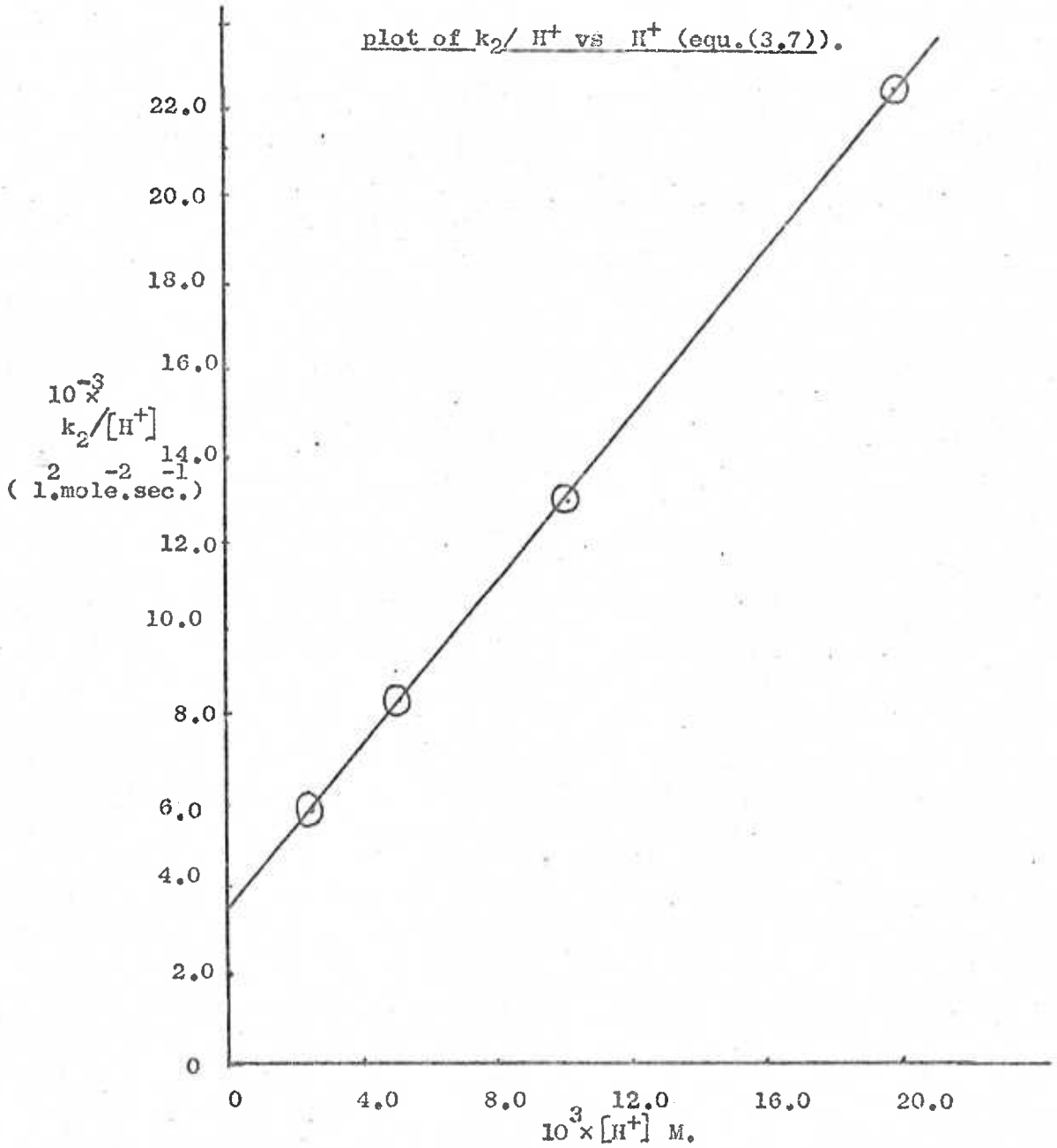


TABLE (3.4).

Nitrosation of azulene in HCl at 2.0°C.

Dependance of k_2 on [HCl].

Run	10^3.[HCl] M.	k_2 $l.mole^{-1}.sec^{-1}$.	$k_2/[H^+]$ $l^2.mole^{-2}.sec^{-1}$.
1	2.5	14.8	5920
2	5.0	41.8	8360
3	10.0	132.0	13,200
4	20.0	446.0	22300

The linearity of FIGURE (3.2) confirms the validity of equ.(3.5). Values of k_3 and k_4 from the intercept and gradient of FIGURE (3.2) are 3.5×10^3 $l^2.mole^{-2}.sec^{-1}$. and 9.7×10^5 $l^3.mole^{-3}.sec^{-1}$. respectively, and agree well with the values of 3.6×10^3 $l^2.mole^{-2}.sec^{-1}$. and 9.6×10^5 $l^3.mole^{-3}.sec^{-1}$. respectively, obtained for these coefficients from the data of TABLE (3.3) for reaction in $HClO_4$ with added chloride ion. These intercept-derived values of k_3 also compare very well with the value of this constant calculated for acid

catalysis in the absence of Cl^- (TABLE (3.2)), of $k_2 = 3.8 \times 10^3$ $l^2.mole^{-2}.sec^{-1}$.

The full expression for the rate of nitrosation of azulene in the prescence of Cl^- can thus be written in the full form of equ.(3.8) by combining equ.(3.2) and (3.5),

$$\text{rate} = k_3[\text{azulene}][HNO_2][H^+] + k_4[\text{azulene}][HNO_2][H^+][Cl^-] \quad \ldots(3.8).$$

The first term of equ.(3.8) is identical to the rate expression found for the nitrosation of azulene in the absence of Cl^- (equ.(3.4)). Nitrosation according to the rate expressions of equ.(3.4) and the second term of equ.(3.8) have been ascribed, previous studies of the diazotisation of amines[77] and the nitrosation of indoles[37], to rate determining nitrosation reactions involving the H_2ONO^+ and NOCl species respectively. The same conclusions are drawn here.

<u>The Rate-determining Step in the Nitrosation of Azulene; Nitrosation of 1,3-$[^2H_2]$-azulene.</u>

The nitrosation of 1,3-$[^2H_2]$- azulene could not be carried out directly in dilute $HClO_4$ because of the rapid rate of hydrogen-exchange with the solvent under these

conditions[76]. Consequently the reaction has been conducted in D_2O solvent, and compared with the rate of nitrosation of the normal compound in H_2O at the same acidity. The results are shown in TABLE (3.5) where the coefficients k_2^H and k_2^D refer to the rate coefficients defined as in equ.(3.9) for nitrosation of the normal and the deutero compound respectively.

$$\text{rate} = k_2.[\text{azulene}][HNO_2] \quad \ldots\ldots(3.9)$$

TABLE (3.5).

Nitrosation of 1,3-$[^2H_2]$-azulene in $DClO_4$ and of azulene in $HClO_4$ at constant acidity of 8.0×10^{-3}M.

Run	t°C	solvent	k_2^H	k_2^D	k_2^H/k_2^D
39	14.5	H_2O	38.7	-	
38	"	D_2O	-	56.8	0.68
41	25.8	H_2O	81.9	-	
40	"	D_2O	-	108.8	0.75
43	26.8	H_2O	77.7	-	
42	26.8	D_2O	-	112.4	0.69
				mean value	0.71

The observed ratio of the coefficients, k_2^H/k_2^D , for the nitrosation of the normal compound in H_2O and the deutero isomer in D_2O , will contain a term arising from the solvent isotope effect on the preequilibrium formation of H_2ONO^+ and this effect is known for conditions similar to those employed here[78]. The concentration of the H_2ONO^+ is higher in deutero media than in proteo solutions containing the same stoicheiometric concentration of nitrous acid and acidity , by a factor of about 2. Thus the real value of the deuterium isotope effect for nitrosation of azulene by H_2ONO^+ is calculated from equ.(3.10),

$$\frac{k^H_{H_2ONO^+}}{k^D_{H_2ONO^+}} = \frac{k_2^H}{k_2^D} \times \frac{\left[D_2ONO^+\right]^{D_2O}}{\left[H_2ONO^+\right]^{H_2O}} \quad \ldots (3.10)$$

where $k_{H_2ONO^+}$ is the molecular rate coefficient defined in equ.(3.11),

$$\text{rate} = k_{H_2ONO^+} \left[\text{azulene}\right] \left[H_2ONO^+\right] \ldots . (3.11).$$

Thus from the data of TABLE (3.5) and equ.(3.10),

$$\frac{k^H_{H_2ONO^+}}{k^D_{H_2ONO^+}} = 1.4 \pm 0.2$$

The low magnitude of this ratio is more consistent with a secondary hydrogen isotope effect than a primary one.

Calculation of Rate Coefficients k_{NOCl} and $k_{H_2ONO^+}$.

The experimental rate coefficients k_3 and k_4 associated with reaction involving H_2ONO^+ and NOCl respectively, have been defined by equ.(3.11) and (3.12),

$$\text{rate},(H_2ONO^+) = k_3[\text{azulene}][HNO_2][H^+] \quad . \quad (3.11)$$

$$\text{rate}(NOCl) = k_4 [\text{azulene}][HNO_2][H^+][Cl^-] \quad .. (3.12).$$

The molecular rate coefficients $k_{H_2ONO^+}$ and k_{NOCl} are defined in equ.(3.13) and equ.(3.14) respectively,

$$\text{rate},(H_2ONO^+) = k_{H_2ONO^+}[\text{azulene}][H_2ONO^+] \quad . \quad . (3.13)$$

$$\text{rate},(NOCl) = k_{NOCl}[\text{azulene}][NOCl] \quad . \quad . \quad . (3.14)$$

and the preequlilibria formation of H_2ONO^+ and NOCl are governed by equ.(3.15) and equ.(3.16) respectively,

$$K_{H_2ONO^+} = \frac{[HNO_2][H^+]}{[H_2ONO^+]} \quad . \quad . \quad . \quad . \quad . \quad (3.15)$$

$$K_{NOCl} = \frac{[HNO_2][H^+][Cl^-]}{[NOCl]} \quad . \quad . \quad (3.16).$$

it follows from equ.(3.11) to (3.16) that,

$$k_{H_2ONO^+} = k_3 \cdot K_{H_2ONO^+} \quad \ldots (3.17)$$

and $$k_{NOCl} = k_4 \cdot K_{NOCl} \quad \ldots (3.18).$$

Calculation of $k_{H_2ONO^+}$ is impossible at present since no data is available for the preequilibrium formation of H_2ONO^+. However, Schmid and Maschka[79] have determined K_{NOCl} at several temperatures, and a value of K_{NOCl} at 2.0°C of 1680 $l^{-2}.mole^2$. has been interpolated from their data. k_4 at 2.0°C is 9.65 $10^5 l^3.mole^{-3}.sec^{-1}$., and thus $k_{NOCl}(2.0^oC) = 1.6\ 10^9\ l.mole^{-1}.sec^{-1}$.

Temperature Dependance of k_3.

The variation of the rate coefficient k_3 (equ.(3.11)) with temperature has been investigated for the nitrosation of azulene at a constant $HClO_4$ over the temperature range 0° to 25°C . The results are shown in TABLE (3.6).

TABLE (3.6).

Nitrosation of azulene in $HClO_4$ at constant acidity $= 4.0\ 10^{-3}$M.; variation of k_3 with temperature.

Run	$t^{o}C$	k_2(equ.(3.2)) $l.mole^{-1}.sec^{-1}$.	$k_3 = k_2/[H^+]$ $l.mole^{-2}.sec^{-1}$.
25	25.3	92.0	23,000
26	19.6	59.7	14,900
27	14.5	43.2	10,800
28	9.0	25.1	6,300
29	3.9	15.2	3,800
*	2.0		3,600
30	0	11.9	3,000

* mean value from the data of TABLE (3.2) and FIGS.(3.1) and (3.2).

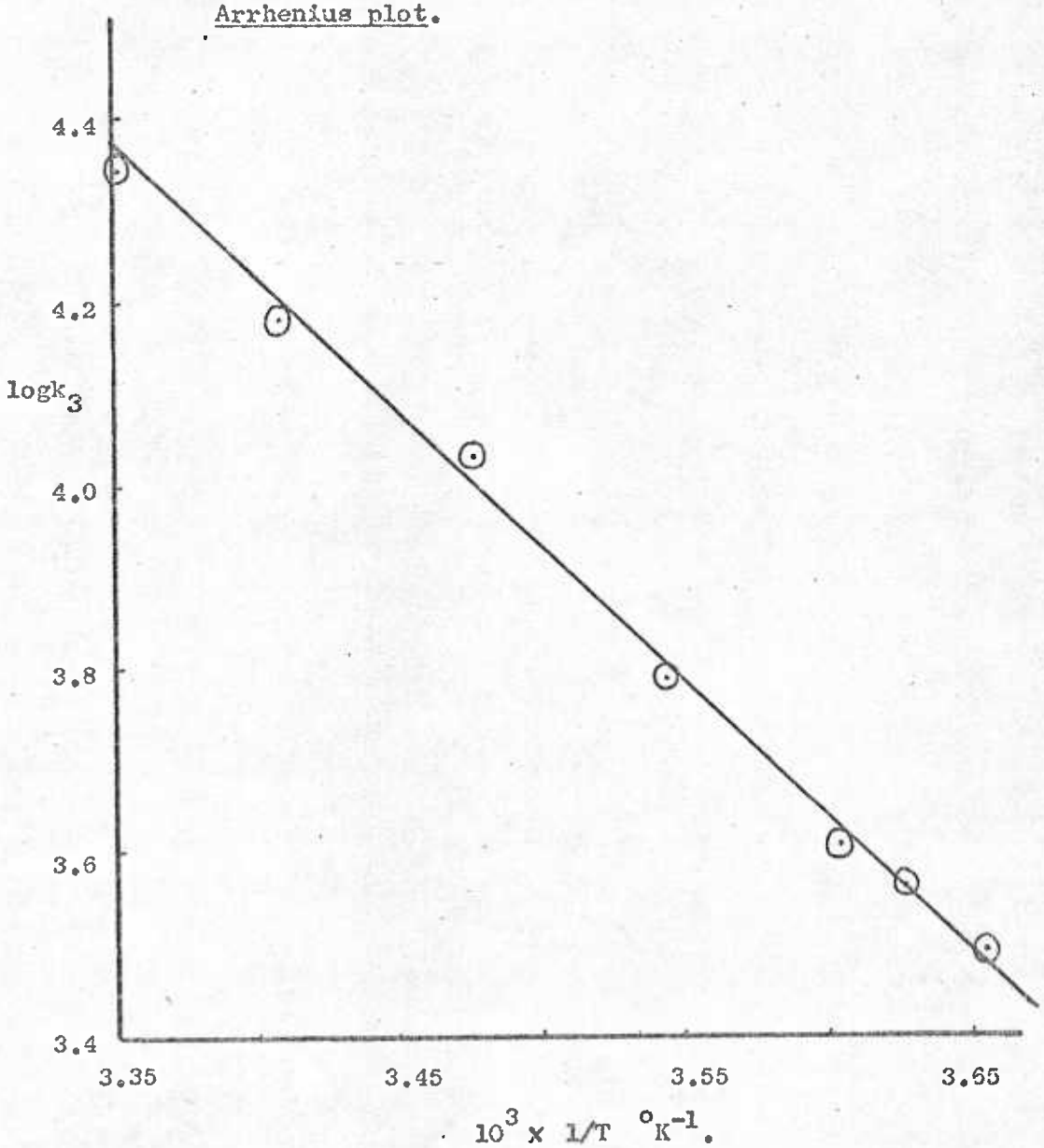
The Arrhenius plot of the data of TABLE (3.6) is shown in FIGURE (3.3) , from which the activation energy has been obtained in the usual way and has a value of,

$$E_{\alpha} = 5.5 \times 10^{4}\ Jmole^{-1}.$$

FIGURE (3.3).

Nitrosation of azulene in 4.0×10^{-3}M $HClO_4$;

Arrhenius plot.



Temperature Dependance of k_{NOCl}.

The rate of nitrosation of azulene in dilute $HClO_4$ has been determined at constant acidity and in the prescence of a constant concentration of Cl^-, at a range of temperatures between $0^o$and 26^oC. The overall observed rate coefficient at each temperature is defined at usual by equ.(3.19)

$$\text{rate} = k_2 [\text{azulene}][HNO_2] \quad \ldots (3.19)$$

and under the experimental conditions,

$$k_2 = k_3[H^+] + k_4[H^+][Cl^-] \ldots (3.20).$$

Values of k_3 at each of the temperatures studied have been interpolated from FIGURE (3.3) . Thus values of k_4 at each temperature are obtained by substitution of the data into equ.(3.20). The results are shown in TABLE (3.7).

As shown on pages(56)and(57),the molecular rate coefficient k_{NOCl} is given by,

$$k_{NOCl} = k_4 . K_{NOCl} \quad \ldots\ldots\ldots (3.21).$$

TABLE (3.8) lists the values of K_{NOCl} at each temperature interpolated from the data of Schmid and Maschka, together with the calculated values of k_{NOCl}, calculated from equ.(3.21). The Arrhenius plot of the data of TABLE (3.8) is shown in FIGURE (3.4) .

TABLE (3.7).

Nitrosation of azulene in $[HClO_4] = 1.0\ 10^{-3}$M, and $[Cl^-] = 1.0\ 10^{-2}$M. Temperature dependance of k_4.

Run	t°C	k_2 $l.mole^{-1}.sec^{-1}$.	$k_3[H^+]^{(a)}$ $l.mole^{-1}.sec^{-1}$.	$10^6 \times k_4$ (equ.(3.20)). $l^3.mole^{-3}.sec^{-1}$.
31	26.1	88.5	25.1	6.34
32	20.2	56.5	16.3	4.02
33	13.8	36.8	9.44	2.74
34	8.8	26.1	6.84	1.93
35	2.0	13.6	3.60	1.01

(a) k_3 values interpolated from FIGURE (3.3).

TABLE (3.8).

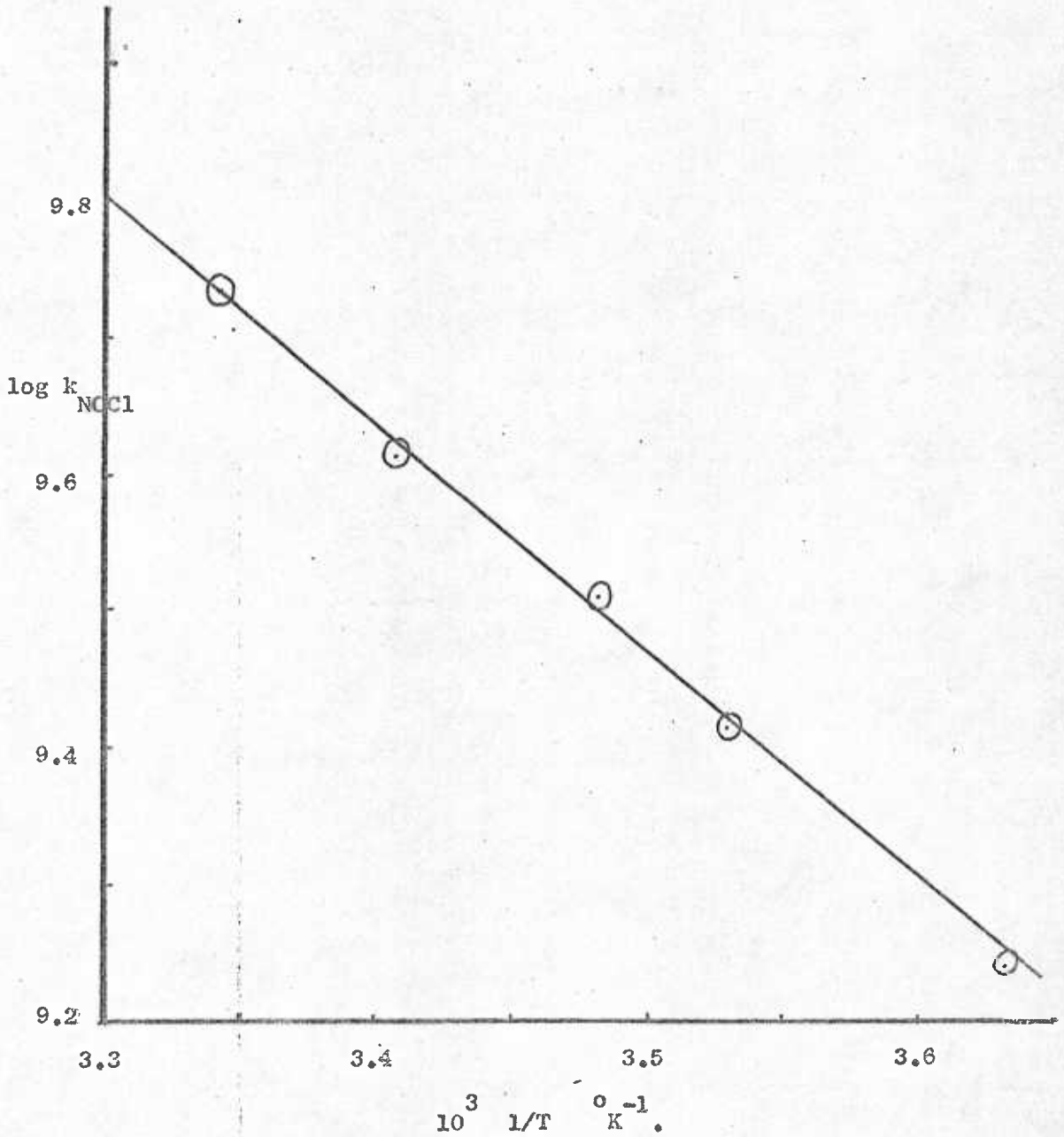
Nitrosation of azulene; temperature dependance of k_{NOCl}.

t°C	$10^{-6} \times k_4$ $l^3.mole^{-3}.sec^{-1}$.	$K_{NOCl}^{(a)}$ $l^{-2}.mole^2$.	$10^{-9} \times k_{NOCl}$ (equ.(3.21)) $l^{-1}.mole.sec^{-1}$.
26.1	6.34	848	5.48
20.2	4.02	990	4.27
13.8	2.74	1180	3.16
8.8	1.93	1360	2.63
2.0	1.01	1680	1.70

a) interpolated from the data of Schmid and Maschka, ref(79).

FIGURE (3.4).

Nitrosation of azulene by NOCl; Arrhenius plot.



The value of the activation energy for the nitrosation of azulene by NOCl, obtained in the usual way from the gradient of the Arrhenius plot of FIGURE (3.4), is

$$\underline{E_{\alpha} = 2.5 \times 10^{4} \text{ J.mole}^{-1}}.$$

Employing the value of $\log k_{NOCl} = 9.70$ at $208.2^{\circ}K$ interpolated from FIGURE (3.4), together with the observed activation energy E_{α}, the entropy of activation $\Delta S^{\neq}$ and the free energy of activation $\Delta F^{\neq}$ are obtained by applying the standard equations (3.22) and (3.23),

$$k_{NOCl} = \frac{ekT}{h} \cdot \exp.\left(\frac{\Delta S^{\neq}}{R}\right) \exp.\left(\frac{-E_{\alpha}}{RT}\right) \quad \ldots\ldots (3.22)$$

$$\Delta F^{\neq} = E_{\alpha} - T.\Delta S^{\neq} \quad \ldots\ldots (3.23).$$

This treatment leads to calculated values for the nitrosation of azulene by NOCl of,

$$\underline{\Delta S^{\neq} = +16.3 \text{ J.}^{\circ}\text{K}^{-1}}$$

$$\underline{\Delta F^{\neq} = 2.0 \times 10^{4} \text{ J.mole}^{-1}}.$$

(B). The Nitrosation of 1-Nitroazulene.

At constant acidity, the nitrosation of 1-nitro--azulene in $HClO_4$ with a constant excess of $[HNO_2]$ follows the rate expression of equ.(3.24) ,

$$\text{rate} = k_1.[\text{nitroazulene}] \quad \ldots(3.24).$$

The first order dependance of the rate on $[HNO_2]$ is demonstrated in TABLE (3.9) , leading to the full rate equation at constant acidity of ,

$$\text{rate} = k_2 [HNO_2] [\text{1-nitroazulene}] \quad ,(3.25).$$

TABLE (3.9).

Nitrosation of 1-nitroazulene at 25.0°C in 1.02M $HClO_4$.

Initial [1-nitroazulene] = 6.0×10^{-5}M.

Run	$10^3 \times [HNO_2]$ M.	$10^4 \times k_1$ sec^{-1}.	k_2 $l.mole^{-1}.sec^{-1}$.
43	1.50	4.95	0.33
23	2.90	9.30	0.32
44	4.50	15.8	0.35
		mean	0.33

The Rate-determining Step ; Nitrosation of 3-$^{2}H_{1}$ -1-Nitroazulene.

The rate of nitrosation of 3-$[^{2}H_{1}]$-1-nitroazulene has been determined in $HClO_4$ and compared directly with the rate for the normal compound measured under identical conditions of acidity and temperature. The rate of proto-dedeuteration under these conditions[76] ($t_{\frac{1}{2}}$ of about 12 hours in 1M $HClO_4$) is extremely small compared with the rate of nitrosation ($t_{\frac{1}{2}}$ of about 20 minutes) and so no significant exchange of the 1-proton occurs during the kinetic runs. The results are shown in TABLE (3.10).

TABLE (3.10).

Nitrosation of 3-$[^{2}H_{1}]$-1-nitroazulene at 25.0°C in 1.02M $HClO_4$.

Initial 3-$[^{2}H_{1}]$-1-nitroazulene = 6.0×10^{-5}M.

Run	$10^{3} \times [HNO_2]$ M.	$10^{4} \times k_1$ sec^{-1}	k_2 $l.mole^{-1}.sec^{-1}$
24	2.90	3.30	0.116
45	4.50	5.40	0.120
		mean	0.118

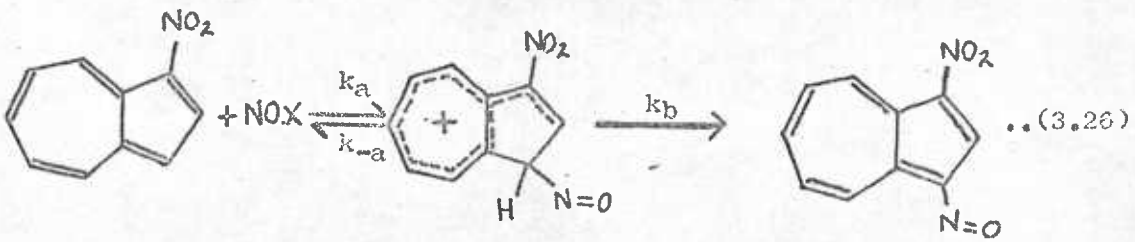
Direct comparison of the data of TABLES (3.9) and (3.10) reveals a substantial reduction in the rate of nitrosation of the deuterated nitroazulene compared with that of the normal isomer under identical conditions, and

$$k_2^H / k_2^D = 2.8 \pm 0.2 .$$

The magnitude of this ratio is consistent with a primary deuterium isotope effect, indicating appreciable C-H bond loosening in the rate-determining step of the reaction.

(C).Discussion.

The substantial primary hydrogen isotope effect ($k_H/k_D = 2.8$) observed for the nitrosation of 1-nitroazulene is firm evidence that the rate-limiting step for the reaction is proton loss from the Wheland-type intermediate (I) , formed in a fast preequilibrium step (equ.(3.26)). The



..(3.26)

(I)

alternative possibility that the nitrosation occurs in a one step process with synchronous proton-loss is entirely out of line with related electrophilic substitutions and is therefore discounted.

On going from 1-nitroazulene ($pK_a^{76} = < -4.7$) to the more basic azulene ($pK_a^{76} = -0.92$) a change in rate-determining step is apparent. Evidence for this conclusion is the incidence of chloride ion catalysis in the nitrosation of azulene, and the low isotopic rate ratio ($k_H/k_D = 1.4 \pm 0.2$) which is more consistent with a secondary than primary isotope effect. Clearly, the rate-determining step in the nitrosation of azulene involves very little C-H bond stretching at the site of substitution, in contrast to nitro-azulene. The observed change in rate-determining step with substrate reactivity is unusual, since previous deductions have suggested that primary isotope effects in electrophilic substitution reactions should increase with decreasing acidity of the leaving proton. However, a viable explanation for the observed behaviour comes from the large magnitude of the molecular rate coefficients, which for the reaction of azulene with NOCl has a value of $k_{NOCl} = 5.0 \times 10^9$ $l.mole^{-1}.sec^{-1}$

at 25°C. The magnitude of this coefficient is very similar to that expected for encounter of two neutral molecules in aqueous solution at 25°C ($k_{en}^{64} = 10^{10}$ l.mole^{-1}.sec^{-1}.). Thus, the lack of a primary hydrogen isotope effect in the nitrosation of azulene by NOCl comes directly from the onset of diffusion control. The rate-determining process is the approach of the reactants which will be governed mainly by the viscosity of the solvent. This explanation is supported by the low activation energy of 2.5×10^4 J.mole^{-1}. observed for the reaction, which is of the order expected for the change in viscosity of the medium with temperature[63].

Assuming that H_2ONO^+ is more electrophilic than NOCl, the reaction of the former reagent with azulene will also occur on encounter. The observed activation energy for this reaction (5.5×10^4 J.mole^{-1}.) includes the temperature dependance of solvent viscosity and the enthalpy for pre-equilibrium formation of H_2ONO^+. Assuming the viscosity term is the same as for NOCl, the enthalpy associated with the H_2ONO^+ formation is about 3×10^4 J.mole^{-1}.

Since the nitrosation of azulene in dilute mineral acid by H_2ONO^+ is encounter-controlled, the kinetic isotope

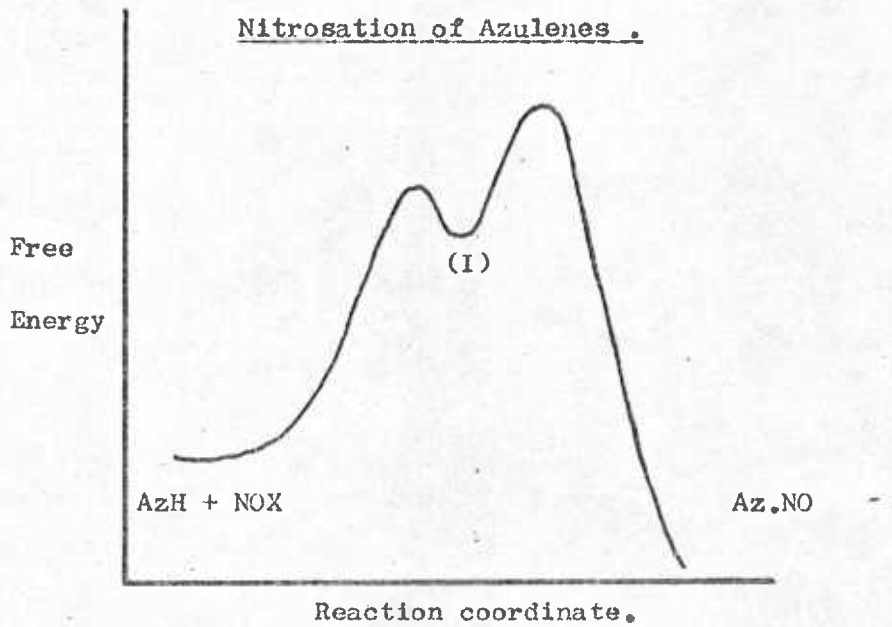
effect of 1.4 $\pm$ 0.2 obtained from a comparison of the rate in H_2O and D_2O will also include a factor for the difference in viscosity of the two solvents. This has been calculated as $k_{H_2O}/k_{D_2O} = 1.25$ at 25^oC [80], which reduces the kinetic isotope effect for the nitrosation of azulene to $k_H/k_D = 1.1$.

The preceding observations are consistent with an A-S_E2 mechanism for the nitrosation of azulenes (equ.(3.27)) in

$$AzH \quad NO.X \overset{k'}{\rightsquigarrow} AzH + NO.X \underset{k_{-a}}{\overset{k_a}{\rightleftharpoons}} \overset{+}{AzHNO} \overset{k_b}{\rightarrow} AzNO + H^+ \quad . \quad (3.27)$$

which $k_{-a} \gg k_b$. The 'energy profile' is therefore given by FIGURE (3.5) .

FIGURE (3.5).



With very reactive compounds such as azulene, itself, it is evident that diffusion of the reactants is rate-limiting. Electron-withdrawing substituents would be expected to reduce the substrate reactivity towards electrophilic attack. This is observed for 1-nitroazulene and the reaction is then reactivity controlled.

Similar conclusions have been drawn in recent studies of the nitrosation of indoles at the C-3 position, under similar conditions[37] and it is of interest to compare the rates of nitrosation of the azulenes with the indole series. The rates of reaction of both series of compounds by H_2ONO^+ and NOCl can be defined by equations (3.28) and (3.29) respectively,

$$H_2ONO^+ \; ; \qquad \text{rate} = k_3[\text{substrate}][HNO_2][H^+] \quad . \; . \; . (3.28)$$

$$NOCl \; ; \qquad \text{rate} = k_{NOCl}[\text{substrate}][NOCl] \quad . \; . \; . \; (3.29).$$

k_3 is an experimental rate coefficient which includes terms associated with the preequilibrium formation of H_2ONO^+, and k_{NOCl} is the molecular rate coefficient, as defined. TABLE (3.11) compares both coefficients for the reactions of azulenes and indoles. The experimentally obtained rate coefficients for the reaction of azulene have been divided by a factor of

2 , since this molecule has two equivalent reactive sites. Thus, TABLE (3.11) shows a comparison of the reactivity of a single C-site toward nitrosating agents in the two series of compounds.

TABLE (3.11).

Reactivity toward Nitrosating Agents.

Substrate	pK_a	t^oC	k_3 $l^2.mole^{-2}.sec^{-1}$	$10^{-8}k_{NOCl}$ $l.mole^{-1}.sec^{-1}$
1,2-dimethylindole	+0.3	3.0	530	10.8
2-methylindole	-0.28	3.0	500	--
Azulene	-0.92	2.0	1850	8.5
2-phenylindole	-1.85	3.0	650	8.4
2-methyl-5-nitro--indole	-3.58	3.0	250	3.2
1-nitroazulene	-4.7	25.0	0.12	___
5-cyanoindole	-6.0	0.5	21.0	--
5-nitroindole	-7.4	0.5	4.5	--

TABLE (3.12) shows a comparison of the observed kinetic isotope effects (k_H/k_D) for the nitrosation of azulenes and

indoles of varying basicity.

TABLE (3.12).

Deuterium Isotope Effects in the Nitrosation of Azulenes and Indoles.

Substrate	pK_a	$t^{\circ}C$	$[HClO_4]$ M.	k_3^H/k_3^D
1,2-dimethylindole	+0.3	3.0	0.01	1.26 ± .02
Azulene	-0.92	14.5	0.008	1.4 ± 0.2
1-nitroazulene	-4.7	25.0	1.02	2.8 ± 0.2
5-cyanoindole	-6.0	0.5	0.012	1.8 ± 0.2

It is apparent from TABLE (3.11) that the reactivity of the indole and azulene nuclei toward the nitrosating reagents have a remarkably similar magnitude , bearing in mind the great structural differences in these two series. This is completely consistent with the operation of diffusion control for the nitrosation of both azulene and the most reactive indoles. TABLE (3.12) illustrates the similar trend in the change in rate-determining step with variation of the basicity of the azulene and indole nuclei. The similarity

in behaviour of the indoles and the azulenes in nitrosation would appear to remove any doubt that the nitrosation of indoles is not truly representative of normal C-nitrosation . It has been suggested that the nitrosation of indoles may involve an initial N-nitrosation , followed by a fast transfer of NO^+ to the C-3 position. However, the results for azulene are unambiguous and it can be concluded that the mechanism discussed above is generally operative in the C-nitrosation of the azulenes and indoles.

CHAPTER IV.

ORTHO-NITROSATION OF PARA-SUBSTITUTED PHENOLS.

Lawson and Challis[37] also examined the nitrosation of benzene, and of several mono-substituted benzenes more reactive than benzene itself, in moderately concentrated $HClO_4$ solutions where the reagent was the NO^+. The rate of nitrosation of these compounds was found to be only moderately increased by electron donating substituents -Me, -OMe, and -OPh *para* to the site of attack, as reflected by the relatively low ρ -value of -6.9 obtained from a Hammett $\log f^X_{para} - \sigma^+_{para}$ correlation.

To reaffirm the low ρ - value for nitrosation by the NO^+ reagent, the *ortho*-nitrosation of a series of *para*--substituted phenols has been studied, for which a wider range of activating and deactivating substituents *meta* to the site of reaction can be employed. Nitrosation in the *ortho* - rather than the *para* - position in phenol should not induce a major change in mechanism, but to establish this fact

the nitrosation of p-cresol has been examined in detail over a wide range of acidity.

(A). Nitrosation of p-Cresol in Aqueous $HClO_4$.

At constant acidity, and in the prescence of a constant excess of $[p\text{-cresol}]$ over $[HNO_2]$, the rate of nitrosation of p-cresol follows equ.(4.1),

$$\text{rate} = k_1 [HNO_2] \quad \ldots\ldots\ldots\ldots (4.1).$$

This equation is rigorously obeyed over at least 95% of the reaction. The pseudo first order coefficient k_1 (equ.(4.1)) has a first order dependence on $[p\text{-cresol}]$, and thus the reaction rate at any acidity may be specified by equ.(4.2),

$$\text{rate} = k_2 [p\text{-cresol}] [HNO_2] \quad \ldots\ldots (4.2)$$

Evidence for this relationship is presented in TABLE (4.1).

TABLE (4.1).

Nitrosation of p-cresol at 0°C in aqueous $HClO_4$; dependance of k_1 on [p-cresol].

Initial stoich. $[HNO_2] = 10^{-4}$M.

Run	$[HClO_4]$ M	10^2.[p-cresol] M	10^3. k_1 sec^{-1}.	k_2(equ.(4.2)) $l.mole^{-1}.sec^{-1}$.
143	4.06	1.03	0.170	0.0165
145	4.06	2.06	0.350	0.0170
151	4.57	0.518	0.182	0.033
150	4.57	1.036	0.333	0.031
395	6.10	0.126	0.440	0.35
396	6.10	0.503	2.07	0.41
398	6.10	1.01	3.84	0.38

The variation of k_2 defined in equ.(4.2) with acidity is recorded in TABLE (4.2) for the acidity range 10^{-2} to 9M $HClO_4$. TABLE (4.2) also lists values of the H_R acidity function[61]. Features in the acidity dependence of k_2 are more easily seen from a plot of log k_2 against $-H_R$, shown in FIGURE (4.1).

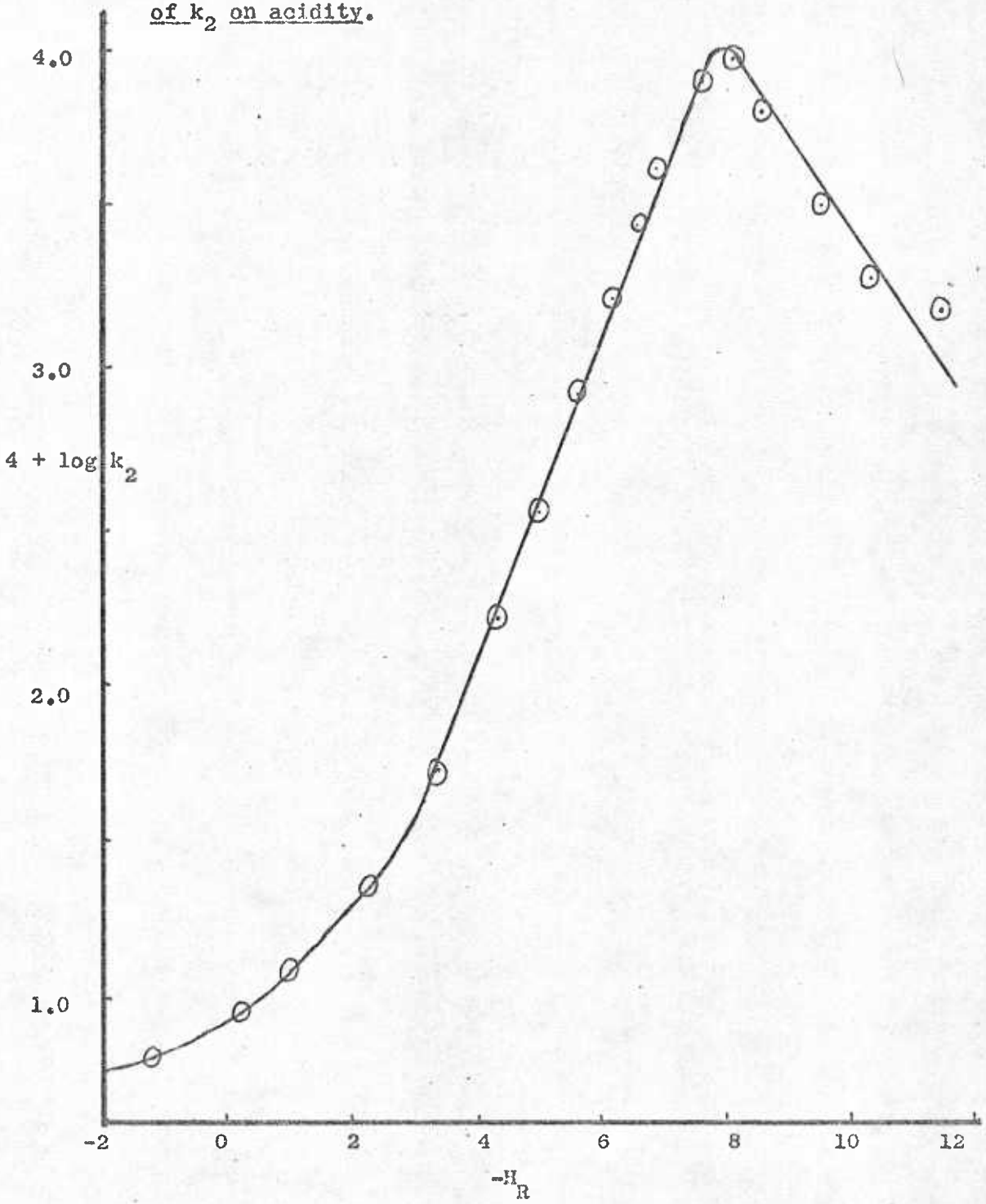
TABLE (4.2).

Nitrosation of p-Cresol in $HClO_4$ at 0°C; variation of $-k_2$ (equ.(4.2)) with acidity.

Run	$[HClO_4]$ M.	$-H_R$	$10^4 \times k_2$ $l,mole^{-1}.sec^{-1}$.
190	0.0097	-2.0	5.29
201	0.048	-1.3	5.64
156	0.508	0.23	9.03
155	1.02	0.99	12.8
141	2.03	2.20	21.6
142	3.05	3.30	52.2
143	4.06	4.31	160
150	4.57	4.88	332
146	5.08	5.48	798
157	5.59	6.08	1630
186	6.12	6.72	4090
187	6.70	7.49	7640
178	6.90	7.78	8750
161	7.32	8.39	6000
188	7.96	9.34	3130
149	8.54	10.22	1850
193	9.28	11.41	1520

FIGURE (4.1).

Nitrosation of p-Cresol in $HClO_4$ at 0°C ; dependence of k_2 on acidity.



The nitrosation of p-cresol shows three distinct regions of acid catalysis, as seen by inspection of FIGURE (4.1) ;

(i). Below 0.5M $HClO_4$, the rate coefficient k_2 is virtually independent of solvent acidity.

(ii). From about 2M to 7M $HClO_4$, k_2 increases rapidly with acidity and the slope of FIGURE (4.1) in this region is +0.53. k_2 reaches a maximum at $H_R = -8.0$.

(iii). Above 8M $HClO_4$, k_2 decreases with increasing acidity and the slope of the plot in this region is about -0.22.

Striking similarities exist between these features of the acidity dependence of the rate of nitrosation of p-cresol and thoso reported previously [52] for the nitrosation of phenol, suggesting that a common mechanism is operating for these compounds. Before discussing these aspects in detail, evidence is presented as to the nature of the rate-determining step in the nitrosation of p-cresol.

<u>The Rate-Determining Step : The Nitrosation of 2,6-$[^2H_2]$-</u>

<u>-p-cresol</u>.

The rate of nitrosation of 2,6-$[^2H_2]$-p-cresol in $HClO_4$ has been measured under conditions comparable to those for

p-cresol itself and values of k_2^D at 0°C are listed in TABLE (4.3) for $[HClO_4]$ up to 5.68M. This upper limit arose from the onset of appreciable exchange of the deuterium label with solvent at higher acidities. TABLE (4.3) also records the isotopic rate ratios k_2^H/k_2^D derived from values of k_2^H interpolated from the data of TABLE (4.2). The 2,6-$[^2H_2]$-p--cresol used in these studies had an incorporation of deuterium in the 2,6-positions of 69%.

TABLE (4.3).

Deuterium Isotope Effect for the Nitrosation of p-Cresol in $HClO_4$ at 0°C.

Run	$[HClO_4]$ M.	$10^4 \times k_2^H$ (a) $l.mole^{-1}.sec^{-1}$.	$10^4 \times k_2^D$ (b) $l.mole^{-1}.sec^{-1}$.	k_2^H/k_2^D
191	0.0097	5.29	4.06	1.40
202	0.048	5.64	4.02	1.30
195	4.30	234	139	1.70
181	5.10	724	560	1.29
194	5.68	1740	1070	1.63

(a) Interpolated from Table(4.2).

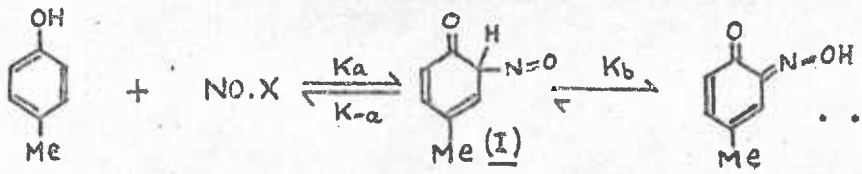
(b) For 2,6-$[^2H_2]$-p-cresol containing 69% deuterium.

Bearing in mind that the the extent of isotopic substitution in the compound is only 69%, it is apparent that the nitrosation of p-cresol is subject to an appreciable deuterium isotope effect which is of similar magnitude for the acid - -dependent and independent regions. The average observed value corresponds to a calculated k_2^H/k_2^D of 2.0 ± 0.3 for the fully deuterated substrate, the magnitude of which is consistent with a primary deuteriun isotope effect. The rate-determining step in the nitrosation of p-cresol is therefore concluded to be C-H bond fission at the site of substitution.

Discussion.

Striking similarities exist between the kinetic acidity depedence and the deuterium isotope effect for the nitrosation of p-cresol and phenol[52], suggesting that a common mechanism is operating for both compounds. As for phenol, the rate coefficient for the reaction of p-cresol is virtually independent of acidity below 0.5M $HClO_4$ apart from the small enhancement expected from a salt effect. This evidence, together with the observation of a primary deuterium isotope effect, suggests that nitrosation proceeds via the formation of a

neutral dienone intermediate (I) (equ.(4.3)) , the decomposition of which to products is largely rate-limiting. Attempts to



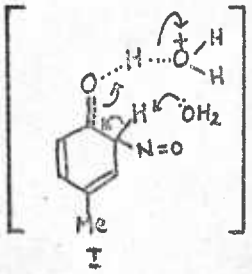
. . (4.3)

isolate (I) or detect it spectrophotometrically were un--successful and so it must be formed in a rapid and reversible step, thus not accumulating in detectable proportions. The data are not inconsistent with a single transition state mechanism in which the C-H bond breaking occurs synchronously with the attack of the electrophile, but such a mechanism is considered to be unlikely in aromatic substitution reactions.[13] The formation of (I) is also supported by other convincing evidence of quinonoid intermediate formation in other electro--philic substitutions such as iodination.[5] Since the k_b step of equ.(4.3) is rate-determining, the observed rate expression is equally compatible with the formation of (I) in several ways. Interaction of either molecular p-cresol or the cresolate anion with HNO_2, NO^+, H_2ONO^+ or N_2O_3 could, in principle, produce (I). However; HNO_2 is known to be an ineffectual reagent for the N-nitrosation of amines[77] and the

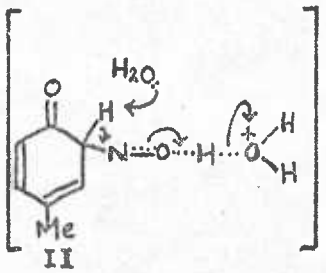
same must be true of the less reactive p-cresol. Interaction of NO^+ and H_2ONO^+ with the cresolate anion can also be discounted, since the combined concentrations of these species is so low that even an encounter process would lead to a rate very much less than that observed. Also, NO^+ has been ruled out as an active electrophile in dilute acid since it is unlikely to be formed under these conditions. The observed rate expression in the acid independent region is therefore consistent with a fast preequilibrium formation of (I) from interaction of either p-cresol with H_2ONO^+ or p-cresolate anion with N_2O_3, followed by a rate determining proton loss from the intermediate.

The onset of acid catalysis above 0.5M $HClO_4$ for the nitrosation of p-cresol also parallels quite closely the behaviour of phenol. Since the rate-determining step is still C-H bond fission (k_b step equ.(4.3)) as indicated by the substantial primary deuterium isotope effect, the acidity dependence implies protonation of the intermediate in the rate-determining step. The transition state for this step may then resemble one of the two possibilities (II) or (III) , involving protonation on the phenolic or the nitroso-oxygen respectively: studies on phenol have implicated the

latter possibility[52]. Thus, effects of protonation of the intermediate in the rate-determining step will be super-



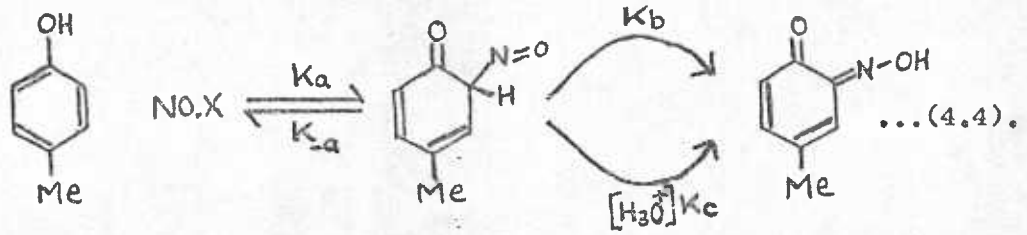
I



II

imposed upon the effect of changing acidity on the nature of the electrophilic nitrosating species operating in the reaction. For this reason, the observed reduced dependence of log k_2 on the H_R acidity function is not a true reflection of the form of the nitrosating agent and so does not necessarily exclude NO^+, which is known to follow this function, as the active electrophile.

Thus the mechanism of the nitrosation of p-cresol can be summarised for both the acid dependent and independent regions as shown in equ.(4.4),



...(4.4).

The maximum in the rate of nitrosation of p-cresol occurs at about 7M $HClO_4$, after which the rate decreases with further increase in acid concentration. Similar maxima occurring in the rates of nitrosation of phenol and anisole at 7.5M $HClO_4$ have been proposed by Challis and Lawson as evidence for NO^+ as the active electrophile, since the concentration of this species reaches a maximum in solutions of comparable acidity. The result for p-cresol is reasonably consistent with this conclusion ; the small difference in acidity at which the maxima in the rates occur could arise from variations in the influence of acidity on the activity coefficients of the transition states for the different substrates .

The fall in rate with the increasing acidity after the rate maximum for p-cresol is attributed mainly to the decreasing concentrations of water in this acidity region, since water is the strongest base available for removal of the proton from the protonated intermediate in the rate-limiting step.

(B). Nitrosation of Other Para-Substituted Phenols.

Four other para-substituted phenols have been examined to investigate the sensitivity of aromatic nitrosation to substituent effects. To obviate complications arising from

reaction via several nitrosating agents, these measurements have been made at 0°C in 6.8M $HClO_4$, where the maximum rate is observed for p-cresol, and where the major notrosating species is the NO^+. Under these conditions, spontaneous decomposition of the nitrous acid solutions is quite slow, but it is, nonetheless, of similar order to the rate of nitrosation of the most deactivated substrates. This unproductive loss of nitrous acid follows an approximate first order rate with a rate coefficient designated k'.

With an excess substrate concentration, the observed rate of disappearance of HNO_2 follows equ.(4.5),

$$-\frac{d(HNO_2)}{dt}_{.obs} = k^o[HNO_2] \quad .....(4.5)$$

where k^o is the overall first order observed rate coefficient. However, k^o is the sum of the rate coefficients for the spontaneous decomposition of HNO_2 (k') and the nitrosation of the aromatic substrate (k_1),

$$k^o = k' + k_1 \quad .....(4.6)$$

where the rate of nitrosation of the aromatic substrate is given by equ.(4.7) which reduces to equ.(4.8) in the

prescence of a constant excess of the aromatic substrate over HNO_2,

$$\text{rate} = k_2 [\text{p-X-phenol}][HNO_2] \quad \ldots\ldots (4.7)$$

$$= k_1 [HNO_2] \quad \ldots\ldots (4.8).$$

Values of k' obtained by independent determinations in the absence of aromatic substrate are shown in TABLE(4.4).

TABLE (4.4).

Spontaneous Decomposition of HNO_2 in 6.8M $HClO_4$ at 0^oC.

Run	241	242	245
$10^5 \times k'(sec^{-1})$	0.61	0.58	0.60

mean value $k' = 0.60 \times 10^{-5} sec^{-1}$.

Experimental values of k^o, k_1 and k_2 are listed in TABLE (4.5) on the following page.

TABLE (4.5).

Experimental Rate Coefficients (k^o, k_1 and k_2) for Nitrosation of Para-Substituted Phenols in 6.8M $HClO_4$ at 0°C.

Run	$10^2 \times$ [substrate] M.	$10^5 \times k^o$ sec^{-1}.	$10^5 \times k'$ sec^{-1}.	$10^5 \times k_1$ sec^{-1}.	$10^5 \times k_2$ $l.mole^{-1}.sec^{-1}$.
p-Fluorophenol.					
379	0.530	2.57	0.60	1.97	372
381	0.530	2.62	0.60	2.02	381
382	0.530	2.78	0.60	2.18	411
383	1.06	4.84	0.60	4.24	400
p-Chlorophenol.					
210	1.02	3.45	0.60	2.85	279
211	1.02	3.27	0.60	2.67	262
212	1.01	3.37	0.60	2.77	274
213	2.02	6.29	0.60	5.69	282
p-Cyanophenol.					
243	5.51	1.78	0.60	1.18	21.4
244	5.51	1.86	0.60	1.26	22.9
245	5.51	1.90	0.60	1.30	23.6
p-Nitrophenol.					
251	5.50	0.73	0.60	0.13	2.4
252	5.50	0.72	0.60	0.12	2.2
253	5.50	0.71	0.60	0.11	2.0

Discussion.

Mean values of the second order rate coefficient (k_2) defined by equ.(4.9) are summarised in TABLE (4.6) for the

$$\text{rate} = k_2 \left[\text{p-X-phenol}\right] \left[HNO_2\right] \quad \ldots\ldots (4.9)$$

nitrosation of p-substituted phenols in 6.8M $HClO_4$ at 0^oC. Under these conditions, none of the substrates is appreciably protonated and HNO_2 exists mainly as NO^+. Thus the k_2 values listed in TABLE (4.6) are, to a good approximation, equivalent to molecular rate coefficients for reaction by NO^+. TABLE (4.6) also lists the substituent parameters σ^+_m.

TABLE (4.6).

Mean values of k_2 for Nitrosation of Para-Substituted Phenols in 6.8M $HClO_4$ at 0^oC.

Substituent	σ^+_m (a)	$10^5 \times k_2$ ($l.mole^{-1}.sec^{-1}$.)
Me	-0.066	91,000 (b)
F	0.352	390
Cl	0.399	270
CN	0.562	23
NO_2	0.674	2.2

(a) Ref.(33). (b) Interpolated from data of TABLE (4.2).

FIGURE (4.2).

Hammett Plot for Nitrosation of Para-Subsituted-Phenols in 6.8M $HClO_4$ at 0°C.

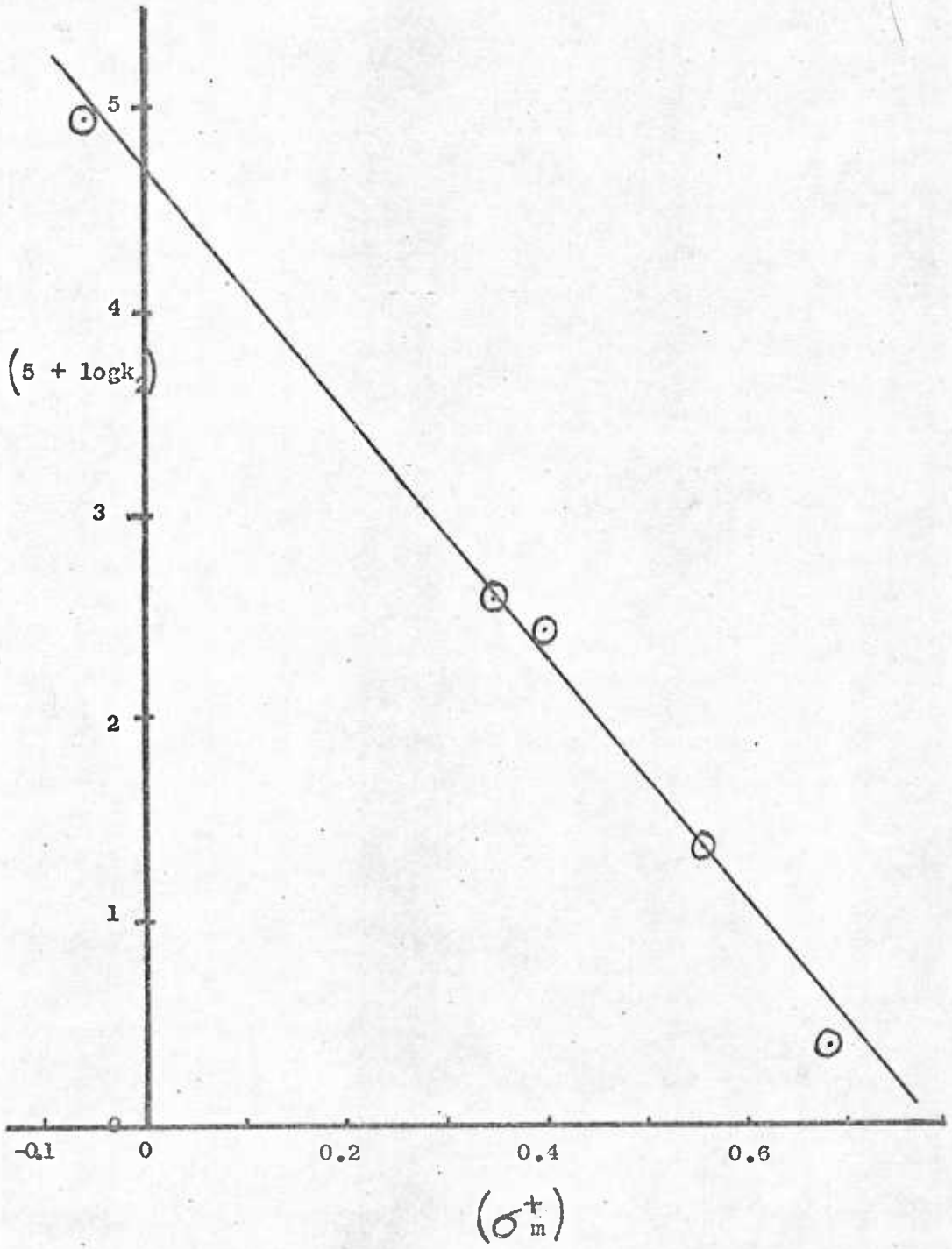


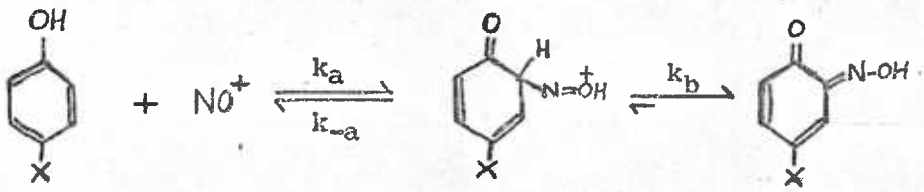
FIGURE (4.2) shows a plot of log k_2 against Hammett σ_m^+ substituent parameters : this is linear with a slope of ρ = -6.2 . The linearity of the plot suggests no change of rate--determining step or mechanism occurs with changing para--substituents. It also rules out the possibility of π-complex formation between the aromatic substrate and NO^+ being kinetically significant. This deduction is important because π-complexes have been reported to form in concentrated H_2SO_4 with aromatic substrates when the substrate and HNO_2 concentrations are relatively high[81]. U.V. spectral examination of the reaction solutions of the para-substituted phenols has revealed no positive evidence for π-complex formation under these conditions.

As discussed more fully on page (245), the only products isolated from the nitrosation of all the para-substituted phenols are the ortho-nitro derivatives. This raises the question of whether these studies refer to an initial nitrosation reaction followed by a rapid oxidation, or to a direct nitration by nitric acid formed in situ. All of the available evidence supports the former explanation, and discounts the possibity of a direct nitration pathway. Firstly, the extremely facile oxidation of ortho -nitrosophenols to their

ortho-nitro counterparts is well known[38,39], and has been confirmed under the conditions used here, for independently prepared 2-nitroso-4-methyl- and 2-nitroso-4-chloro-phenol (see chapter 8, pp (248)). There can be no doubt that the reaction of p-cresol involves an initial nitrosation, since direct nitration is known to proceed without a primary deuterium isotope effect[4]. The reaction of p-cresol shows a substantial primary deuterium isotope effect, and the linearity of the Hammett $\rho - \sigma_m^+$ plot in FIGURE (4.2) leaves little possibity of a change in rate-limiting step or mechanism over the range of substrates studied. Further--more, recent studies of nitration in concentrated $HClO_4$ suggest that aromatic compounds more reactive than benzene, which includes all the compounds examined here, undergo nitration at an encounter rate[28]. Thus, the marked difference in reactivity observed for the series of substrates studied here is wholly inconsistent witha direct nitration reaction.

The low ρ-value of -6.2 found for ortho - nitrosation of para - substituted phenols confirms satisfactorily the value of -6.9 obtained previously from studies of the nitrosation of activated mono-substituted benzenes. This relatively low ρ - value for a reagent which has been widely considered

to be unreactive and selective can be rationalised by consideration of the rate-determning stop operating in these nitrosation reactions. The rate-limiting step in the reactions studied here has been identified as proton loss from the dienone intermediate (I) (equ.(4.10)) which is formed in small stationary concentrations in the A-S_E2 sceme outlined below.



...(4.10).

For the A-S_E2 scheme in equ.(4.10) the overall observed rate coefficient defined by

$$\text{rate} = k_2 \left[\text{Substrate}\right] \left[NO^+\right] \quad \ldots\ldots(4.11)$$

is given by equ.(4.12),

$$k_2 = \frac{k_a\, k_b}{k_{-a} + k_b} \quad \ldots\ldots\ldots(4.12).$$

Since a primary deuterium isotope effect ie observed for the reaction, $k_{-a} \gg k_b$, and equ.(4.12) reduces to (4.13),

$$k_2 \approx \frac{k_a\, k_b}{k_{-a}} \quad \ldots\ldots(4.13).$$

Thus, a natural consequence of equ.(4.13) is that the sensitivity of the overall observed rate coefficient k_2 to electron withdrawing substituents is in fact resultant difference of their opposite effects on k_a and k_b. Electron withdrawal from the aromatic nucleus will increase the free energy of the transition state associated with the k_a step, and of the protonated intermediate. However, electron withdrawal has the opposite effect on k_b, whereby it decreases the free energy of the transition state for this step. Hence in the case that k_b is partly rate-controlling, the overall reaction will show a reduced sensitivity of the rate toward electronic effects of the substituents.

From these results, it is apparent that the ρ - value for an electrophilic substitution reaction cannot be used indiscriminately to make deductions about the reactivity of the electrophile and the timing of the transition state on the reaction coordinate, in the absence of additional information determining the rate-limiting step of such a reaction. The original concepts to the reactivity-selectivity principle, that reactions with low ρ-values have early transition states and are not predisposed toward isotope

effects, must be considered with great caution, especially when there are other factors that may be effective in deciding the rate-determining step.

CHAPTER V.

NITROSATION IN CONCENTRATED AQUEOUS MINERAL ACID SOLUTIONS.

It is evident from the previous chapter that rate--determining proton-loss from the intermediate in the nitrosation of *para*-substituted phenols by NO^+ results in a low ρ-value for the reaction . This concurs with earlier deductions for the reaction of mono-substituted benzenes with NO^+ [37], although proof that proton-loss was indeed rate-limiting for the least reactive substrates was in fact not available. To remedy this deficiency, and to establish that slow proton-loss is characteristic for the nitrosation of aromatic substrates of low, as well as high, reactivity the nitrosation of benzene and hexadeuteriobenzene have been re-examined as reported below.

This chapter, too, reports the results of an investigation into the acid catalysed nitrosation of phenol in fairly concentrated H_2SO_4 and H_3PO_4 and these are compared with

those obtained previously for the reaction in $HClO_4$ by Challis and Lawson[52]. These studies demonstrate the incidence of general acid catalysis in the concentrated acidic media and permit assessment of the species responsible for the effect.

(A). The Nitrosation of Benzene and $[^2H_6]$-Benzene.

Nitrosation of benzene, itself, was studied in approximately 12M H_2SO_4 and the deuterated isomer in approximately 12M D_2SO_4 at 52.9°C. Under these conditions, the rate of spontaneous decomposition of nitrous acid which follows equ.(5.1), at constant acidity, has to be taken into account,

$$-\frac{d[HNO_2]}{dt} = k'[HNO_2] \qquad \ldots\ldots (5.1).$$

The rate of nitrosation of the aromatic substrate follows equ.(5.2), which in the prescence of excess benzene reduces to the pseudo-first order expression of equ.(5.3),

$$\text{rate} = k_2[\text{benzene}][HNO_2] \qquad \ldots (5.2)$$

$$= k_1 \cdot [HNO_2] \qquad \ldots (5.3)$$

Thus, the overall observed rate of loss of nitrous acid follows equ.(5.4),

$$\frac{-d[HNO_2]}{dt} = (k_1 + k')[HNO_2]$$

$$= k^o [HNO_2] \qquad \ldots\ldots (5.4).$$

Since the value k' for spontaneous decomposition of nitrous acid has been measured under the experimental conditions, the coefficient k_1 of equ.(5.3),and hence the coefficient k_2 of equ.(5.2), for the nitrosation of benzene can be calculated from the observed overall rate coefficient k^o. The results for both benzene and $[^2H_6]$-benzene are recorded in TABLE (5.1).

TABLE (5.1).

Experimental Rate Coefficients (k^o, k_1 and k_2) for Nitrosation of Benzene and $[^2H_6]$-Benzene at 52.9°C.

Initial stoich. $[HNO_2] = 10^{-4}$M.

Run	Acid M.	$10^2 \times$[substrate] M.	$10^5 \times k^o$ sec^{-1}.	$10^5 \times k_1$ sec^{-1}.	$10^3 \times k_2$ $l.mole^{-1}.sec^{-1}$.
Benzene / H_2SO_4.					
52	12.46	--	2.83	--	--
53	12.46	--	2.65	--	--
56	12.12	1.19	21.5	18.8	15.8
55	12.24	1.20	19.7	17.0	14.2
$[^2H_6]$-Benzene / D_2SO_4.					
57	11.7	--	0.20	--	--
58	11.8	1.10	2.21	2.01	1.83
59	12.0	1.10	1.96	1.76	1.60

Discussion.

Under the reaction conditions, neither of the substrates is appreciably protonated and nitrous acid exists mainly as NO^+ [36]. Thus the experimental k_2 values (equ.(5.2)) listed in TABLE (5.1) are to a good approximation equivalent to molecular

rate coefficients for reaction by NO^+. It is evident from the data of TABLE (5.1) that $[^2H_6]$-benzene in D_2SO_4 nitrosates about 8.5 x slower than normal benzene in H_2SO_4. Since the H_o acidity of these two solvents for the experiments is closely similar[82] and in any event, the reaction rate is not strongly dependent on acidity under these conditions, the rate difference for the benzene isomers is indicative of a substantial primary deuterium isotope effect.

Comparison of the rate data of TABLE (5.1) with previous data obtained for the nitrosation of benzene in $HClO_4$[37] at the same temperature, reveals that the reaction rate is dependent on the nature of the solvent acid even when nitrous acid is totally converted to NO^+. In 10.4M $HClO_4$, which has a similar H_R value to the 12M H_2SO_4 solutions employed here, the value of k_2 for the nitrosation of benzene at 52.9°C has a value of 3.9×10^{-3} $l.mole^{-1}.sec^{-1}$. Thus for solvents of similar H_R acidity, nitrosation of benzene in H_2SO_4 is about 50x faster than in $HClO_4$. This difference cannot in any way be attributed to interference in the reaction through sulphonation of the substrate[83], since the sulphonation of benzene is at least 30 x slower than nitrosation under similar conditions.

It is concluded that the difference in nitrosation rates for the reaction in H_2SO_4 and $HClO_4$ is a direct consequence of the rate-limiting proton transfer from the Wheland intermediate , characteristic of this reaction. The proton--loss will be catalysed by the extra basic species HSO_4^- and SO_4^{--} present in H_2SO_4 (as well as by water) but not by the ClO_4^- anion, which is only feebly basic.

The same argument suggests that the observed large reduction in the rate of nitrosation of $[^2H_6]$-benzene in D_2SO_4 compared to benzene in H_2SO_4 will include factors arising from the change in solvent (i.e. the different basic strengths of HSO_4^-, SO_4^{--} and DSO_4^-) as well as from a primary deuterium isotope effect. For this reason an exact value cannot be given to the k_H/k_D ratio for the nitrosation of benzene, although it appears to be large.

These results suggest that rate-limiting proton transfer from the intermediate on the S_E2 pathway is characteristic of aromatic nitrosation with substrates of widely different reactivity and is not a special effect related to the relatively low acidity of the leaving proton for reactive compounds such as phenol, cresol and anisole.

(B). Nitrosation of Phenol in Concentrated Aqueous Solutions of H_2SO_4 and H_3PO_4.

One of the conclusions drawn from the above investigation is that nitrosation is catalysed by one or both of the anions of sulphuric acid, as well as by water, itself. This should be a general phenomenon observable for other substrates and other polybasic acids. Thus studies of nitrosation present an excellent opportunity to examine the incidence of general acid catalysis in concentrated acid solutions. This phenomenon has been observed recently for aromatic hydrogen exchange [84,85], but the circumstances are less clear-cut. Accordingly, the nitrosation of phenol (a well defined reaction) has been examined in H_2SO_4 and H_3PO_4 for comparison with earlier results in $HClO_4$ [52].

The rate expression for the nitrosation of phenol in mineral acid solutions is well established and follows equ.(5.5) at any given acidity. The variation of k_2 with sulphuric

$$\text{rate} = k_2 [\text{phenol}] [HNO_2] \quad \ldots . (5.5)$$

acid concentration ranging from 5M to 13.6M is shown in TABLE (5.2), for nitrosation in aqueous H_2SO_4 solutions at $0^{\circ}C$. Results for nitrosation of phenol in H_3PO_4 solutions varying from 48.9% to 81.9% (by wt.) H_3PO_4 are shown in TABLE (5.3). Both tables also list values of the H_R acidity function.

TABLE (5.2).

Variation of k_2 (equ.(5.5)) with Acidity for Nitrosation of Phenol in H_2SO_4 at $0^{\circ}C$.

Run	$[H_2SO_4]$ M.	$-H_R$ [61]	k_2 (l.mole^{-1}.sec^{-1}.)
367	4.88	6.30	0.32
366	4.94	4.35	0.42
373	5.36	4.80	0.68
368	5.74	5.20	1.65
363	6.18	5.70	1.76
365	6.44	5.95	4.62
364	6.96	6.52	10.2
376	7.28	6.88	14.2
403	7.98	7.63	33.2
400	9.20	8.92	58.2
402	9.12	8.83	61.4
404	10.22	10.00	40.7
408	10.36	10.15	42.8
406	11.14	11.00	30.0
410	11.24	11.10	22.5
409	11.34	11.20	21.9
405	12.26	12.20	13.0
411	13.58	13.60	6.1

TABLE (5.3).

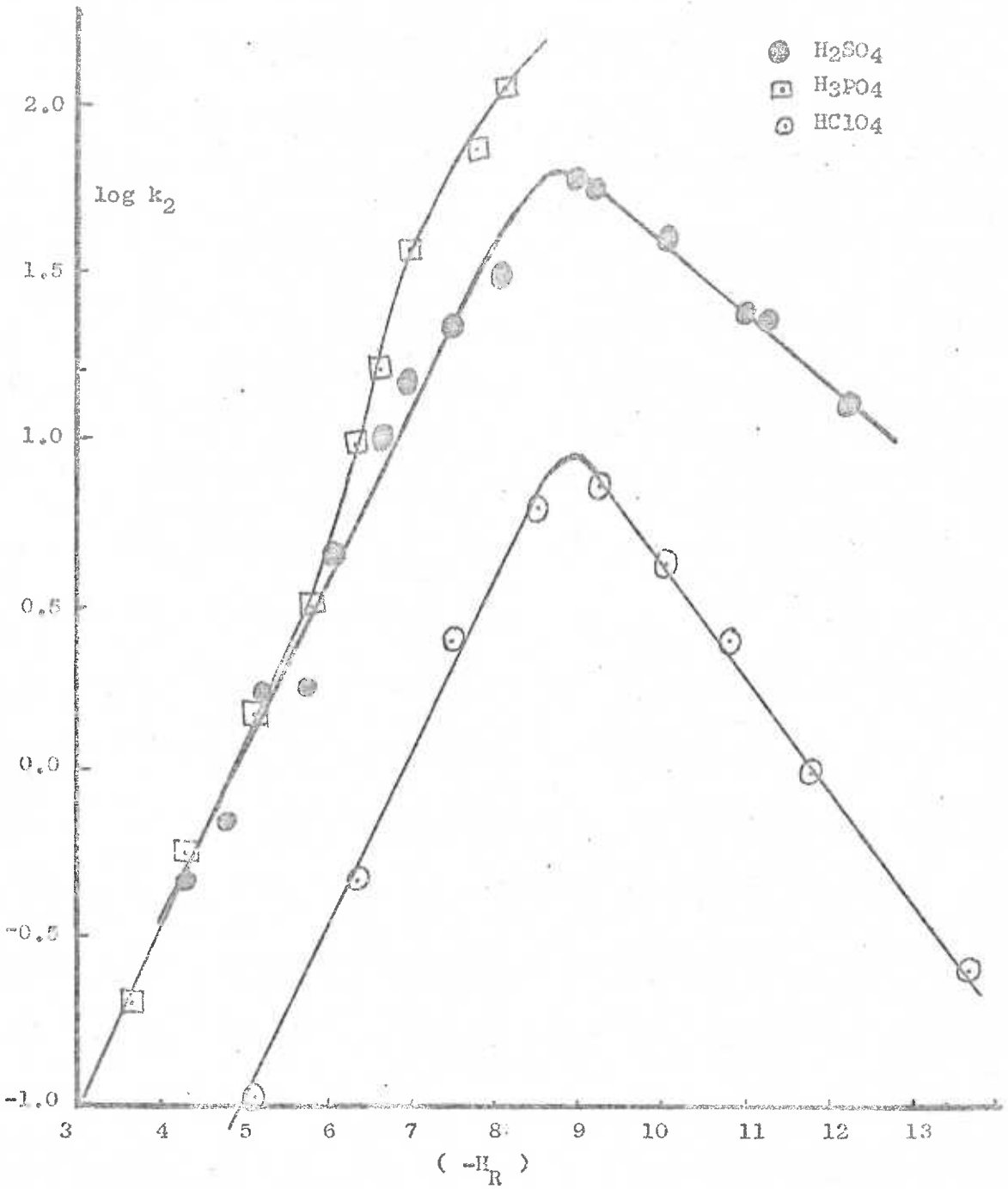
Variation of k_2 (equ.(5.5)) with Acidity for the Nitrosation of Phenol in H_3PO_4 at 0°C.

Run	wt.% H_3PO_4	$-H_R$ [86]	k_2(l.mole.sec^{-1}.)
471	48.87	3.11	0.10
469	52.84	3.62	0.20
466	57.77	4.33	0.53
467	62.72	5.17	1.66
468	65.56	5.68	3.42
465	69.21	6.32	9.56
485	70.53	6.54	17.5
484	72.56	6.89	34.3
482	74.58	7.26	50.9
479	76.64	7.62	74.0
481	77.67	8.03	114
478	81.86	8.56	182

A comparison of the results for nitrosation of phenol in $HClO_4$, H_2SO_4 and H_3PO_4 is most conveniently made by plotting log k_2 *versus* the acidity function $-H_R$ for all the acids. These plots of the data of TABLES (5.2) and (5.3) are shown in FIGURE (5.1), together with a similar plot of the data of Challis and Lawson[52] for $HClO_4$.

FIGURE (5.1).

Dependence of log k_2 on $-H_R$ for Nitrosation of Phenol in H_2SO_4 , H_3PO_4 and $HClO_4$ at 0^oC.

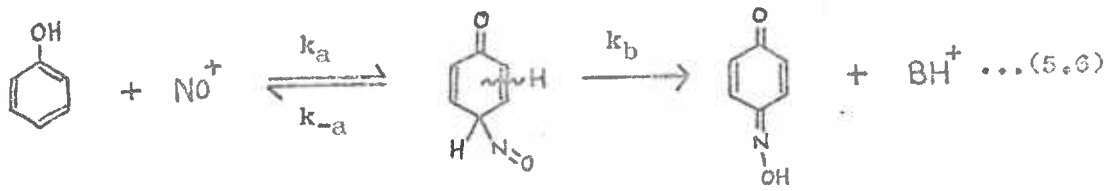


Inspection of FIGURE (5.1) reveals that at identical H_R values, the rate of nitrosation of phenol in H_2SO_4 is faster than that in $HClO_4$ by a factor varying from 10 to 20. Also, the rate reaches a maximum at a similar H_R value in both acids, but the rate after the maximum decreases less rapidly with increasing acidity in H_2SO_4 than in $HClO_4$; the slope of FIGURE (5.1) in this region is -0.2 for H_2SO_4 compared to a value of -0.35 for $HClO_4$. Interference in the kinetics of the reaction from sulphonation can be ruled out, since the rate of sulphonation of phenol[87] under the conditions employed here will be negligible compared with the rate of nitrosation.

The rate of nitrosation of phenol in H_3PO_4 exceeds that in $HClO_4$ at identical acidity as measured by the H_R acidity function, by a factor varying from 12 to 30.

Discussion.

Challis and Lawson[52] established that the nitrosation of phenol proceeds *via* an $A\text{-}S_E2$ mechanism in which proton-loss from a protonated dienone intermediate is slow (equ.(5.6)). The proton-



...(5.6)

-transfer must, of course, be to a basic species (B), which in the case of $HClO_4$ is probably H_2O. In other polybasic acids additional anions are present and evidence that these are important comes from the higher reaction rate in H_2SO_4 and H_3PO_4 compared to $HClO_4$, at the same H_R acidity. Since the dienone intermediate is protonated in concentrated acid, catalysis by solvent anions results kinetically in the observation of general acid catalysis. General acid catalysis in concentrated solutions of strong acids is difficult to observe, but has been established for aromatic hydrogen exchange, an A-S_E2 reaction closely related to nitrosation, by Kresge and coworkers [84,85]. They invoked catalysis by the undissociated species HSO_4^- and H_3PO_4, in addition to the H_3O^+ species, as responsible for the enhanced rates of detritiation of 1,3-dimethoxybenzene-4-t in polybasic acids compared with those in mono-basic acids , when compared at equal extents of equi--librium protonation of azulene as a measure of thermodynamic acidity. In this reaction there is a rate-determining proton-transfer from solvent acid to the substrate (equ,(5.7)). Thus,

$$ArH' + HA \rightleftharpoons H'.\overset{+}{Ar}.H + A^- \rightleftharpoons H.Ar + H'A \quad ..(5.7)$$

the observation of general acid catalysis for the nitrosation of phenol in concentrated solutions of strong acids is a useful confirmation for slow proton-transfer.

A full analysis of the type which can be applied in a straight--forward manner to general acid catalysed reactions occurring in dilute solution, cannot be applied to these results for any single polybasic acid, since it is difficult to evaluate the much greater medium effects produced by the massive amounts of solute present in concentrated solutions. In dilute solutions, of course, salt effects on rate and equilibrium constants can be treated quite accurately, since ideal behaviour can be assumed for all interactions.

It was thought likely that some simple empirical correlation might be found in the data for the rate of nitrosation of phenol in the region of acidity in which the rate decreases with increasing acidity i.e. after the rate maxima in the log k - H_R profile of FIGURE (5.1). The maximum corresponds to complete conversion of HNO_2 to NO^+ and the kinetic data should therefore not be complicated by preequilibrium effects.

1. Nitrosation of Phenol in Concentrated $HClO_4$; Correlation of the Rate with Water Activity.

The data of Challis and Lawson for the nitrosation of phenol

in concentrated aqueous solutions of $HClO_4$ in the region of acidity after the rate maximum at 7.5M $HClO_4$ is listed in TABLE (5.4). Also listed in this table are values of a_w interpolated from the data of Robinson and Baker[88].

TABLE (5.4).

Nitrosation of Phenol in $HClO_4$ at 0.7°C at $[HClO_4] \geq 7.5M$.

Correlation of k_2 (equ.(5.5)) with a_w.

$[HClO_4]$ M.	a_w (a)	k_2 (b) $l.mole^{-1}sec^{-1}$.	k_2/a_w^2 $l.mole^{-1}.sec^{-1}$.
7.87	0.205	7.18	170.6
8.28	0.164	4.58	170.1
8.90	0.110	2.05	169.8
9.40	0.077	1.02	172.6

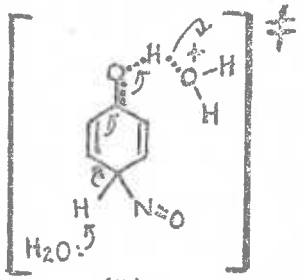
(a) Interpolated from the data of reference (88).

(b) From the data of reference (52).

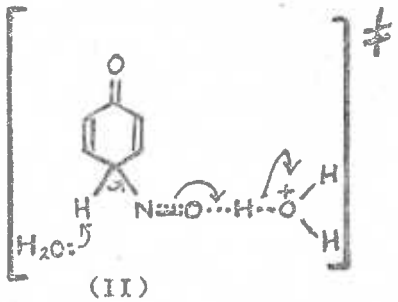
The consistency of k_2/a_w^2 shown by TABLE (5.4) indicates that the rate constant for the nitrosation of phenol in this region of acidity, can be expressed by equ.(5.8),

$$k_2(\text{equ.}(5.5)) = k'_w \cdot a_w^2 \quad \ldots\ldots (5.8)$$

where $k'_w = 171 \pm 2$ l.mole^{-1}.sec^{-1}. , when a_w is expressed in activity terms. The dependence of k_2 on the square of a_w indicates that two molecules of H_2O are associated with removal of the proton in the rate-determining step. This is not an unreasonable result, particularly since Challis and Lawson previously proposed that the transition state for the reaction may resemble structures such as (I) and (II) below, both of which involve two molecules of H_2O.

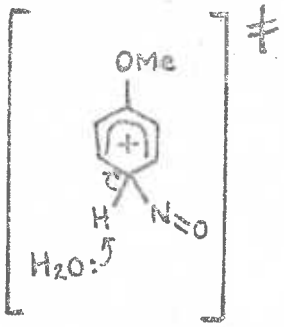


(I)



(II)

In order to test the validity of this treatment, the data of Challis and Lawson for the nitrosation of anisole in concentrated aqueous $HClO_4$ has been analysed in a similar fashion. This reaction also proceeds with a primary deuterium isotope effect, and also shows a rate maximum at a similar acidity as for phenol. Assuming the arguments for phenol to be valid, the rate decrease after this maximum should be some function, only, of the decrease in a_w. However, in the reaction of anisole, there is no possibility of dienone-intermediate formation as for phenol, and so the rate-determining transition state will probably resemble (III) and will only



(III)

accomodate one molecule of H_2O. In this case, only a first order dependence of the rate on a_w would be expected. TABLE (5.5) lists the relevant rate and a_w data for the nitrosation of anisole in $HClO_4$.

TABLE (5.5).

Correlation of k_2 with a_w for Nitrosation of Anisole in $HClO_4$ > 7.5M at 0.7°C.

$[HClO_4]$ M.	a_w (a)	k_2 (b) $l.mole^{-1}.sec^{-1}$.	k_2/a_w $l.mole^{-1}.sec^{-1}$
8.00	0.192	3.00	15.6
8.50	0.144	2.15	14.9
8.72	0.124	1.70	13.7
9.41	0.076	1.18	15.5
10.22	0.042	0.568	13.5
10.33	0.038	0.515	13.6

The reasonable constancy of k_2/a_w = 14.5 ± 1.1 $l.mole^{-1}.sec^{-1}$. , adequately confirms the linear relationship expected and hence supports the empirical treatment used here. Thus it appears that the decrease in the rate of nitrosation of phenol and anisole in $HClO_4$ with increasing acidity, which occurs after the rate maxima, reflects quite accurately the decreasing availability of H_2O molecules for accomodation in the rate-determining transition state.

2. Nitrosation of Phenol in Concentrated Aqueous H_2SO_4; Correlation of Rate with a_w , $[HSO_4^-]$ and $[SO_4^{--}]$

In order to make an assessment of the relative contributions to the nitrosation rate coefficient for phenol , k_2 ,from the two anions in H_2SO_4, it will be assumed that the empirically-derived dependence of k_2 upon a_w^2 is valid. However, in addition to this term, the coefficient k_2 will also depend on terms arising from catalysis by HSO_4^- or SO_4^{--}.

An unsophisticated analysis shows the dependence of k_2 can be written in the form of equ.(5.9), as a linear summation of the seperate contributing terms. This equation has been empirically

$$k_2 = k_w'.a_w^2 + k_{HSO_4^-}.[HSO_4^-] + k_{SO_4}.[SO_4^{--}] \quad ...(5.9)$$

derived from the data of TABLE (5.6), which lists the measured k_2 values for the nitrosation of phenol in H_2SO_4, the a_w values interpolated from the data of Giaque and coworkers[89], and the $[HSO_4^-]$ and $[SO_4^{--}]$ values, which are interpolated from the data of Robertson and Dunford[90]. The k_w' value used is that derived in TABLE (5.4) from the analysis in $HClO_4$, i.e. $k_w' = 171$ l.mole^{-1}.sec^{-1}. A plot of the data of TABLE (5.6) according to equ.(5.10) (a simple derivation of equ.(5.9)), is shown in FIGURE (5.2).

$$\frac{k_2 - k_w' a_w^2}{[HSO_4^-]} = k_{HSO_4^-} + k_{SO_4^{--}} \frac{[SO_4^{--}]}{[HSO_4^-]} \quad \ldots(5.10).$$

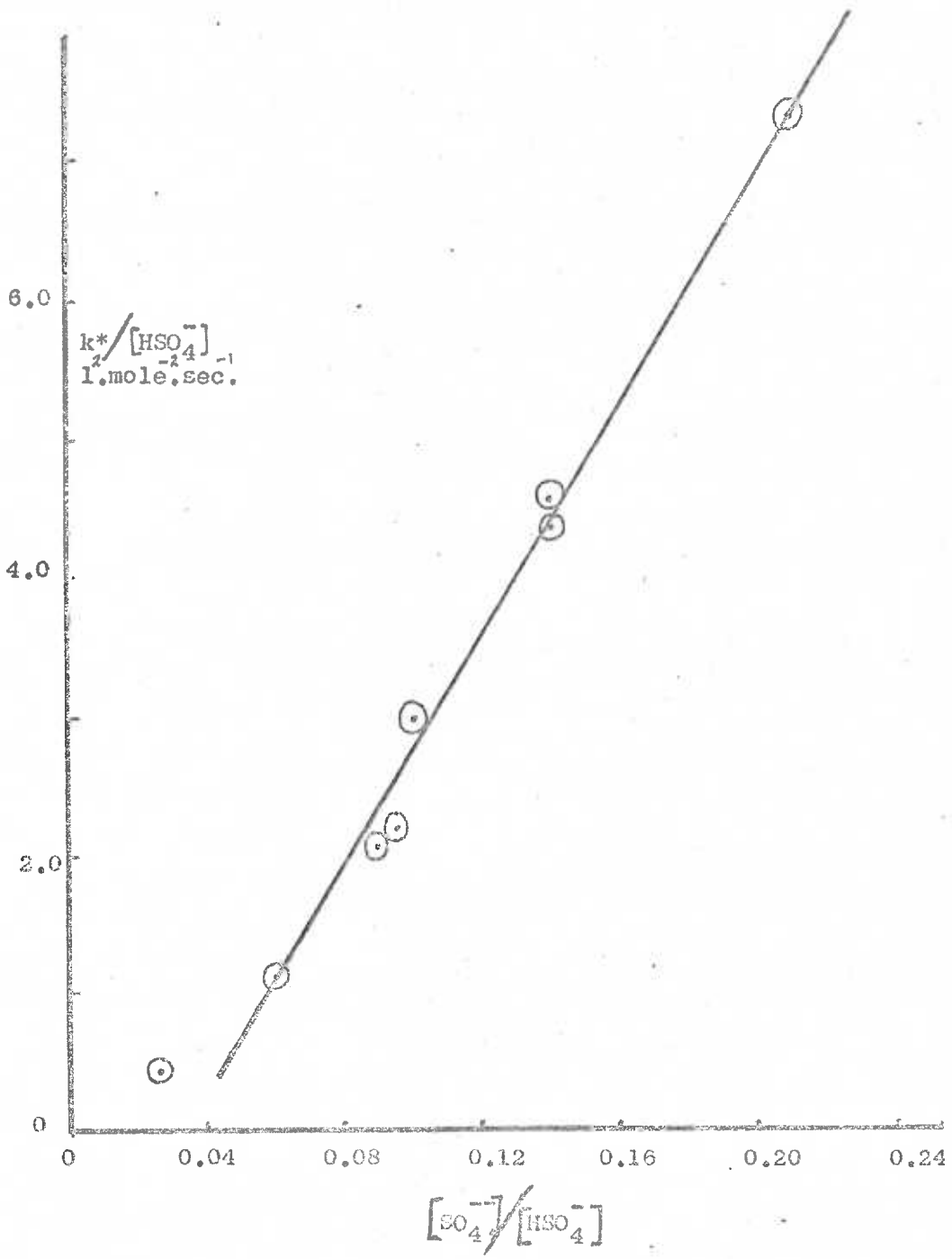
TABLE (5.6).

Nitrosation of Phenol in H_2SO_4 at 0°C. 9M H_2SO_4.

$[H_2SO_4]$ M.	a_w	$[HSO_4^-]$ M.	$[SO_4^{--}]$ M.	$k_2 - 171a_w^2 = k^*$ l.mole^{-1}.sec^{-1}	$k^*/[HSO_4^-]$ l.mole^{-2}.sec^{-1}	$\frac{[SO_4^{--}]}{[HSO_4^-]}$
9.16..	0.162	7.58	1.60	55.3	7.30	0.21
10.22	0.092	8.96	1.29	39.1	4.30	0.14
10.36	0.0885	9.14	1.25	41.4	4.50	0.14
11.14	0.054	10.17	1.008	29.4	2.89	0.099
11.24	0.050	10.31	0.977	22.0	2.14	0.095
11.34	0.050	10.45	0.950	21.5	2.05	0.091
12.26	0.026	11.65	0.703	12.9	1.11	0.060
13.58	0.008	12.92	0.355	6.1	0.47	0.027

FIGURE (5.2).

Nitrosation of Phenol in $[H_2SO_4] > 9M$, at 0°C. Plot of equ.(5.10).



The reasonable linearity of FIGURE (5.2) shows that equ.(5.9) provides a good empirical fit for the data. The slope of this plot gives the value of $k_{SO_4^{--}} = 40\ l^2.mole^{-2}.sec^{-1}$. Less certainty can be placed on the value of $k_{HSO_4^-}$, since the plot in FIGURE (5.2) deviates from linearity at the highest acidity. Nonetheless, it is apparent that the value of $k_{HSO_4^-}$ is small compared with that of $k_{SO_4^{--}}$. Thus the decrease in the rate of nitrosation of phenol, in concentrated aqueous solutions of H_2SO_4, with increasing acidity, reflects mainly the decrease in the $[SO_4^{--}]$, which acts as a base in assisting in proton-removal from the intermediate in the rate-determining step. The effectiveness of SO_4^{--} as a base catalyst relative to HSO_4^- accords with the $pK_{H_2SO_4} = -3.6$[91] and $pK_{HSO_4^-} = +1.9$[92].

Unfortunately, a similar analysis of the data for the nitrosation of phenol in H_3PO_4 cannot be carried out, since no reliable data are available for a_w in this acid. Nonetheless, it is apparent from the increased rate of reaction in H_3PO_4 solutions compared with that in $HClO_4$ solutions of equivalent H_R acidity, that similar catalysis is occurring here, presumably by the $H_2PO_4^-$ species. This is in accord with the observation by Kresge and coworkers[84] that aromatic hydrogen exchange is

catalysed by H_3PO_4 acting as a general acid in concentrated solutions.

Summary.

It has now been proven by studies of isotopically - -substituted substrates that the rate-determining step in the nitrosation of benzene is C-H bond breaking. Thus slow proton transfer is characteristic of the nitrosation of substrates of a wide range of reactivities and is not only related to the acidity of the leaving proton.

A consequence of this rate-determining step in nitrosation is catalysis by the anions of strong polybasic acids in concentrated solutions of these acids. In H_2SO_4, the major contributing species is the SO_4^{--}. In the absence of catalytic bases such as SO_4^{-} and $H_2PO_4^{-}$, H_2O is the effective base in removing the proton.

CHAPTER VI.

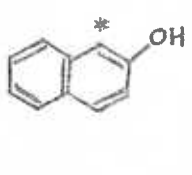
NITROSATION IN BUFFERED AQUEOUS SOLUTIONS OF WEAK ACIDS.

The work described in this chapter is concerned primarily with the dependence of rates and of kinetic isotope effects on the acidity and constitution of aqueous buffer solutions. This information might throw some light on the relative magnitudes of the rate coefficients of the various steps of the A-S_E2 mechanism. The use of buffer solutions provides a convenient way of studying these relationships, since the reactions can be carried out in dilute solution and accurate control of catalyst concentrations is possible.

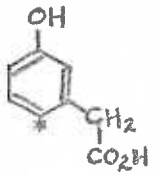
Ibne-Rasa has reported earlier[51] that the nitrosation of 2,6-dibromophenol is general base catalysed by nitrite and acetate ions, although no rigorous analysis of the mechanistic implication of the results was made. A concurrent objective of this work was to investigate the possibility of intramolecular base catalysis in aromatic nitrosation; it was thought that intro-

-duction into the substrate of a neighbouring group with a basic site suitably placed to allow direct approach to the leaving proton of the Wheland intermediate, might result in great acceleration of this step. It is well known that intra--molecular displacements at saturated carbon centres occur at much greater rates than the corresponding intermolecular reactions[93].

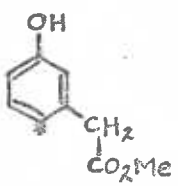
In this chapter then, are reported the results of a detailed investigation into the kinetics of nitrosation in aqueous buffer solutions of phenol, 2-naphthol, (I), m-hydroxy--phenylacetic acid (II), m-hydroxyphenylacetic acid -methyl ester (III), and 7-hydroxy-1-naphthoic acid (IV).



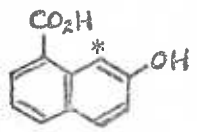
(I)



(II)



(III)



(IV)

* Site of substitution.

(A). Nitrosation of Phenol in aqueous Acetic-acid Buffers.

The kinetics of nitrosation of phenol in aqueous acetic acid-sodium acetate buffer solutions have been investigated over the pH range 1.7 to 5.5 at 25°C under which conditions

nitrosation occurs almost exclusively at the para-position (95%).

Under conditions of a large excess of phenol over the stoicheiometric sodium nitrite concentration, the reaction follows the rate expression of equ.(6.1),

$$\text{rate} = \bar{k}_1 \cdot (NaNO_2) \quad \ldots\ldots\ldots (6.1)$$

where ($NaNO_2$) refers to the total stoicheiometric concentration of nitrite . The rate of nitrosation shows a first order dependence on phenol concentration over the complete acidity range studied, pH 1.7 to 5.5, and so at any fixed pH the rate of nitrosation of phenol is given by equ.(6.2),

$$\text{rate} = \bar{k}_2.(\text{phenol}).(NaNO_2) \ldots\ldots (6.2).$$

The validity of equ.(6.2) is shown by the data of TABLE (6.1). Since the $pK_{PHENOL} = 9.98$ [94], the stoicheiometric and real concentrations of molecular phenol are effectively the same throughout the pH range studied. Thus the concentrations of phenol are denoted by square brackets in all subsequent rate equations.

TABLE (6.1).

Nitrosation of Phenol in AcOH-AcONa Buffer Solutions at 25°C; First Order Dependence of the Rate on Phenol.

Initial $(NaNO_2) = 10^{-4}M$, [Acetate] = 0.15M.

Run	total (AcOH) M.	pH	$10^5 \times \bar{k}_1$ sec^{-1}.	$10^2 \times$ [phenol] M.	$10^3 \times \bar{k}_2$ $l.mole^{-1}.sec^{-1}$.
299	1.27	3.72	21.4	3.78	5.66
280	1.27	3.72	6.94	1.26	5.51
281	0.601	4.19	4.50	1.97	2.29
290	0.601	4.19	9.09	3.94	2.31
291	0.208	5.13	0.568	3.94	0.144
283	0.208	5.13	1.13	7.98	0.142
292	0.170	5.54	0.104	3.94	0.0264
284	0.170	5.54	0.206	7.98	0.0258

The stoicheiometric rate constant $\bar{k}_2$ is dependent on acidity, as is apparent from the data of TABLE (6.1). This is expected since, in the pH range under study, sodium nitrite is only partially converted to nitrous acid (equ.(6.3)). In terms of

$$HNO_2 \rightleftharpoons H^+ + NO_2^- \qquad \ldots (6.3)$$

$$K_{HNO_2} = \frac{[H^+][NO_2^-]}{[HNO_2]} = 4.6 \times 10^{-4} \text{ at } 25^\circ C.$$ [95]

the actual concentrations of HNO_2 and NO_2^-, equ.(6.2) can be written as :- equ.(6.4) which on substitution for $[NO_2^-]$ from

$$\text{rate} = \bar{k}_2 [\text{phenol}] \{[HNO_2] + [NO_2^-]\} \quad \ldots (6.4)$$

equ.(6.3) leads to equ.(6.5) ,

$$\text{rate} = \bar{k}_2 \left\{1 + \frac{K_{HNO_2}}{[H^+]}\right\} [HNO_2] [\text{Phenol}] \quad ..(6.5).$$

Thus the second order rate coefficient for the nitrosation of phenol k_2 (defined by equ.(6.6)) is related to the observed stoicheiometric coefficient $\bar{k}_2$, defined in terms of the total stoicheiometric nitrite concentration, by the expression of

$$\text{rate} = k_2 [\text{phenol}] [HNO_2] \quad \ldots\ldots (6.6)$$

equ.(6.7) ,

$$k_2 = \bar{k}_2 \left\{1 + \frac{K_{HNO_2}}{[H^+]}\right\} \quad \ldots\ldots (6.7)$$

This explains the acidity dependence for $\bar{k}_2$. Since the pH is constant for each kinetic run, and $K_{HNO_2} = 4.6 \times 10^{-4}$ at $25.0^{\circ}C$, values of k_2 (equ.(6.6)) can be computed for each kinetic experiment by equ.(6.7). For the sake of brevity, all subsequent k_2 coefficients reported herein for experiments in

buffer solutions have been calculated from $\bar{k}_2$ in this way.

Acidity Dependence of k_2.

Values of k_2 (equ.6.6) for the nitrosation of phenol in buffer solutions at a constant acetate concentration of 0.15M but varying pH are listed in TABLE (6.2).

TABLE (6.2).

Nitrosation of Phenol in Aqueous AcOH-AcONa Buffer Solutions; Variation of k_2 (equ.(6.6)) with pH.

[Acetate] = 0.15M throughout.

Run	total(HOAc) M.	pH	$10^2 \times k_2$ $l.mole^{-1}.sec^{-1}$.
298	1.62	3.010	1.80
299	1.37	3.720	1.83
289	1.00	3.878	1.82
295	1.00	3.875	1.82
297	0.713	4.060	1.75
287	0.300	4.620	1.53
291	0.208	5.125	0.898
292	0.170	5.540	0.424

These data show that up to pH = 4.62, k_2 is virtually independent of acidity. This is in complete accord with the results of past workers for the reaction in dilute mineral acids. Challis and Lawson[52] showed that the k_2 coefficient was acid independent from pH 1 to 3 in dilute $HClO_4$ and Schmid and coworkers[50] reported similar findings for dilute HCl. However, the results in TABLE (6.2) also show that for pH $>$ 4.6 , k_2 begins to decrease with increasing pH . This result has not been previously observed.

Catalysis by Acetate Ion.

The results in TABLE (6.3) show that, in addition to a pH dependence, the magnitude of k_2 also depends on the acetate ion concentration. These experiments were not carried out at constant ionic strength, but the addition of $NaClO_4$ shows that salt effects are not significant for the reactions. It is therefore concluded that the effect of added acetate is one of base catalysis, and this is in line with previous studies with 2,6-dibromophenol[51].

TABLE (6.3).

Nitrosation of Phenol in AcOH-AcONa Buffers at 25°C; Acetate Catalysis.

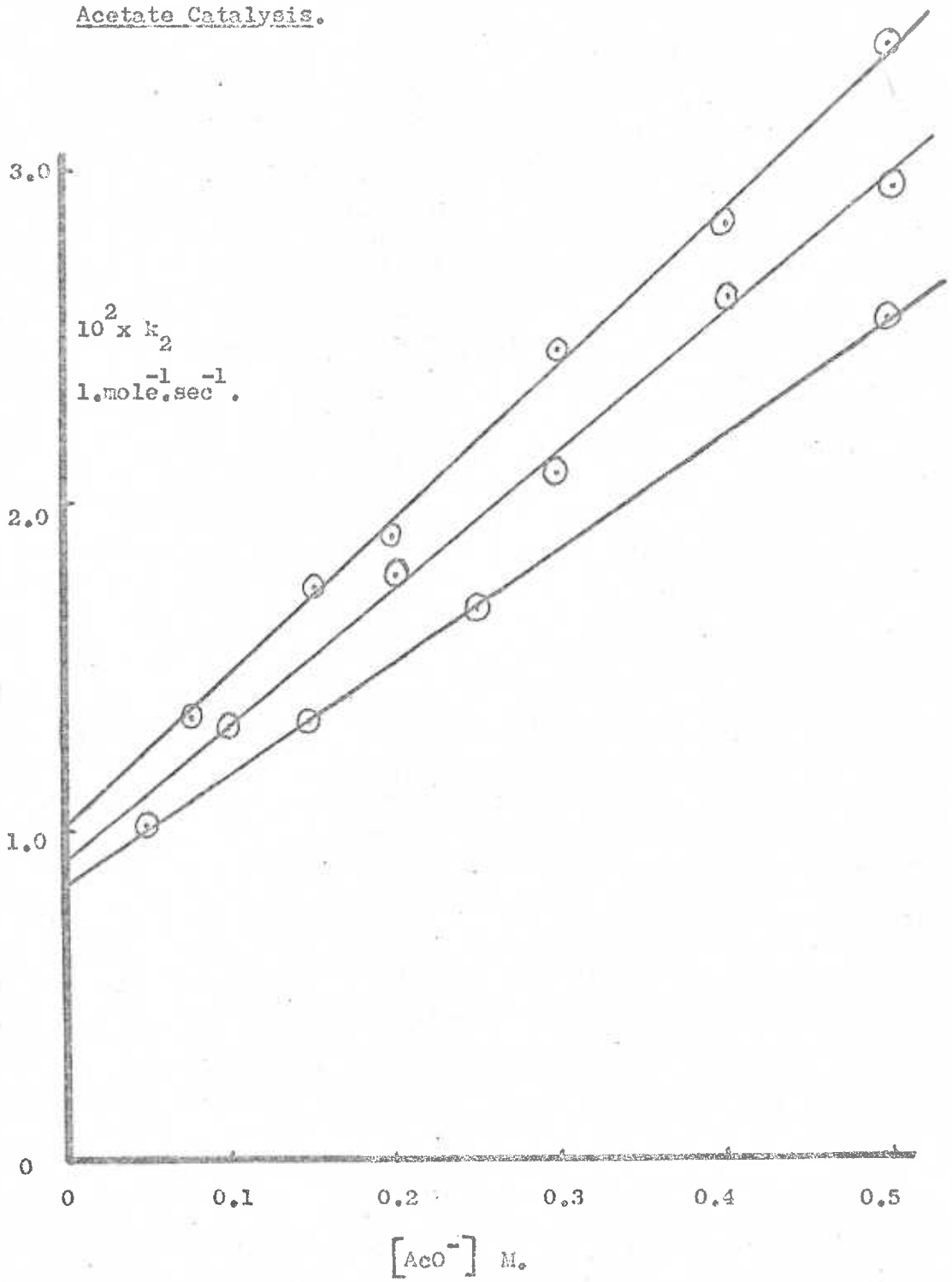
Run	pH	Total(AcOH) M.	$[AcO^-]$ M.	$[ClO_4^-]$ M.	$10^2 \times k_2$ $l.mole^{-1}.sec^{-1}$.
296	4.06	0.357	0.075	-	1.35
297	4.06	0.713	0.15	-	1.75
328	3.91	1.00	0.20	-	1.89
298	4.05	1.62	0.30	-	2.46
325	3.915	2.00	0.40	-	2.82
326	3.92	2.50	0.50	-	3.37
327	3.91	0.357	0.075	0.50	1.25
332	4.54	0.235	0.10	-	1.32
329	4.53	0.470	0.20	-	1.78
330	4.53	0.705	0.30	-	2.08
331	4.54	0.940	0.40	-	2.61
338	4.49	1.175	0.50	-	2.94
339	4.49	0.235	0.10	0.40	1.20
288	4.65	0.10	0.05	-	1.01
287	4.62	0.30	0.15	-	1.33
286	4.61	0.50	0.25	-	1.67
285	4.62	1.00	0.50	-	2.54
301	4.61	1.00	0.50	-	2.50

The data of TABLE (6.3) are shown graphically in FIGURE (6.1) as plots of k_2 against acetate concentration.

FIGURE (6.1).

Nitrosation of Phenol in AcOH-AcONa Buffers at 25°C;

Acetate Catalysis.



All three plots shown in FIGURE (6.1) are reasonably linear and show that the rate of nitrosation of phenol is catalysed by acetate ion according to equ.(6.8),

$$k_2 = k_{2w} + k_{AcO^-}\left[OAc^-\right] \quad \ldots . \quad (6.8)$$

where k_{2w} represents the rate coefficient at zero acetate ion concentration , corresponding to reaction catalysed only be water molecules and k_{AcO^-} represents the catalytic coefficient for catalysis by acetate ion. FIGURE (6.1) again illustrates the onset of acidity dependence for k_2 at pH $>$ 4.6; the k_{2w} values for the reaction at pH 4.0 and 4.5 differ by about 6% (which is similar to the estimated error in determining k_2) but drop by a factor of 15% on increasing the pH from 4.5 to 4.6. It also appears that for pH $>$ 4.5, the reaction becomes increasingly less dependent on acetate ion concentration and the k_{AcO^-} catalytic coefficients decrease accordingly. Values of k_{2w} and k_{AcO^-} obtained from FIGURE (6.1) are given in TABLE (6.4).

TABLE (6.4).

Nitrosation of Phenol in AcOH-AcONa Buffers at 25°C .

pH	$10^2 \times k_{2w}$ (equ.(6.8) $l.mole^{-1}.sec^{-1}$	$10^2 \times k_{AcO^-}$ (equ.6.8) $l^2.mole^{-2}.sec^{-1}$
4.0	1.02 ± 0.02	4.7 ± 0.3
4.5	0.96 ± 0.04	4.0 ± 0.2
4.6	0.84 ± 0.01	3.4 ± 0.2

If the concentration of water in dilute solutions is assumed to be 55.5M, the catalytic coefficient k_w for catalysis of the reaction by water molecules can be estimated from k_{2w} by the simple approximation,

$$k_w = k_{2w} / 55.5$$

from which k_w at pH = 4.0 is 1.8×10^{-4} $l.mole^{-1}.sec^{-1}$.

The magnitudes of the catalytic coefficients k_w and k_{AcO^-} should fit a Bronsted relationship[68] defined by equ.(6.9) and equ.(6.10),

$$k_B = G_B K_B^{\beta} \quad \ldots\ldots\ldots\ldots (6.9)$$

$$\log k_B = -\beta . pK_B + \log G_B \quad \ldots\ldots (6.10).$$

Assuming $pK_{AcO^-} = 9.25$[96] and $pK_{H_2O} = -1.74$[97], the values of the catalytic coefficients lead to a value of $\beta = 0.37$. This value lies between the theoretical limits for the β exponent and confirms that proton-transfer is rate limiting.

Nitrosation of 4-$\left[^2H_1\right]$-Phenol; the Kinetic Isotope Effect.

The nitrosation of 4-$\left[^2H_1\right]$-phenol has been studied in acetic acid buffer solutions of varying pH and acetate ion concentration. The values of the rate coefficients k_2^D (equ.(6.11))

$$\text{rate} = k_2^D \cdot [4\text{-}[^2H_1]\text{-Phenol}][HNO_2] \quad \ldots \quad (6.11)$$

for the deuteriated phenol are listed in TABLE (6.5), which also lists the corresponding coefficients for nitrosation of the normal compound (denoted k_2^H), measured uunder identical conditions. Since the deuteriophenol used in these experiments was found by mass spectral analysis to have a deuterium content of 81% at the 4-position, the experimental k_2^H/k_2^D ratio has been corrected, assuming a linear dependence on % deuterium, and the actual k_H/k_D is given in the last column of TABLE (6.5).

TABLE (6.5).

Nitrosation of Phenol in Aqueous AcOH-AcONa Buffers at 25°C: Deuterium Isotope Effect.

Run	pH	Total (AcOH) M.	$[AcO^-]$ M.	$10^2 \times k_2^H$ ($l.mole^{-1}.sec^{-1}$.)	$10^2 \times k_2^D$ (a)	k_H/k_D (0^oC)
*	1.0	--	-	(0.8)	(0.21)	3.9
442,446	1.695	7.00	(0.006)	1.09	0.39	3.5
444,448	4.32	6.87	2.40	8.02	3.03	3.3
445,449	4.44	10.31	3.60	9.90	4.32	3.0
440,438	5.31	2.80	2.10	5.70	3.23	2.3

* Estimated from data of reference (52), for reaction in $HClO_4$.
( ) denotes estimated values.
(a) for 81% incorporated substrate.

Catalysis at High Acetate Ion Concentration.

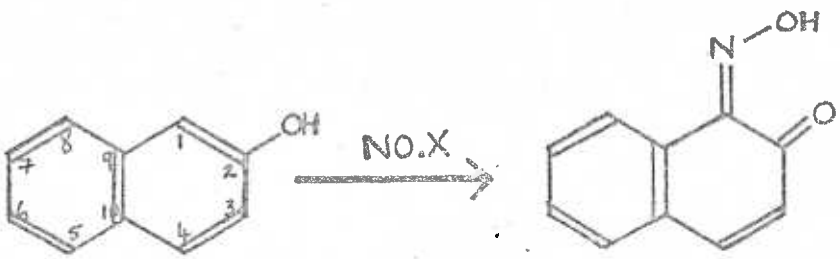
The value of k_{2w} at pH = 4.5 and zero acetate concentration, extrapolated from FIGURE (6.1) is 0.96×10^{-2} l.mole^{-1}.sec^{-1}., which is of similar magnitude to the rate coefficient $k_2 = 0.8 \times 10^{-2}$ estimated from the data of Challis and Lawson for the reaction in $HClO_4$ in the acidity-independent region. Both these values are also reasonably similar to the coefficient determined in 7M acetic acid, in which the acetate concentration is estimated as about 0.006M ($k_2 = 1.09 \times 10^{-2}$) . This confirms the absence of catalysis of the reaction by acetic acid itself, in the pH range 1.0 to 4.5. The data of TABLE (6.5) indicate that even in the prescence of extremely high concentrations of acetate ion there is no significant change in the k^H/k^D ratio. However, at similar acetate concentrations (about 2M), there is a significant decrease in k^H/k^D from 3.3 to 2.3 on increasing the pH from 4.3 to 5.3. Mass spectral analysis of the substrate at the completion of each of the kinetic runs shown in TABLE (6.5) showed that negligible exchange of deuterium with the solvent had occurred during the reaction.

It would appear that this trend towards a reduced deuterium isotope effect at high pH is associated with the onset of acidity

dependence of k_2 at about pH = 4.6 (see page (121)) and the decreasing values of k_{AcO^-} above pH 4.5 (see page 124). A detailed investigation of the kinetics of nitrosation of phenol in this high pH region could not be conveniently carried out, since the rate of reaction is extremely slow. However, such studies are possible with the more reactive, closely-related 2-napthol. Since the results of these studies are particularly relevant to the elucidation of the overall mechanism for the nitrosation of both phenol and 2-napthol, in the pH range 1.0 to 5.5, a full discussion of the preceding results for phenol are deferred until later.

(B). Nitrosation of 2-Napthol in Aqueous Buffer Solutions.

Nitrosation of 2-napthol (I) in aqueous buffer solutions of pH 2.0 to 5.0 occurs exclusively at the 1-position as shown in equ.(6.12) (see chapter 8).



(6.12)

(I)

The rate equation for the nitrosation of 2-napthol has been firmly established by two methods;

(i). In the prescence of a large constant excess of 2-napthol over the initial stoicheiometric concentration of $NaNO_2$ the disappearance of $NaNO_2$ follows the rate expression of equ.(6.13),

$$\frac{-d(NaNO_2)}{dt} = \bar{k}_1(NaNO_2) \quad , \ , \ . \ . \ . \ .(6.13)$$

and $\bar{k}_1$ has a first order dependence on on 2-napthol concentration, as shown by the data of TABLE (6.6).

TABLE (6.6).

Nitrosation of 2-Napthol in AcOH-AcONa Buffers at 25°C; First Order Dependence of $\bar{k}_1$ (equ.(6.13)) on [2-napthol].

Initial $(NaNO_2)$ = 5.0×10^{-5}M. $[OAc^-]$ = 0.02M.

Run	pH	$10^3 \times$[2-napthol] M.	$10^6 \times \bar{k}_1$ sec^{-1}.	$\bar{k}_2 = \bar{k}_1/$[2-napthol] $l.mole^{-1}.sec^{-1}$.
498	2.985	2.84	4200	1.49
499	2.985	1.42	2180	1.53
500	2.985	0.71	1090	1.53
509	4.449	2.13	28.4	0.0136
511	4.450	1.07	14.5	0.0133
504	4.920	2.49	3.55	0.0014
505	4.920	1.42	1.86	0.0013

(ii). In the prescence of a large excess of $NaNO_2$ over the initial concentration of 2-naphthol, the rate of formation of product follows the rate expression of equ.(6.14),

$$-\frac{d[\text{Product}]}{dt} = \bar{k}_1 [\text{2-naphthol}] \quad \ldots\ldots (6.14)$$

and $\bar{k}_1$ has a first order dependence on the stoicheiometric excess $NaNO_2$ concentration, as shown by the data of TABLE (6.7).

TABLE (6.7).

Nitrosation of 2-Naphthol in AcOH-AcONa Buffers at 25°C;

First Order Dependence of $\bar{k}_1$ (equ.(6.14)) on $NaNO_2$.

Initial [2-Naphthol] = 1.71×10^{-4}M.

[Acetate] = 0.1M, μ = 0.2M.

Run	pH	$[NaClO_4]$ M.	$(NaNO_2)$ M.	$10^4 \times \bar{k}_1$ sec^{-1}.	$10^2 \times (\bar{k}_2 = \bar{k}/(NaNO_2))$ $l.mole^{-1}.sec^{-1}$.
618	4.34	0.080	0.020	9.15	4.6
617	4.34	0.090	0.010	3.79	3.9
620	4.34	0.095	0.005	2.09	4.2

The data of TABLES (6.6) and (6.7) establish that the rate of nitrosation of 2-naphthol at any fixed acidity over the range

pH = 3.0 to 4.9 is governed by the rate expression of equ. (6.15),

$$\text{rate} = \bar{k}_2 . (NaNO_2) . [\text{2-Napthol}] \quad \ldots \quad (6.15).$$

The term $(NaNO_2)$ in equs.(6.13) and (6.15) refers to the initial stoicheiometric nitrite concentration ($= [HNO_2] + [NO_2^-]$) and, as in the case of phenol discussed earlier, it is convenient to compute the second order coefficient (k_2) dependent on the actual concentration of HNO_2 present at a given pH i.e. equ.(6.16),

$$\text{rate} = k_2 [\text{2-Napthol}] [HNO_2] \quad \ldots \ldots (6.16).$$

This has been done, as previously, by means of the relationship of equ.(6.17),

$$k_2 = \bar{k}_2 \left\{ 1 + \frac{K_{HNO_2}}{[H^+]} \right\} \quad \ldots \ldots (6.17)$$

where $K_{HNO_2} = 4.6 \times 10^{-4} M.l^{-1}$. and $[H^+]$ is obtained from the measured pH. All the second order coefficients cited consequently for the nitrosation of 2-napthol are k_2 defined by equ.(6.16).

Acidity Dependence of k_2.

Values of k_2 (equ.(6.16)) for the nitrosation of 2-napthol

have been dotermined at a fixed acetate concentration but varying pH, and the ionic strength is therefore constant. These results are tabulated in TABLE (6.8).

TABLE (6.8).

Nitrosation of 2-Naphthol in Aqueous AcOH-AcONa Buffers at 25°C. Variation of k_2 (equ.(6.16)) with pH.

[Acetate] = 0.02M. throughout.

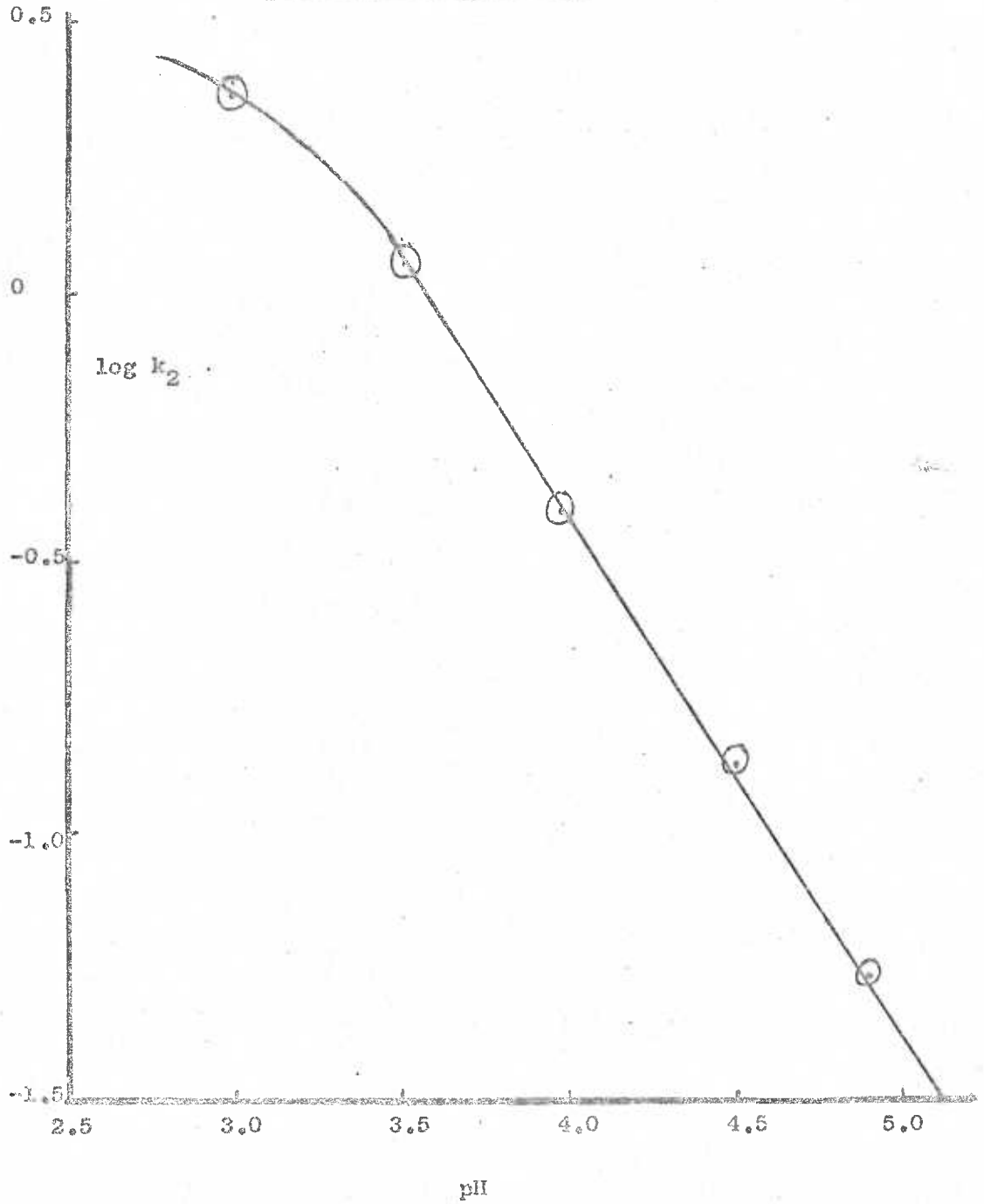
Run	pH	[HOAc] M.	k_2 $l.mole^{-1}.sec.^{-1}$
498 - 500	2.983	1.125	2.22
592	3.508	0.356	1.13
512	3.970	0.113	0.380
514	4.506	0.0356	0.135
504	4.920	0.0112	0.054

The corresponding plot of log k_2 against pH is shown in FIGURE (6.2). It is evident from FIGURE (6.2) that k_2 is strongly dependent on acidity, and from pH = 3.5 to 5.0, this plot is linear with slope = -0.97. Thus the rate of nitrosation of 2-naphthol in the pH range 3.5 to 5.0 has a first order dependence on H^+. At pH < 3.5, however, the k_2 coefficient is less

FIGURE (6.2).

Nitrosation of 2-Naphthol in AcOH-AcONa Buffers at 25°C;

Plot of log k_2 vs pH at [Acetate] = 0.02M.



dependent on acidity.

Acetate Catalysis.

The variation of the k_2 coefficient (equ.(6.16)) with $[AcO^-]$ but constant pH has been investigated for the acidity range pH = 2.7 to 4.5 . These results are listed in TABLES (6.9) and (6.10) for catalysis by the chloroacetate and acetate ions , respectively. Evidently, the rate of nitrosation of 2-naphthol is dependent to varying degrees on the $[OAc^-]$, partly because the accompanying change in ionic strength exerts a secondary salt effect (i.e. pH varies), but mainly because there is catalysis by AcO^-. This is evident from the lower effect of added $NaClO_4$. To ascertain the degree of base-catalysis by AcO^-, (as opposed to the secondary salt effect), the data of TABLES (6.9) and (6.10) have been corrected to a constant pH for each buffer ratio by an empirical correction based on the variation of k_2 with pH in FIGURE (6.2). Values of $k_2^{corr.}$ are listed in the last column of TABLES (6.9) and (6.10). The question of whether the reaction is subject to a primary salt effect still remains, but this is answered by the information given in TABLE (6.11). This shows that k_2 is virtually independent of added 0.08M $NaClO_4$, if an empirical correction for the change

in pH is made as before. The k_2^{corr} in the presence of $NaClO_4$ is within 5 - 10% of the corresponding coefficient in the absence of $NaClO_4$. Thus primary salt effects must be small. This justifies the assumption that only the secondary salt effect (i.e. change in pH) must be allowed for.

TABLE (6.9).

Nitrosation of 2-Naphthol in Chloroacetic acid Buffer Solutions at 25°C. Variation of k_2 with $[ClAcO^-]$.

Run	pH	$[ClAcOH]$ M.	$[ClAcO^-]$ M.	$[NaClO_4]$ M.	k_2 $l.mole^{-1}.sec^{-1}$	k_2 corr. to pH = 2.703
634	2.773	0.028	0.020	--	3.14	3.31
635	2.703	0.056	0.040	--	3.56	3.56
636	2.648	0.112	0.080	--	4.23	4.06
637	2.620	0.168	0.120	--	4.91	4.61
638	2.610	0.028	0.020	0.10	3.46	3.25

TABLE (6.10).

Nitrosation of 2-Naphthol in Aqueous AcOH-AcONa Buffers at 25°C.

Variation of k_2 with $[AcO^-]$.

Run	pH	$[AcOH]$ M.	$[AcO^-]$ M.	$[NaClO_4]$ M.	k_2 $l.mole^{-1}.sec^{-1}$	k_2 corr. $l.mole^{-1}.sec^{-1}$
498	2.983	1.125	0.02	--	2.22	2.35 at pH =
501	2.905	2.251	0.04	--	2.49	2.49
502	2.822	3.941	0.07	--	2.71	2.55 2.905.
503	2.770	5.060	0.09	--	3.01	2.80
504	2.760	1.125	0.02	0.07	2.40	2.22
592	3.508	0.356	0.02	--	1.13	1.13 at pH =
593	3.450	0.712	0.04	--	1.34	1.21
507	3.418	0.890	0.05	--	1.48	1.26 3.508
581	3.970	0.113	0.02	--	0.380	0.380 at pH
508	3.927	0.283	0.05	--	0.523	0.497
510	3.901	0.452	0.08	--	0.634	0.568 = 3.950
513	3.880	0.678	0.12	--	0.772	0.660
604	3.850	0.113	0.02	0.08	0.460	0.360
514	4.506	0.0356	0.02	--	0.135	0.135 at pH
509	4.454	0.0712	0.04	--	0.189	0.169
515	4.440	0.142	0.08	--	0.223	0.192 = 4.508
516	4.425	0.178	0.10	--	0.277	0.231

TABLE (6.11).

Nitrosation of 2-Naphthol in Aqueous AcOH-AcONa Buffers at 25°C.

Effect on k_2 of added $NaClO_4$.

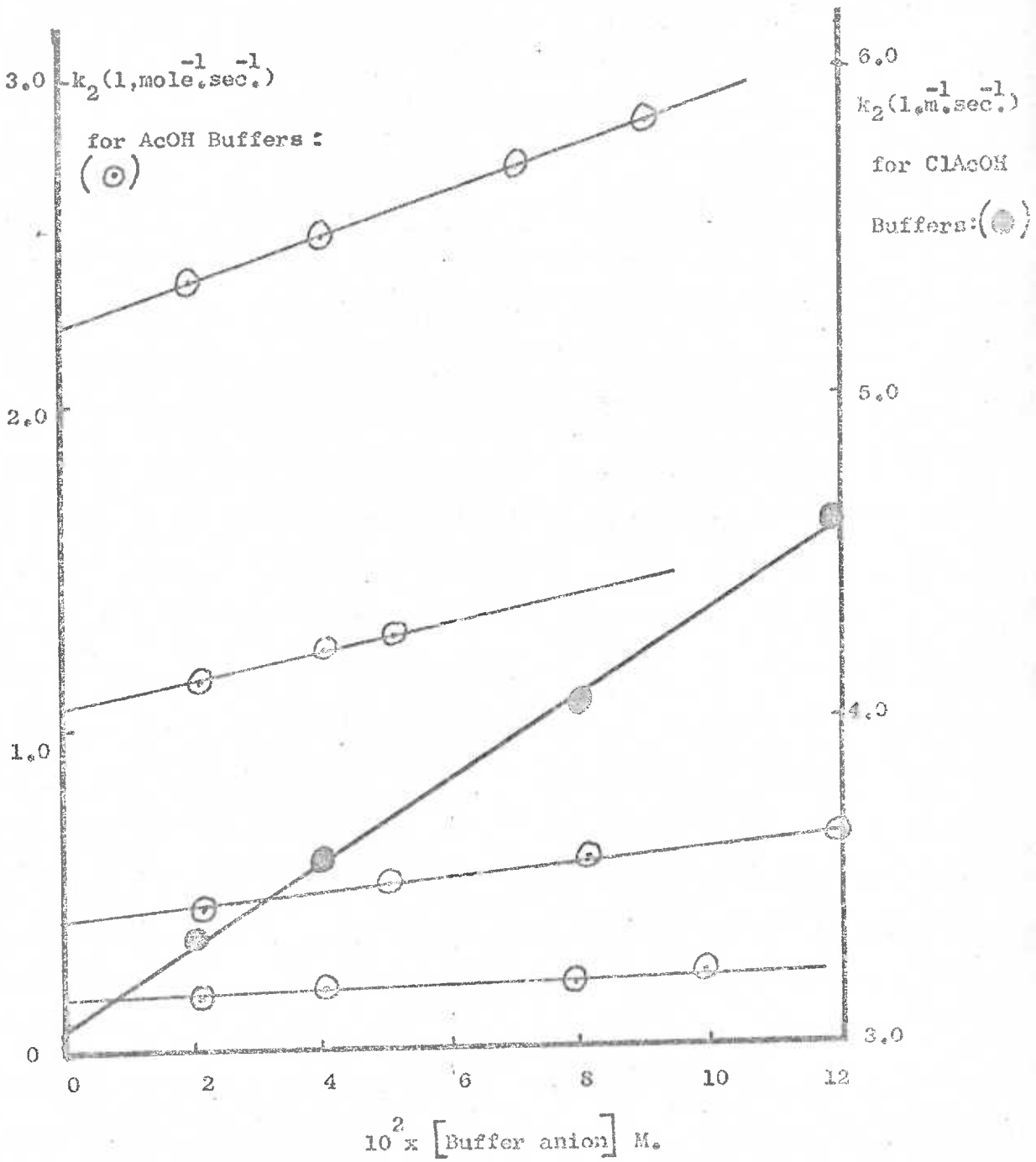
Run	pH	[HOAc] M.	[OAc^-] M.	[$NaClO_4$] M.	k_2 $l.mole^{-1}.sec^{-1}$
603	3.85	0.113	0.02	0.08	0.46
*	3.85	0.113	0.02	0	0.48
645	4.38	0.0356	0.02	0.08	0.16
*	4.38	0.0356	0.02	0	0.166

* Interpolated from FIGURE (6.2).

The variation of k_2^{corr} for the buffer-catalysed runs with [buffer salt] are plotted in FIGURE (6.3).

FIGURE (6.3).

Dependence of k_2 on [Buffer Anion] for Nitrosation of 2-Napthol at 25°C.



Two features are apparent from the plot of FIGURE (6.3). The first is that the reaction shows a first order dependence of the rate on [buffer base] and k_2^{corr} is described by equ.(6.18),

$$k_2^{corr} = k_{2w} + k_{A^-}[A^-] \quad \ldots\ldots (6.18)$$

where k_{2w} corresponds to the intercept value at zero buffer salt concentration i.e. the 'water rate', and k_{A^-} is the catalytic coefficient for the buffer anion A^-. The second is that the degree of buffer catalysis (i.e. the slopes of the plots in FIGURE (6.3)) decreases with increasing pH.

Values of the catalytic coefficients k_{2w} and k_{A^-} derived from FIGURE (6.3) and equ.(6.18) are listed in TABLE (6.12).

TABLE (6.12).

Nitrosation of 2-Naphthol in Aqueous Buffer Solutions at 25°C.

Values of k_{2w} and k_{A^-} (equ.(6.18)).

pH	k_{2w} ($l.mole^{-1}.sec^{-1}$)	k_{OAc^-} ($l^2.mole^{-2}.sec^{-1}$)	k_{ClOAc^-} ($l.m^{-1}.sec^{-1}$)
2.70	3.04	---	13.1
2.91	2.22	7.1	---
3.51	1.05	4.3	---
3.95	0.35	2.6	---
4.51	0.15	0.5	---

Nitrosation of 2-Naphthol in Dilute Aqueous $HClO_4$.

Values of k_2w (equ.(6.18)) have also been determined directly at higher acidities than those pertaining to buffer solutions (ie. pH < 2.7) by measuring the rate of nitrosation of 2-naphthol in dilute aqueous solutions of $HClO_4$. These reactions were assumed to follow the same rate expression as for reaction in buffer solutions, ie. equ.(6.16) on page(132). The k_2 coefficient will in this case be equal to the k_2w coefficient defined earlier in equ.(6.18). These data are listed in TABLE (6.13).

TABLE (6.13).

Nitrosation of 2-Naphthol at 25°C in aqueous $HClO_4$.

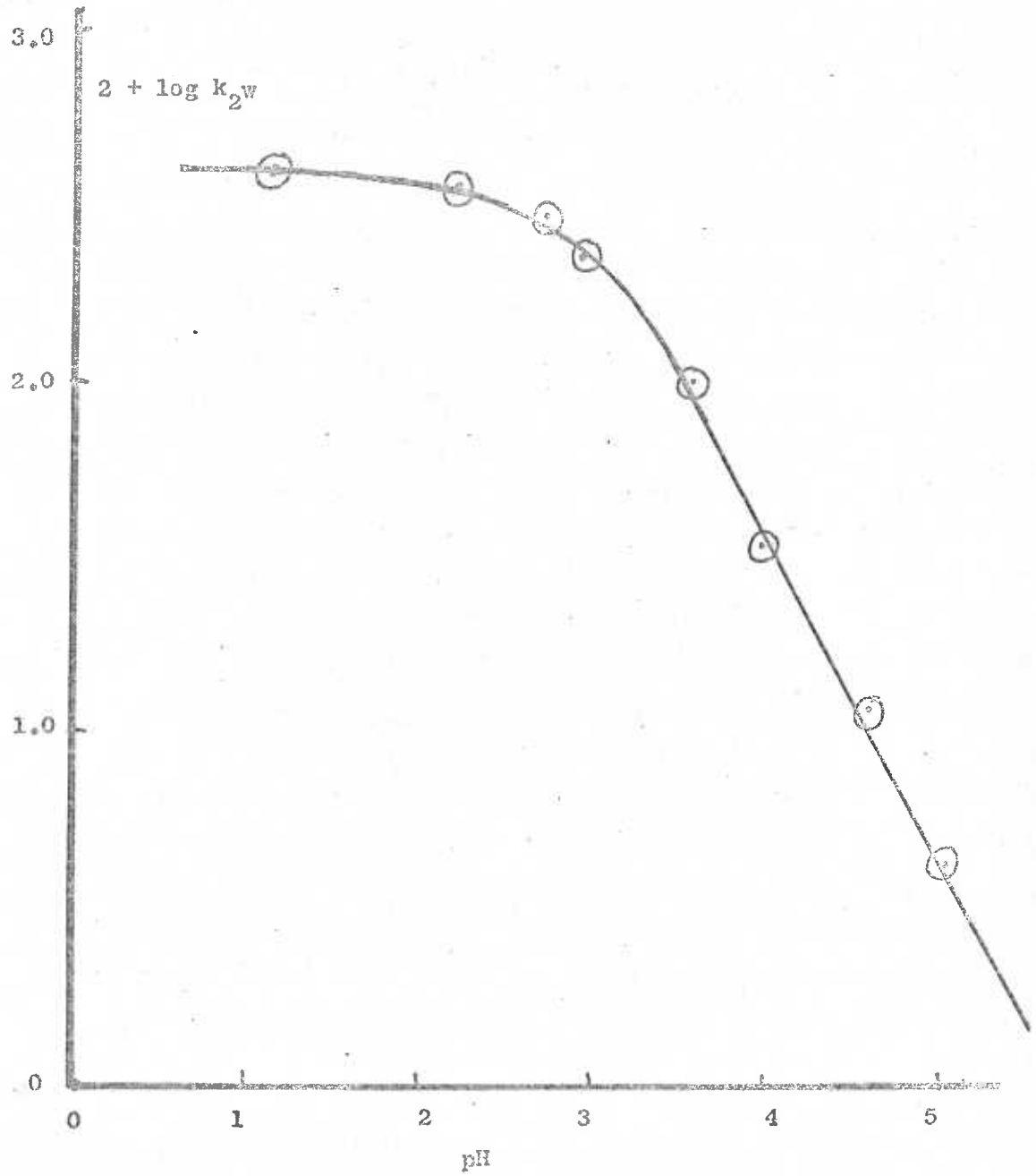
Run	pH	k_2w ($l.mole^{-1}.sec^{-1}$).
588	1.130	4.27
587	2.225	3.68

Acidity Dependence of k_2w.

FIGURE (6.4) shows the plot of log k_2w against pH for reaction in both $HClO_4$ and the buffer solutions (ie. from TABLES (6.12) and (6.13)). The datum for pH = 4.92 refers to

FIGURE (6.4).

Nitrosation of 2-Naphthol at 25°C: Plot of log k_2w vs pH.



reaction in 0.02M $[AcO^-]$, but buffer catalysis at this pH is negligible and so the value must correspond closely to k_2w. It is apparent from FIGURE (6.4) that the rate of nitrosation of 2-naphthol is independent of acidity at pH $<$ 2.7. At pH $>$ 2.7, the nitrosation rate is dependent on acidity and the slope of log k_2w versus pH is -0.97 in the region of pH = 3.3 to 5.0 ie. there is a first order dependence on $[H^+]$.

The Rate-Determining Step; Nitrosation of 1-$^2H_1$-2-Naphthol.

The nitrosation rate of 1-$[^2H_1]$-2-naphthol has also been determined in acetic acid buffers, and in dilute $HClO_4$ under identical conditions to the previous experiments. Values of the second order coefficient k_2^D obtained (equ.(6.19)) are listed in TABLE (6.14). Also listed in TABLE (6.14) are

$$\text{rate} = k_2^D[1\text{-}[^2H_1]\text{-2-naphthol}][HNO_2] \quad \ldots \quad (6.19)$$

equivalent values of k_2^H, the corresponding coefficient for reaction of the undeuteriated naphthol. Since the compound was fully deuteriated in the 1-position, the ratio k_2^H/k_2^D shown in TABLE (6.14) represents the real kinetic isotope effect for the reaction.

TABLE (6.14).

Deuterium Isotope Effects for the Nitrosation of 2-Naphthol at 25°C.

Run	pH	[HOAc] M.	[OAc⁻] M.	k_2^H (a) ($l.mole^{-1}.sec^{-1}$)	k_2^D ($l.mole^{-1}.sec^{-1}$)	k_2^H/k_2^D
In Dilute Aqueous $HClO_4$.						
650	2.15	0	0	--	0.88(0.87) (b)	4.2
*	2.15	0	0	3.71	--	
In Aqueous AcOH-AcONa Buffer Solutions.						
651	2.98	1.125	0.02	--	0.88(0.87)	2.5
498-500	2.98	1.125	0.02	2.22	--	
629	3.51	0.356	0.02	--	0.55(0.54)	2.0
592	3.51	0.356	0.02	1.13		
653	3.97	0.113	0.02	--	0.26(0.26)	1.45
512	3.97	0.113	0.02	0.38	--	
652	4.51	0.0356	0.02	--	0.098(.099)	1.4
514	4.51	0.0356	0.02	0.135	--	

(a) From data of TABLE (6.8). (b) Duplicate runs in parentheses.

* Interpolated from FIGURE (6.4).

Evidently, the nitrosation of 2-naphthol is subject to a primary deuterium isotope effect, as expected from previous studies with phenol. However, the magnitude of k^H/k^D decreases from $k_2^H/k_2^D = 4.2$ at pH = 2.15 to $k_2^H/k_2^D = 1.4$ at pH $>$ 3.5. This suggests that no primary deuterium isotope effect occurs at the higher pH values. Independent investigations have shown that negligible exchange of the 1-proton occurs at pH = 4.5 during a period of time corresponding to several half-lives of the nitrosation reaction. Also, the reaction has been shown to occur exclusively at the 1-position by product studies (see chapter 8). It is therefore concluded that a change in rate-determining step occurs as the pH is raised, and that at pH values $>$ 3.5, the rate-determining step in the nitrosation of 2-naphthol involves very little stretching of the C-H bond at the site of substitution.

Effect of Added Chloride Ion on the Rate of Nitrosation of 2-Naphthol.

The effect of added Cl^- on the rate of nitrosation of 2-naphthol at high pH has been investigated and the results are given in TABLE (6.15).

TABLE (6.15).

Effect of added NaCl and $NaClO_4$ on k_2 for the Nitrosation of 2-Naphthol in AcOH-AcONa Buffer Solutions at 25°C.

Run	pH	$[HOAc]$ M.	$[OAc^-]$ M.	$[ClO_4^-]$ M.	$[Cl^-]$ M.	k_2 $l.mole^{-1}.sec^{-1}$
*	3.85	0.113	0.02	0	0	0.50
603	3.85	0.113	0.02	0.08	0	0.46
604	3.85	0.113	0.02	0	0.08	0.70
*	4.38	0.0356	0.02	0	0	0.165
645	4.38	0.0356	0.02	0.08	0	0.160
646	4.38	0.0356	0.02	0	0.08	0.29

* Interpolated from the data in TABLE (6.8).

It is evident that whereas $NaClO_4$ only affects the rate of nitrosation of 2-naphthol through a secondary salt effect, the enhancement by NaCl is much larger, suggesting that specific Cl^- catalysis also occurs.

(C). Summary and Discussion of the Results for the Nitrosation of Phenol and 2-Napkthol in the Acidity Range pH 1 to 5.5.

The kinetics of nitrosation of phenol and 2-napkthol in the pH range 1.0 to 5.5 show remarkable similarities. The overall reaction scheme for both compounds must accomodate the following observations:

1. At any given acidity in the range pH 1 to 5, the rate of nitrosation of both phenol and 2-napkthol is governed by the rate expression of equ.(6.20),

$$\text{rate} = k_2 [\text{ArOH}][\text{HNO}_2] \quad \ldots\ldots\ldots (6.20)$$

where ArOH represents C_6H_5OH or $C_{10}H_7OH$.

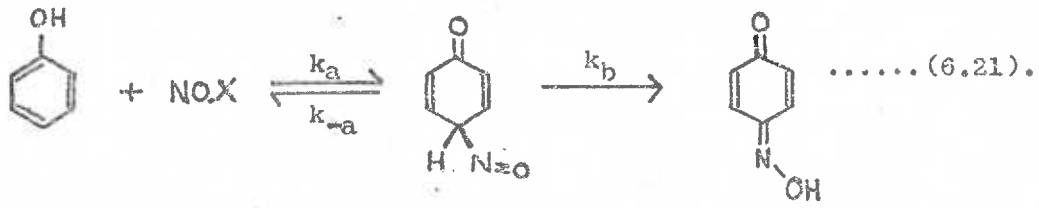
2. Coefficent k_2 (equ.(6.20)) is independent of acidity over the pH range 1.0 to 4.6 for the reaction of phenol, and over the range 1 to 2.5 for the reaction of 2-napkthol. In this acid independent region, both compounds are subject to large primary deuterium isotope effects (k_H/k_D = 3.5 for phenol and k_H/k_D = 4.2 for 2-napthol.), indicating that the rate-determining step is C-H bond breaking. The reactions are catalysed by bases and k_2 shows an approximate first order dependence on base concentration at low concentrations.

3. In the intermediate pH range 2.5 to 3.5, k_2 for 2-napkthol

begins to decrease with decreasing acidity. The magnitude of the deuterium isotope effect decreases concurrently from $k_H/k_D = 4.2$ to $k_H/k_D = 2.0$, and the degree of base catalysis progressively decreases. Similar changes are observed for the nitrosation of phenol, but the changes are observed at the higher pH = 4.6 .

4. At pH $>$ 3.5, k_2 for 2-naphthol is linearly dependent on $[H^+]$ and the kinetic isotope effect virtually disappears. The reaction is catalysed by chloride ion but not by basic species.

Because of their similar structure, the nitrosation of phenol and 2-naphthol should follow a similar mechanism and this is borne out by the close similarity in the experimental results for the two compounds. The acid independent rate and large primary isotope effect observed for the nitrosation of phenol in dilute mineral acid at pH $<$ 4 has been interpreted by Challis and Lawson as consistent with reaction *via* an A-S_E2 mechanism involving a neutral dienone intermediate, proton-loss from which is rate-determining (equ.(6.21)),



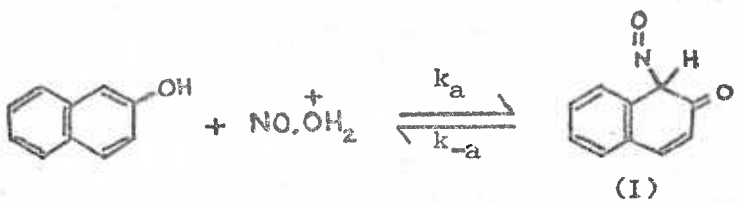
.....(6.21).

The disappearence of primary isotope effect at high pH values is most significant. It suggests that either a change in the rate-determining step or the mechanism occurs with decreasing acidity . Certain options can be readily eliminated. For instance, there is no possibility that formation of a potential nitrosating agent becomes rate-limiting, as observed in other electrophilic substitution, because the first order dependence on substrate concentration is maintained up to the highest pH values. More realistic explanations are that the rate-determining step at high pH is either the initial attack of the nitrosating species on the substrate, or the diffusion of the reactants, which then react on encounter, as observed for other reactive substrates. The latter can be discounted, however, because 2-naphthol, itself, does not react on encounter at lower pH ($k_2^H/k_2^D > 1$), and because the dependence of k_2 on $[H^+]$ at pH $>$ 3.5 is inconsistent with any reaction, encounter or otherwise, of the naphthoate ion. It therefore seems most likely that the rate-determining step in the nitrosation of 2-naphthol at pH $>$ 3.5 is the initial attack of the electrophile on the substrate.

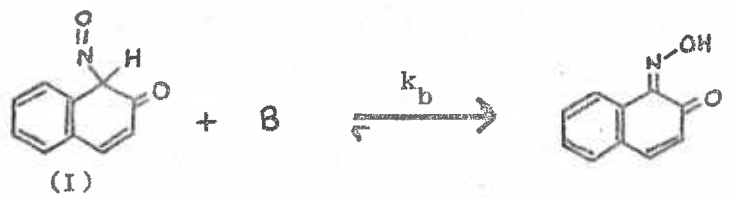
The nature of the electrophilic reagent is as yet unspecified. N_2O_3 can be ruled out, however, since only a first

order dependence of the rate on nitrite concentration has been observed, even with fairly high concentrations of nitrite and high pH (conditions favourable to the formation of this species). Attack by HNO_2 on molecular 2-naphthol can also be discounted, since this would be inconsistent with the observed acid catalysis. This leaves the remaining possibility of rate-determining attack by H_2ONO^+ on molecular 2-naphthol. We will now examine the evidence in the light of this deduction.

The S_E2 mechanism for the nitrosation of 2-naphthol, involving the formation of a steady-state neutral dienone intermediate (I), can be written as equ.(6.22),



....(6.22)



The neutral dienone intermediate (I) is formed in a reversible step k_{-a}, which is acid catalysed. The base catalysed break--down of the intermediate k_b, is essentially irreversible. An expression for the overall observed rate coefficient k_2,

in terms of rate coefficients for the component steps, may be derived from application of steady-state kinetic theory. Thus :-

$$\frac{d(I)}{dt} = 0 = k_a[\text{2-Naphth.}][H_2ONO^+] - k_{-a}[I][H_3O^+] - k_b[B][I] \quad . . (6.23)$$

and hence,

$$[I] = \frac{k_a[\text{Naphthol}][H_2ONO^+]}{k_{-a}[H_3O^+] + k_b[B]} \quad . . . . (6.24).$$

If the reaction rate is defined by equ.(6.25),

$$\text{rate} = k_2[I][B] \quad . . . . . (6.25)$$

then substitution for $[I]$ from equ.(6.24) gives equ.(6.26).

$$\text{rate} = \frac{k_a\, k_b\, [\text{Naphthol}][H_2ONO^+][B]}{k_{-a}[H_3O^+] + k_b[B]} \quad . . . (6.26)$$

The H_2ONO^+ reagent is formed in the preequilibrium step,

$$HNO_2 + H_3O^+ \underset{}{\overset{K}{\rightleftharpoons}} H_2ONO^+ + H_2O \quad . . (6.27)$$

$$K = \frac{[H_2ONO^+]}{[HNO_2][H_3O^+]}$$

Substituting for H_2ONO^+ in equ.(6.26), gives,

$$\text{Rate} = \frac{k_a k_b K[\text{Naphthol}][HNO_2][B][H_3O^+]}{k_{-a}[H_3O^+] + k_b[B]} \quad \ldots\ldots(6.28).$$

Since the observed rate expression is given by equ.(6.29),

$$\text{Rate} = k_2[\text{Naphthol}][HNO_2] \quad \ldots\ldots\ldots (6.29)$$

comparison of equ.(6.28) and (6.29) shows that,

$$k_2 = \frac{k_a k_b K[B][H_3O^+]}{k_{-a}[H_3O^+] + k_b[B]} \quad \ldots\ldots\ldots(6.30)$$

All the observations for the nitrosation of phenol and 2-naphthol are quite consistent with the steady-state rate equation (6.30). Thus, at high acidity ie. low pH, $k_{-a}[H_3O^+] > k_b$ and thus equ.(6.30) reduces to equ.(6.31).

Low pH; $$k_2 = \frac{k_a k_b K[B]}{k_{-a}} \quad \ldots\ldots\ldots (6.31)$$

The observed rate coefficient (k_2) is therefore dependent on k_2 and should show a primary deuterium isotope effect, and base catalysis ($k_2 \propto [B]$). Both effects are observed for phenol and 2-naphthol , at pH < 4.6 and < 2.5 respectively,

including the acidity-independent rate predicted by equ.(6.31). In contrast, when the pH is high, ie. at very low acidity, $k_{-a}[H_3O^+] \ll k_b[B]$ and equ.(6.30) reduces to equ.(6.32).

High pH; $$k_2 = k_a K[H_3O^+] \quad \ldots\ldots\ldots (6.32).$$

Thus under these conditions, equ.(6.32) predicts a linear dependence of k_2 on $[H^+]$, no kinetic isotope effect, and no base catalysis. This behaviour is observed for 2-naphthol at pH $>$ 3.5. Further supporting evidence for this scheme comes from the observation of chloride ion catalysis of the nitrosation of 2-naphthol at pH $>$ 3.6, which is consistent with an additional term in k_2 arising from rate-determining attack of NOCl on 2-naphthol.

Equation (6.30) also predicts the observed behaviour for the nitrosation of 2-naphthol in the intermediate pH range of 2.5 to 3.5. Thus as the acidity is decreased, $k_{-a}[H_3O^+]$ becomes of the same order of magnitude as k_b and so the over-all coefficient k_2 becomes less dependent on k_b. Thus in this region, the k_2^H/k_2^D ratio should decrease with decreasing $[H_3O^+]$ and the reaction should show an increasingly lower degree of acetate catalysis. This is in complete agreement with the observed results: as the reaction becomes increasingly acid-

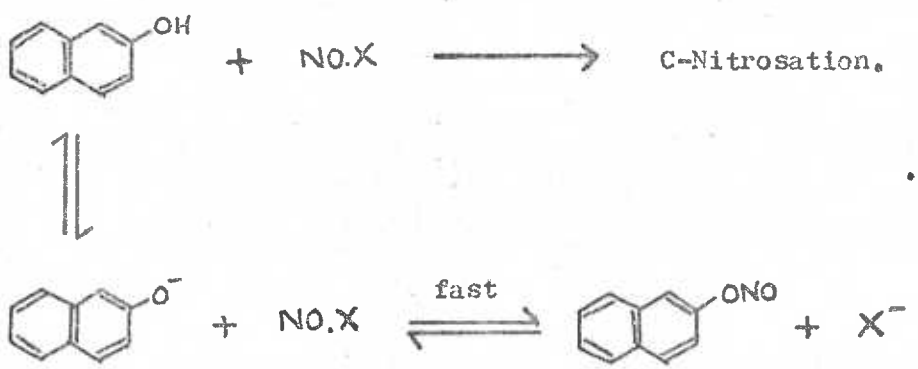
-dependent in the pH region 2.5 to 3.5, the kinetic isotope effect decreases from $k_H/k_D = 4.2$ at pH = 2.0, to 2.5 at pH = 3.0, and 2.0 at pH = 3.5 and the buffer-salt catalytic coefficients decrease concurrently.

The observed correlation of the rate with the steady-state equation shown in equ,(6.30) allows a simple estimation of the magnitude of k_{-a}/k_b for the nitrosation of 2-naphthol. Since at pH = 2, $k_{-a} > k_b$, and at pH = 4.0 $k_b < k_{-a}$, and since these pH values represent the 'threshold' values, then k_{-a}/k_b must be of the order of 10^2.

The results for phenol at high pH are equally consistent with the mechanistic scheme proposed above, and the overall observed rate coefficient is similarly given by the steady--state equ.(6.30). It is apparent, however, that the relative magnitudes of k_{-a} and k_b for 2-naphthol and phenol are quite different, such that a complete change in the rate-determining step,resulting from the inequality $k_b[B] > k_{-a}[H_3O^+]$, cannot be observed at pH < 5. Nonetheless, the kinetic deuterium isotope effect for the nitrosation of phenol shows a significant decrease from $k_2^H/k_2^D = 3.3$ at pH = 4.3 to $k_2^H/k_2^D = 2.3$ at pH = 5.3 and the acetate catalytic coefficients k_{AcO^-} show a

decreasing trend with pH ($k_{AcO^-} = 4.7 \times 10^{-2}$, 3.96×10^{-2} and $3,4 \times 10^{-2}$ $l.mole.sec^{-1}$. at pH = 4.0, 4.5, and 4.6 respectively).

The foregoing analysis excludes the possibility of reaction via the 2-naphthoate anion. It therefore seems that neutral 2-naphthol undergoes C-nitrosation more readily than its conjugate base. The only reasonable explanation for this surprising result is that nitrosation of the 2-naphthoate anion occurs predominantly, and reversibly, at the oxygen atom to give an unstable nitrite, as shown in equ.(6.33). This suggests



. . . (6.33)

that the tendency for nitrosation to proceed at the α-carbon with neutral phenolic compounds, and at the oxygen atom of their conjugate bases, may be a general phenomenon, and has interesting implications on the properties of phenolic compounds

as ambident nucleophiles[98,99].

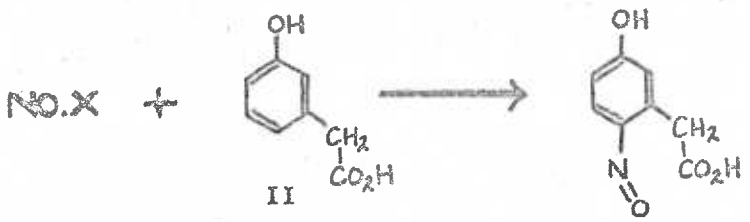
The apparent ambident nucleophilic properties of the 2-naphthoxide ion towards alkylation have been discussed by Kornblum[100]. Through the results of studies on the alkylation of sodium 2-naphthoxide in various solvents, he has demonstrated the ability of the choice of solvent to decide the course of the reaction. Several factors were postulated to determine the predominance of C- or O- alkylation, all of which were of electrostatic origin. For example, the dependence of the course of the reaction upon the dielectric constant of the solvent, in the case of aprotic media, was proposed by Kornblum to arise from the operation of differing electro--static interactions in the transition state of the O- and C- alkylation reactions, and the differing abilities of the solvents to decrease such interactions. Similar hypotheses explained the influence of the nature of the cation on the course of the reaction, although this effect was un--important for the reaction carried out in protic solvents. For both protic and aprotic solvents, C-alkylation was apparently favoured in solvents having excellent H-bonding capacities.

The alternative explanation for the ambident nucleo-

-philic properties of phenols, offered by the nitrosation results discussed above, is that electrophilic substitution proceeds at carbon with neutral phenols, and at oxygen with the phenoxide anions. Although this would appear to be inconsistent with Kornblum's findings, there is some evidence which prevents immediate dismissal of this hypothesis, and would warrent further investigation. Prior to Kornblum's work, with very few exceptions, the literature reports only the ether as the product of alkylation of the salts of 2-naphthol in alkaline solution. Also, since alkylations have usually been carried out in alkaline media, no evidence exists to contradict the hypothesis of alkylation of the neutral compounds at carbon. Finally, there may be some significance in the fact that in Kornblum's alkylation reactions, the cases where he observed predominant C-alkylation corresponded to reactions carried out in heterogeneous phase. The inference is that there is no certainty that the reacting molecule is the naphthoxide salt, but could conceivably be neutral 2-naphthol in one of the heterogeneous phases.

(D). Nitrosation of m-Hydroxyphenylacetic Acid.

The nitrosation kinetics of m-hydroxyphenylacetic acid, (II), was also investigated in aqueous buffered solutions,



in the acidity range pH 3.0 to 4.7. The upper limit was dictated by the desirability to confine investigation to an acidity range for which the reaction of phenol was acidity independent. Rate comparison for the two compounds are then relatively uncomplicated. All determinations were made under conditions of a large excess of (II) over the initial stoicheiometric sodium nitrite concentration, when the rate of reaction, as expected, follows equ.(6.34). In equ.(6.34), the $(NaNO_2)$

$$\text{rate} = \bar{k}_1^{o} (NaNO_2) \quad \ldots\ldots\ldots\ldots (6.34).$$

represents the total stoicheiometric concentration of nitrite in the reaction. When carried out in buffered solutions containing a large excess of acetic acid/sodium acetate buffer concentration over the stoicheiometric substrate concentration, the reaction is first order in total (II), as shown by the data

of TABLE (6.16).

TABLE (6.16).

Nitrosation of m-OH-Phenylacetic Acid in excess HOAc-NaOAc Buffer Solutions at 25°C.

[Acetate] = 0.5M., pH = 4.42; Initial stoich.$(NaNO_2) = 5.0 \times 10^{-5}$M

Run	(II) (a) M.	$10^5 \times \bar{k}_1^o$ sec^{-1}.	$10^3 \times \bar{k}_2^o$ $l.mole^{-1}.sec^{-1}$.	$10^2 \times \bar{k}_2$ $l.mole^{-1}.sec^{-1}$.
355	0.008	1.50	1.88	2.46
356	0.010	1.90	1.90	2.48
337	0.0195	3.77	1.93	2.52

(a) Total stoicheiometric concentration.

The effect of the conjugate base of (II), present in the reaction solution, as an intermolecular base is minimised, since the major part of the reaction will occur through the acetate ion which is present in much higher concentrations. Thus the secondary effects of changing the concentration of (II) are kept as low as possible. The full observed rate expression for the nitrosation of m-hydroxyphenylacetic acid at a fixed pH is therefore the same as that for phenol, and

is shown as equ.(6.35).

$$\text{Rate} = \bar{k}_2^{o}\left(\text{II}\right)\left(\text{NaNO}_2\right) \quad \ldots\ldots(6.35)$$

Values of the rate coefficient $\bar{k}_2$ (equ.(6.36)) have been computed from $\bar{k}_2^{o}$ as described earlier (see page 120) for similar coefficients in the nitrosation of phenol.

$$\text{Rate} = \bar{k}_2\left(\text{II}\right)\left[\text{HNO}_2\right] \quad \ldots\ldots\ldots(6.36).$$

In equ.(6.36), the rate coefficient $\bar{k}_2$ is defined in terms of the total stoicheiometric concentration of m-hydroxyphenylacetic acid in the reaction solution ie. the sum of the concentrations of the free acid and conjugate base forms, which are in equilibrium with each other at the pH of the kinetic run.

Catalysis by Added Acetate.

The variation of $\bar{k}_2$ with buffer concentration at a fixed pH has been investigated for the nitrosation of m-hydroxy--phenylacetic acid in acetic acid buffer solutions, under conditions of a large excess of buffer component concentration over the total stoicheiometric concentration of (II). The results are shown in TABLE (6.17).

TABLE (6.17).

Nitrosation of m-OH-phenylacetic Acid in AcOH-AcONa Buffer Solutions at 25°C. Acetate Catalysis.

Total (II) = 2.0×10^{-2}M., Initial ($NaNO_2$) 10^{-4}M

Run	pH	Total(AcOH)M.	$[AcO^-]$M.	$10^2 \times \bar{k}_2$ (l.mole^{-1}.sec^{-1})
327	3.910	1.00	0.20	1.50
318	3.887	1.62	0.30	1.65(1.68)
320	3.890	2.00	0.40	1.85
321	3.890	2.50	0.50	2.05
334	4.412	0.470	0.20	1.74
335	4.420	0.705	0.30	2.01
331	4.415	0.940	0.40	2.27
337	4.420	1.175	0.50	2.52

The data of TABLE (6.17) is shown graphically as plots of $\bar{k}_2$ against $[AcO^-]$ in FIGURE (6.5). FIGURE (6.5) also contains the plot for the data for phenol at pH 4.0 (shown as a broken line) for comparison. Values of $\bar{k}_{2w}$ and k_{AcO^-} obtained from FIGURE (6.5) are listed in TABLE (6.18), and are defined by equ.(6.37).

$$\bar{k}_2 = \bar{k}_{2w} + k_{AcO^-}[AcO^-] \quad \ldots(6.37)$$

FIGURE (6.5).

Nitrosation of m-OH-phenylacetic Acid in AcOH-AcONa Buffer Solutions at 25°C; Acetate Catalysis.

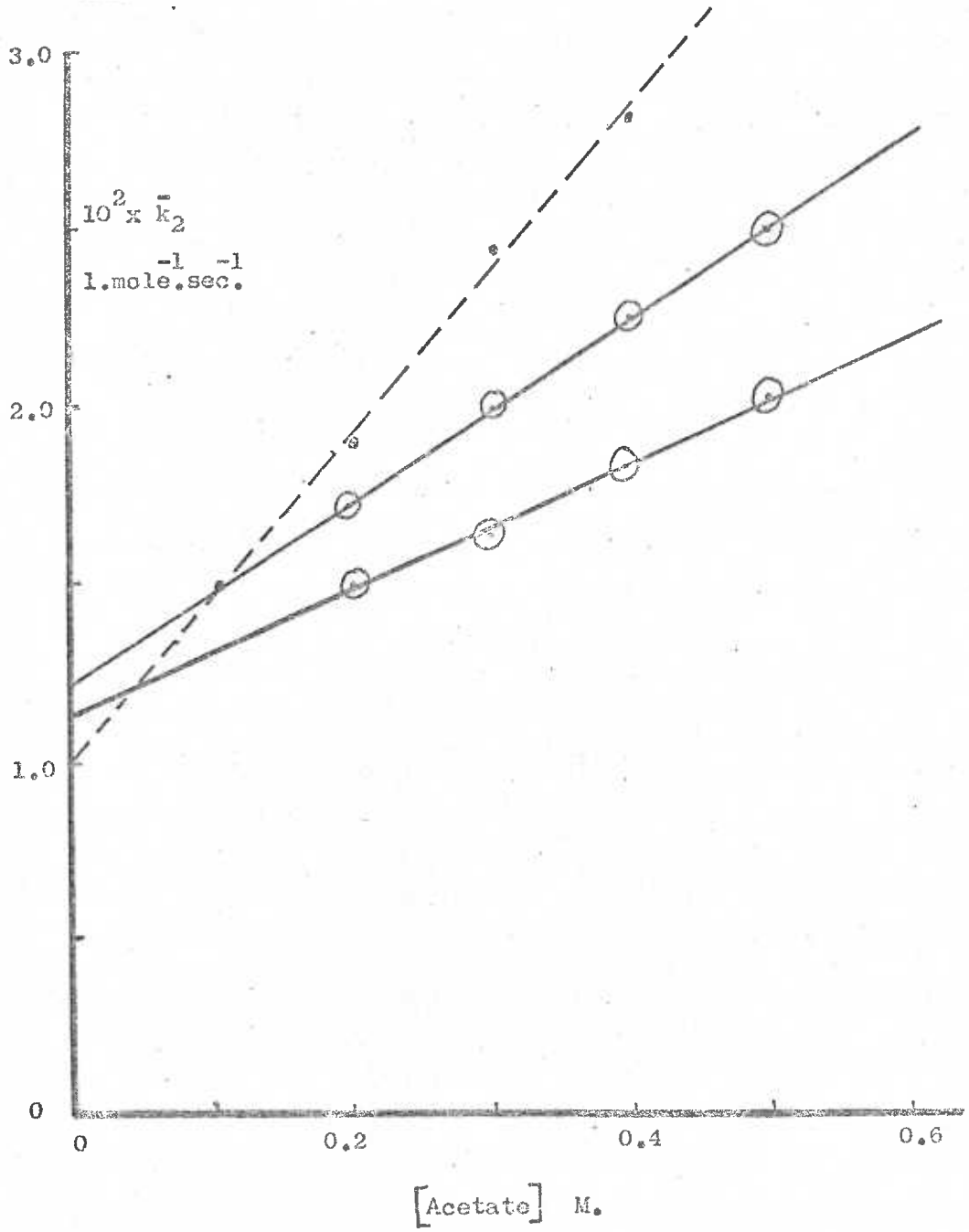


TABLE (6.18).

Nitrosation of m-hydroxyphenylacetic Acid at 25°C.

Values of $\bar{k}_{2w}$ and k_{AcO^-} (equ.(6.37)).

pH	$10^2 \times \bar{k}_{2w}$ (l.mole^{-1}.sec^{-1})	$10^2 \times k_{AcO^-}$ (l^2.mole^{-2}.sec^{-1})
3.9	1.12	2.02
4.4	1.24	2.03

Acidity Dependence of $\bar{k}_{2w}$(equ.(6.37)).

The variation of $\bar{k}_{2w}$ with pH has been investigated for the nitrosation of m-hydroxyphenylacetic acid in the pH range 3.0 to 4.7. In these determinations, the $\bar{k}_{2w}$ coefficient has been determined directly by employing the substrate, itself, as a buffer. Since all the kinetic runs were carried out with a large excess of m-hydroxyphenylacetic acid over the initial stoicheiometric $(NaNO_2)$, the reaction solution could be buffered simply by adding the required amount of NaOH. TABLE (6.19) lists values of $\bar{k}_{2w}$ (equ.(6.38)), defined in terms of the

$$\text{rate} = \bar{k}_{2w} \cdot (II)[HNO_2] \quad \ldots\ldots (6.38)$$

total stoicheiometric concentration of m-hydroxyphenylacetic acid.

TABLE (6.19).

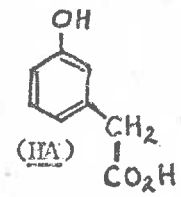
Nitrosation of m-OH-Phenylacetic Acid at 25°C; Variation of $\bar{k}_{2w}$ (equ. (6.38)) with pH.

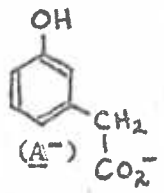
Run	10^2 x Total (II) M.	pH	$10^2 \times \bar{k}_{2w}$ (l.mole^{-1}.sec^{-1})
369	3.55	3.055	0.62
378	3.55	3.732	0.83
357	3.32	4.260	1.16
371	3.23	4.215	1.09
372	4.31	4.283	1.16
377	4.27	4.455	1.20
423	4.53	4.725	1.23

It is apparent from the data of TABLE (6.19) that the rate of nitrosation of m-hydroxyphenylacetic acid increases with decreasing acidity. The nitrosation of phenol up to pH 4.6 has been shown to be acid independent, and at higher pH, the rate falls with decreasing acidity. Thus the increase in the nitrosation rate for m-hydroxyphenylacetic acid must be a result of the enhanced rate of reaction of the m-hydroxyphenylacetate species , the concentration of which increases as the pH is

raised.

The rate coefficient, $\bar{k}_{2w}$, is defined by equ.(6.38) in terms of the total stoicheiometric concentration of m-hydroxy--phenylacetic acid, which is the sum of the concentrations of the free acid and conjugate base forms , denoted HA and A^- respectively, which are in equilibrium at the pH of the reaction.





It is possible to seperate this observed stoicheiometric coefficient into individual rate coefficients for the nitro--sation of the free acid and conjugate base form, denoted k_{2HA} and k_{2A^-} respectively (equ.(6.39) and (6.40)), in the

$$\text{rate (acid)} = k_{2HA}\left[HA\right]\left[HNO_2\right] \quad \ldots . (6.39)$$

$$\text{rate (conj,base)} = k_{2A^-}\left[A^-\right]\left[HNO_2\right] \quad \ldots . (6.40).$$

following way:

The overall observed second order rate coefficient can be written as,

$$\text{rate} = \bar{k}_{2w}\left\{\left[HA\right]+\left[A^-\right]\right\}\left[HNO_2\right] \quad \ldots (6.41)$$

which is also equivalent to equ.(6.42).

$$\text{rate} = \left\{k_{2HA}[HA] + k_{2A^-}[A^-]\right\}[HNO_2] \quad \ldots\ldots (6.42).$$

Thus, equating equ.(6.41) and equ,(6.42),

$$\bar{k}_{2w}\left\{[HA] + [A^-]\right\} = k_{2HA}[HA] + k_{2A^-}[A^-] \ldots (6.43)$$

The species HA and A^- are in equilibrium according to,

$$HA \rightleftharpoons H^+ + A^- \quad ; K_{HA} = \frac{[H^+][A^-]}{[HA]} \ldots (6.44).$$

Combining equs.(6.43) and (6.44) gives the expression,

$$\bar{k}_{2w}\left\{1 + \frac{K_{HA}}{[H^+]}\right\} = k_{2HA} + \frac{k_{2A^-}.K_{HA}}{[H^+]} \quad \ldots\ldots (6.45).$$

$[H^+]$ for each kinetic run is calculated from the measured pH, and $K_{HA}^{101} = 5.5 \times 10^{-5} M.l^{-1}$. at 25^oC.

An analysis of the data of TABLE (6.19) according to equ.(6.45) is given in TABLE (6.20), and the corresponding plot of $\bar{k}_{2w}\left\{1 + K_{HA}/[H^+]\right\}$ versus $K_{HA}/[H^+]$ is shown in FIGURE (6.6).

TABLE (6.20).

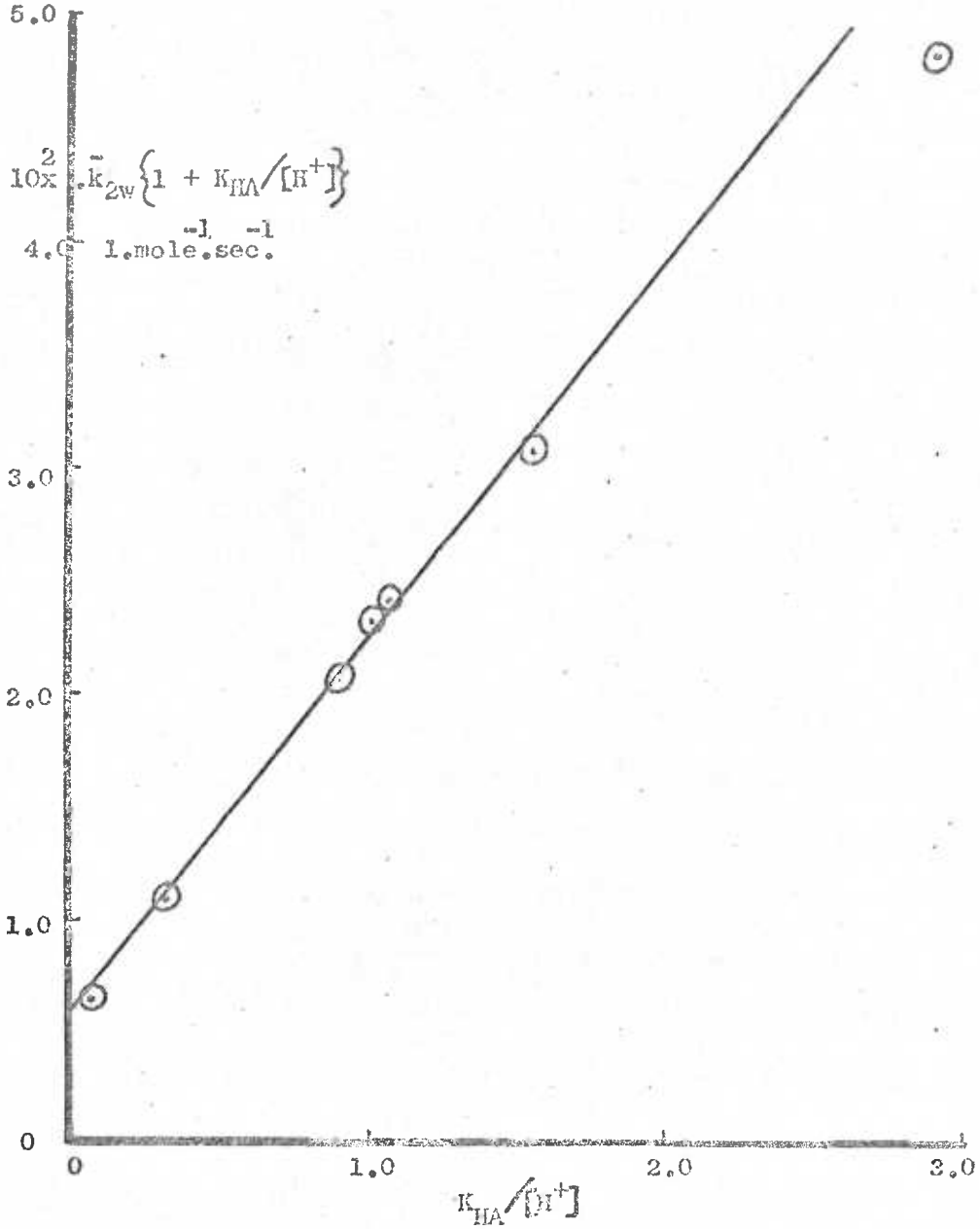
Nitrosation of m-Hydroxyphenylacetic Acid at 25°C. Analysis of Data of TABLE (6.19) according to equ.(6.45).

pH	$10^2 \times \bar{k}_{2w}$ $l.mole^{-1}.sec^{-1}$	$K_{HA}/[H^+]$	$10^2 \times \bar{k}_{2w}\left\{1 + K_{HA}/[H^+]\right\}$ $l.mole^{-1}.sec^{-1}$
3.055	0.620	0.0624	0.659
3.372	0.826	0.297	1.13
4.260	1.16	1.00	2.32
4.215	1.09	0.902	2.072
4.283	1.16	1.054	2.383
4.455	1.20	1.567	3.080
4.725	1.23	2.917	4.818

Inspection of the plot of FIGURE (6.6) reveals a good straight line through all of the points except that corresponding to the kinetic experiments carried out at pH = 4.725, the highest pH. That this point lies below the line is not altogether surprising, since it has already been found that, above pH = 4.6, the rate of nitrosation of phenol begins to decrease with increasing pH. It is evident that the same effect is in operation here, and so this point is

FIGURE (6.6).

Nitrosation of m-OH-phenylacetic Acid at 25°C. Plot of $\bar{k}_{2w}\left\{1 + K_{HA}/[H^+]\right\}$ vs $K_{HA}/[H^+]$



not included in the general analysis.

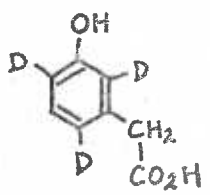
From the slope and intercept of FIGURE (6.6), values of the second order coefficients for the nitrosation of the free acid and conjugate base forms of m-hydroxyphenylacetic acid have been obtained and,

$$k_{2HA} = 5.6 \times 10^{-3} \text{ l.mole}^{-1}.\text{sec}^{-1}$$

$$k_{2A^-} = 1.6 \times 10^{-2} \text{ l.mole}^{-1}.\text{sec}^{-1}$$

Nitrosation of 2,4,6-$^{2}H_3$ -3-Hydroxyphenylacetic Acid.

The nitrosation of 2,4,6-$[^{2}H_3]$-3-hydroxyphenylacetic acid (IID) has been investigated under similar conditions as for the normal compound and the results are listed in TABLE (6.21). The rate coefficient $\bar{k}_{2w}$ has been determined for the deutero-compound and is notated $\bar{k}_{2w}^{D}$, and defined in equ. (6.46). As for the normal compound, the measured $\bar{k}_{2w}^{D}$ values



(IID)

$$\text{Rate} = \bar{k}_{2w}^{D} \left(\text{IID}\right)\left[HNO_2\right] \quad \ldots (6.46).$$

represent the total stoicheiometric rate coefficient at zero

'external' buffer concentration. A similar treatment has been applied to these results to seperate the terms for the reaction of the free acid and conjugate base. These results are also shown in TABLE (6.21).

TABLE (6.21).

Nitrosation of 2,4,6-[$^2H_3$]-3-Hydroxyphenylacetic Acid at 25 °C.

Variation of $\bar{k}^D_{2w}$ with pH ; Analysis according to equ.(6.45).

Run	pH	$10^3 \times \bar{k}^D_{2w}$ l.mole^{-1}.sec^{-1}.	$K_{HA}/[H^+]10^2 \times \bar{k}^D_{2w}$	$\bar{k}^D_{2w}\left\{1 + K_{HA}/[H^+]\right\}$ l.mole^{-1}.sec^{-1}.
420	3.055	1.90	0.062	0.202
424	3.832	2.51	0.373	0.345
421	4.285	3.47	1.054	0.713

The plot of the data of TABLE (6.21) according to equ.(6.45) is shown in FIGURE (6.7) . From the intercept and slope of this plot, the rate coefficients k^D_{2HA} and $k^D_{2A^-}$ for nitrosation of the deuterio free acid and conjugate base of IID have been calculated;

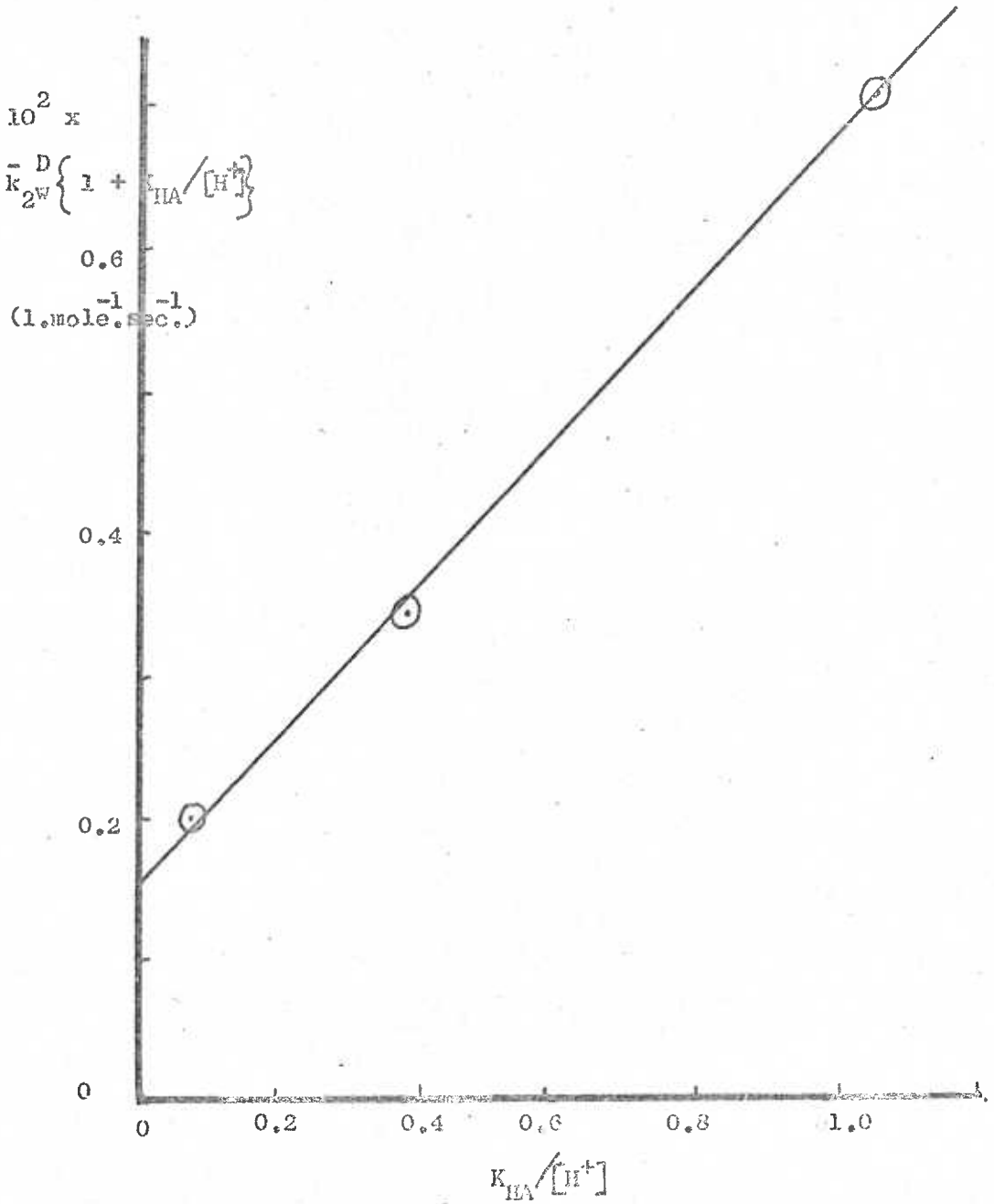
$$k^D_{2HA} = 1.6 \times 10^{-3} \text{ l.mole}^{-1}.\text{sec}^{-1}.$$

$$k^D_{2A^-} = 5.3 \times 10^{-3} \text{ l.mole}^{-1}.\text{sec}^{-1}.$$

FIGURE (6.7).

Nitrosation of 2,4,6- $^{2}H_{3}$ -3-OH-phenylacetic Acid at 25°C.

Plot of $\bar{k}^{D}_{2w}\{1 + K_{HA}/[H^+]\}$ vs $K_{HA}/[H^+]$ (equ.(6.45)).



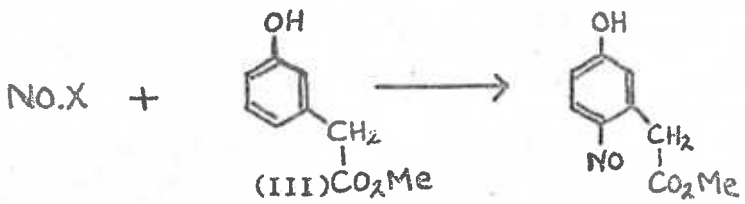
Direct comparison of the k_{2HA} and k_{2A^-} coefficients for nitrosation of the normal and deuterio substrates gives the following values for the kinetic isotope effects in the reaction of m-hydroxyphenylacetic acid;

$$\text{Free acid : } \frac{k^H_{2HA}}{k^D_{2HA}} = 3.5 \pm 0.7$$

$$\text{Conjugate base: } \frac{k^H_{2A^-}}{k^D_{2A^-}} = 3.0 \pm 0.6$$

(E). Nitrosation of m-Hydroxyphenylacetic Acid - Methyl Ester.

The rate of nitrosation of the methyl ester (III) of m-hydroxyphenylacetic acid has been measured in aqueous



acetic acid buffer solutions. The variation of k_2 (equ.(6.47)) with acetate concentration is given in TABLE (6.22).

$$\text{Rate} = k_2 . [\text{III}][HNO_2] \quad \ldots (6.47).$$

TABLE (6.22).

Nitrosation of m-OH-phenylacetic Acid-Methyl Ester, at 25°C in AcOH-AcONa Buffer Solutions, Acetate Catalysis.

Run	pH	$[AcOH]$ M.	$[AcO^-]$ M.	$10^3 \times k_2$ (equ.(6.47)) $l.mole^{-1}.sec^{-1}$
430	4.175	0.158	0.05	3.56
431	4.142	0.316	0.10	4.44
432	4.115	0.632	0.20	6.20
433	4.105	0.948	0.30	7.45

The plot of the data of TABLE (6.22) is shown in FIGURE (6.8). The linearity of this plot indicates that the rate coefficient k_2 for the nitrosation of III can be written,

$$k_2 = k_{2w} + k_{AcO^-}[AcO^-] \quad \ldots\ldots (6.48)$$

as expected. Thus the intercept and gradient of FIGURE (6.8) give values for k_{2w} and k_{AcO^-} (equ.(6.48)) of,

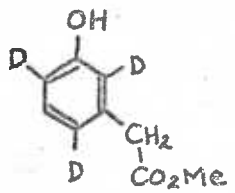
$$k_{2w} = 2.9 \times 10^{-3}\ l.mole^{-1}.sec^{-1}.$$
$$k_{AcO^-} = 1.6 \times 10^{-2}\ l^2.mole^{-2}.sec^{-1}.$$

The value of the Bronsted β, calculated from these coefficients

by the same method as used on page(126) for phenol, is $\beta = 0.38$.

Nitrosation of 2,4,6-$\left[^2H_3\right]$-3-Hydroxyphenylacetic Acid-Methyl Ester; The Kinetic Isotope Effect.

The nitrosation of the methyl ester of 2,4,6-$\left[^2H_3\right]$-3-hydroxyphenylacetic acid,(IIID), has been investigated in acetic acid buffer solutions, and the rate coefficient k_2 (equ.(6.49))



(IIID)

determined at several acetate ion concentrations, at a fixed pH. The results are listed in TABLE (6.23).

$$\text{rate} = k_2^D \left[\text{IIID}\right] \left[HNO_2\right] \quad \ldots\ldots\ldots (6.49).$$

TABLE (6.23).

Nitrosation of Methyl Ester of 2,4,6-$\left[^2H_3\right]$-3-OH-phenylacetic Acid in AcOH-AcONa Buffer Solutions at 25°C.

Run	[AcOH] M.	[AcONa] M.	pH	$10^3 \times k_2^D$ (equ.(6.49)) $l.mole^{-1}.sec^{-1}$
434	0.316	0.10	4.128	1.47
435	0.632	0.20	4.115	2.06
436	0.948	0.30	4.102	2.51

A plot of k_2^D *vs* $[AcO^-]$ from the data of TABLE (6.23) is shown in FIGURE (6.8), from which the intercept gives a value of,

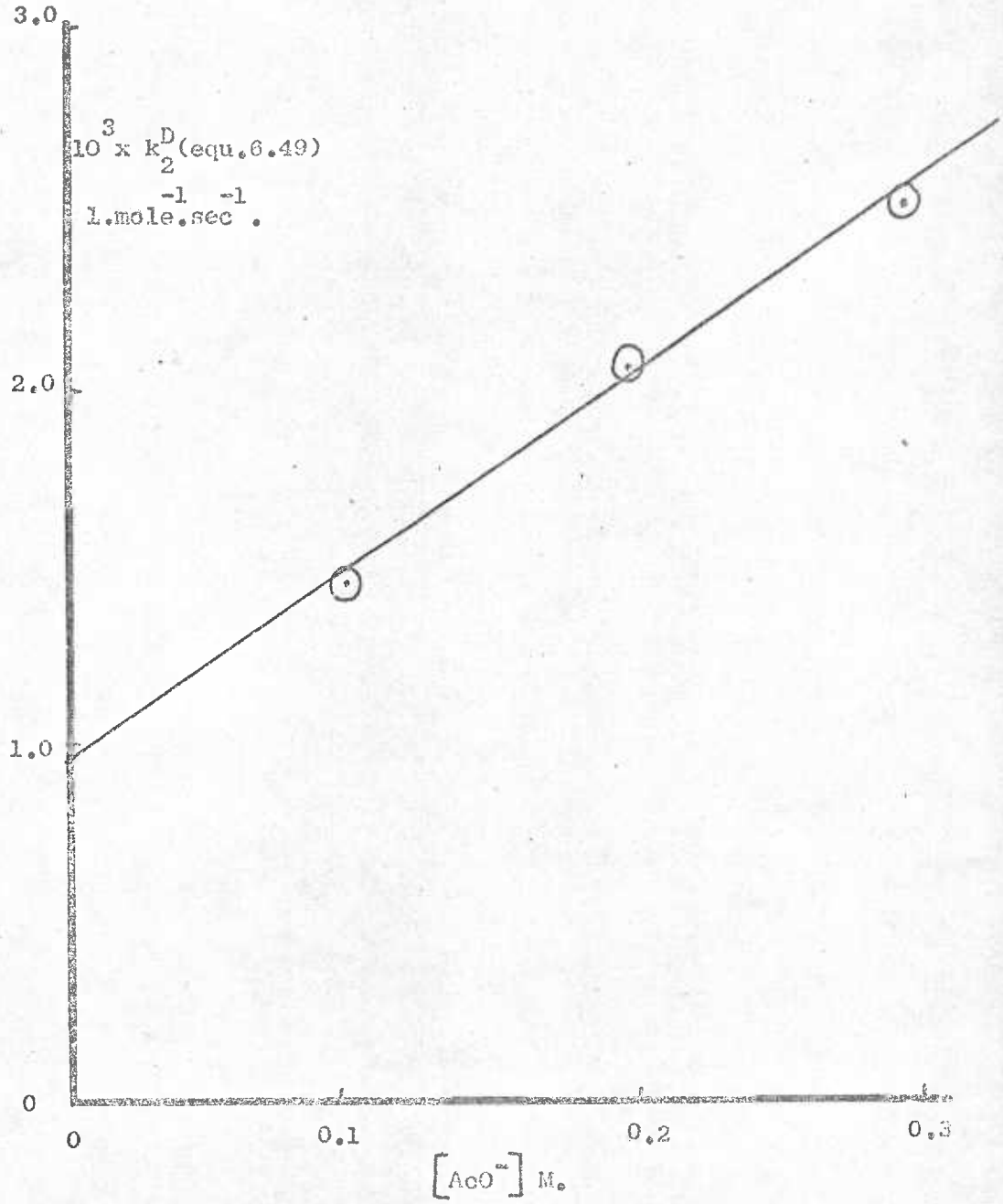
$$k_{2w}^D = 0.96 \times 10^{-3} \text{ l.mole}^{-1}.\text{sec}^{-1}$$

Direct comparison of this rate coefficient with the corresponding value for the normal compound obtained previously gives a value for the kinetic isotope effect for the nitrosation of the methyl ester of m-hydroxyphenylacetic acid of,

$$\frac{k_{2w}^H}{k_{2w}^D} = 3.0 \pm 0.3$$

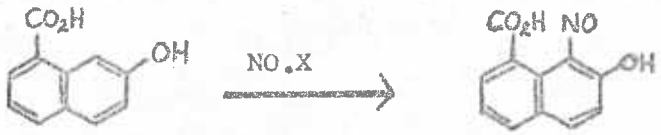
FIGURE (6.8).

Nitrosation of the Methyl Ester of 2,4,6-$[^2H_3]$-3-hydroxy-phenylacetic Acid in AcOH-AcONa Buffer Solutions at 25°C.



(F). Nitrosation of 7-Hydroxy-1-Napthoic Acid.

The kinetics of nitrosation of 7-hydroxy-1-napthoic acid,(IV), have been investigated under similar conditions as previously for 2-napthol. With a large excess of IV over the



(IV)

initial stoicheiometric $NaNO_2$ concentration, the reaction rate follows the pseudo first order expression of equ.(6.50).

$$\text{Rate} = \bar{k}_1^{o} \cdot (NaNO_2) \quad \ldots\ldots\ldots\ldots (6.50).$$

TABLE (6.24) shows the first order dependence of the rate on the total stoicheiometric concentration of IV , which leads to the full expression for the observed rate as in equ.(6.51).

$$\text{Rate} = \bar{k}_2^{o} (IV)(NaNO_2) \quad \ldots\ldots\ldots\ldots (6.51).$$

From the measured $\bar{k}_2^{o}$ coefficient for each kinetic experiment, the second order rate coefficient $\bar{k}_2$ (equ.(6.52)) has been calculated as usual, where $\bar{k}_2$ is defined in terms of the total

$$\text{Rate} = \bar{k}_2 (IV)[HNO_2] \quad \ldots\ldots\ldots\ldots (6.52).$$

stoicheiometric concentration of IV in the reaction solution.

TABLE (6.24).

Nitrosation of 7-OH-1-Naphthoic Acid in AcOH-AcONa Buffer Solutions at 25°C; First Order Dependence of Rate on (IV).

Initial Stoich. $(NaNO_2) = 10^{-5}M$.

Run.	pH	$[AcO^-]$ M.	$10^4 \times (IV)$ M.	$10^5 \times \bar{k}_1^o$ $sec.^{-1}$	$10^2 \times \bar{k}_2^o$ $l.m.^{-1}sec.^{-1}$	$\bar{k}_2$ $l.m.^{-1}sec.^{-1}$.
542	4.43	0.02	8.08	2.11	2.60	3.51
543	4.43	0.02	4.04	1.21	2.70	3.65
527	4.43	0.04	7.07	2.04	2.90	3.86
529	4.43	0.04	3.03	0.90	3.00	4.00

Acidity Dependence of $\bar{k}_2$ (equ.(6.52)).

TABLE (6.25) lists values of $\bar{k}_2$ (equ.(6.52)) determined in acetic acid buffer solutions of constant acetate ion concentration but varying pH.

TABLE (6.25).

Nitrosation of 7-OH-1-Naphthoic Acid in AcOH-AcONa Buffer Solutions at 25°C; Variation of $\bar{k}_2$ (equ.(6.52)) with pH.

$[AcO^-]$ = 0.02M throughout. Stoich. (IV) = 8.08×10^{-4}M.

Initial $(NaNO_2)$ = 10^{-5}M.

Run	pH	$[AcOH]$ M.	$\bar{k}_2$ ($l.mole^{-1}.sec^{-1}$)
533	2.988	1.125	1.04
609	3.044	1.010	1.28
615	3.488	0.356	1.19
547	3.930	0.113	0.70
542	4.430	0.036	0.36(0.35)

Nitrosation of 7-hydroxy-1-Naphthoic Acid in dilute $HClO_4$.

TABLE (6.26) lists values of $\bar{k}_2$ (equ.(6.52)) for the nitrosation of 7-hydroxy-1-naphthoic acid in dilute aqueous $HClO_4$.

TABLE (6.26).

Nitrosation of 7-OH-1-Naphthoic Acid in dilute aqueous $HClO_4$.

Run	pH	$\bar{k}_2$ ($l.mole^{-1}.sec^{-1}$.)
595	1.108	0.393
593	1.610	0.446
594	2.215	0.523

Dependence of $\bar{k}_2$ (equ.(6.52)) on Buffer Concentration.

TABLE (6.27) lists $\bar{k}_2$ values (equ.(6.52)) for nitrosation of 7-hydroxy-1-naphthoic acid in acetic acid buffer solutions of constant buffer ratio but varying buffer concentration. Since the variation of $\bar{k}_2$ with pH, shown in TABLES(6.25) and (6.26), is rather complex, no reliable correction to the data of TABLE (6.27) for secondary salt effects can be applied. Nonetheless, it is apparent that there is little significant change in $\bar{k}_2$ with increasing buffer component concentration.

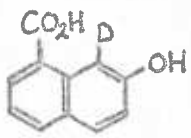
TABLE (6.27).

Run	pH	[HOAc] M.	[NaOAc] M.	$\bar{k}_2$ $l.mole^{-1}.sec^{-1}$
534	2.988	1.125	0.02	1.02
531	2.873	2.810	0.05	0.98
535	2.760	4.50	0.08	1.01

Nitrosation of 8-[$^2H_1$]-7-Hydroxy-1-Naphthoic Acid: The Kinetic Isotope Effect.

The rate of nitrosation of 8-[$^2H_1$]-7-hydroxy-1-naphthoic acid, (IVD), has been determined in dilute $HClO_4$ and in

acetic acid buffer solutions, in the pH range 2.2 to 4.4.



(IVD)

TABLE (6.28) lists values of the rate coefficient $\bar{k}_2^D$ (equ. 6.53), together with the corresponding rate coefficients $\bar{k}_2^H$ for the normal compound, determined under identical conditions.

$$\text{Rate} = \bar{k}_2^D \left(\text{IVD}\right) \left[HNO_2\right] \quad . \quad . \quad . \quad . \quad . \quad (6.53).$$

The deuterio substrate used in these experiments had an incorporation of deuterium in the 8-position of 88%; the value of $\bar{k}_2^H/\bar{k}_2^D$ corresponding to nitrosation of the fully deuteriated compound has been computed and is shown in the last column of TABLE (6.28)

TABLE (6.28).

Nitrosation of 7-OH-1-Naphthoic Acid in AcOH-AcONa Buffers at 25°C; Kinetic Isotope Effects.

Run	pH	[AcOH] M.	[AcO⁻] M.	$\bar{k}_2^H$ $l.m^{-1}.sec^{-1}$.	$\bar{k}_2^D$ $l.m^{-1}.sec^{-1}$.	$\bar{k}_2^H/\bar{k}_2^D$ (a) (obs)	$\bar{k}_2^H/\bar{k}_2^D$ (real).
607	2.216	0	0	---	0.165	3.2	3.7
594	2.215	0	0	0.523	---		
609	3.044	1.125	0.02	---	0.399	3.2	3.7
612	3.044	1.125	0.02	1.28	---		
608	3.515	0.356	0.02	---	0.574	2.1	2.4
611	3.515	0.356	0.02	1.19	---		
573	3.933	0.113	0.02	---	0.45	1.5	1.7
547	3.930	0.113	0.02	0.70	---		
575	4.431	0.036	0.02	---	0.30	1.2	1.4
542	4.430	0.036	0.02	0.36	---		

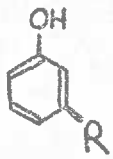
(a) For substrate of 88% incorporation of deuterium in 8-position.

Independent investigations revealed that the extent of exchange of deuterium in the substrate with the solvent at pH 4.43 was negligible compared with the extent of nitrosation under identical conditions. This was shown by mass spectral analysis of the substrate at the end of each kinetic run.

(G). Discussion.

(i). Nitrosation of m-Hydroxyphenylacetic Acid and its Derivatives.

The rates of nitrosation, in acetic acid buffer solutions, of m-hydroxyphenylacetic acid (I, R = CH_2CO_2H) its conjugate base (I, R = $CH_2CO_2^-$) and methyl ester (I, R = CH_2CO_2Me) are given by the rate expression of equ.(6.54).



In all cases, nitrosation occurs almost exclusively (> 93%)

$$\text{Rate} = k_2 [I][HNO_2] \quad \ldots\ldots (6.54).$$

at the site para to the phenolic function. The reactions are catalysed by acetate acting as a general base according to equ.(6.55);

$$k_2 = k_{2w} + k_{AcO^-}[AcO^-] \quad \ldots (6.55)$$

where k_{2w} gives the rate at zero buffer concentration and is termed the'water' catalysed' rate, and k_{AcO^-} is the catalytic coefficient for catalysis by acetate ion. TABLE (6.29)

summarises the experimental data obtained for these compounds over the pH range 3.0 to 4.5 , in which the rate coefficient k_2 (equ.(6.54)) is independent of acidity. The table also lists the corresponding data for phenol under similar conditions, for comparison. The last column of TABLE (6.29) lists the kinetic isotope effect (k_H/k_D) for the reaction of each substrate.

TABLE (6.29).

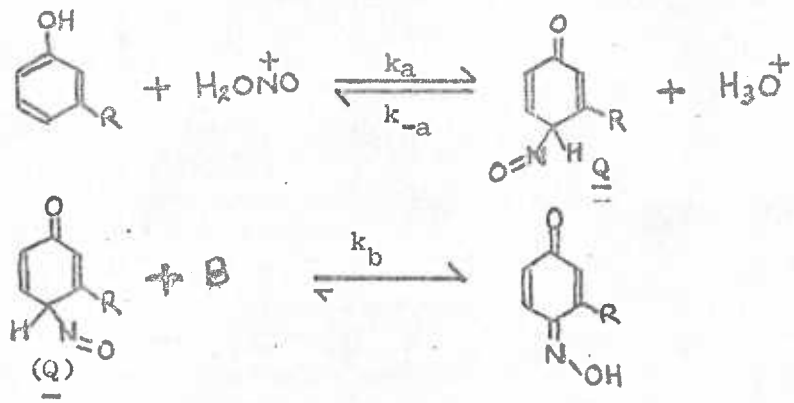
Nitrosation of (I) in Aqueous Buffer Solutions at 25°C, pH 3.0 to 4.5.

Substrate (I)	$10^2 \times k_{2w}$ $l.mole^{-1}.sec^{-1}$	$10^2 \times k_{AcO^-}$ $l^2.mole^{-2}.sec^{-1}$	Bronsted β [a]	k_2^H/k_2^D
Phenol (R = H)	1.00	4.7	0.37	3.5 ±0.2
Methyl ester (R = CH_2CO_2Me)	0.29	1.6	0.38	3.0 ±0.3
Acid (R = CH_2CO_2H)	0.65	--	---	3.5 ±0.5
Anion (R = $CH_2CO_2^-$)	1.60	--	--	3.0 ±0.5

(a) Based on catalytic coefficients k_{AcO^-} and $k_w (= k_{2w}/55.5)$.

It is apparent that nitrosation of each of the substrates in TABLE (6.29) in the pH range 3.0 to 4.5, and at zero buffer

concentration, shows a large primary isotope effect of similar magnitude, within the experimental error, to that for the reaction of phenol. The rate-determining step in all cases is concluded to be proton-loss from a neutral dienone intermediate Q (equ.(6.56)).



.....(6.56)

The overall observed rate coefficient k_2 is given by the expression,

$$k_2 = \frac{K.k_a k_b[H_3O^+][B]}{k_{-a}[H_3O^+] + k_b[B]} \quad .... (6.57).$$

It is evident from the data of TABLE (6.29) that introduction of a ($-CH_2CO_2Me$) group into phenol, ortho to the site of substitution, results in a reduction in the k_{2w} coefficient by a factor of about 3.5. The electronic effect of this substituent on the reaction rate can only be guessed, since little data is available. However, the Stock-Brown substituent

parameter σ_p^+ for the ($-CH_2CO_2Et$) group is about -0.16[33], and so the ortho ($-CH_2CO_2Me$) group will almost certainly have an (+I) effect increasing the reactivity of the substituted compound with respect to phenol, itself. However, the observed reduction in the rate of reaction of the substituted phenol indicates that such electronic effects are far outweighed by the steric effect of the neighbouring ester function on the rate of reaction. Steric crowding in the intermediate (Q) might be expected to bring about a reduction in the overall rate by acceleration of the k_{-a} step. An alternetive explanation is that the swinging of the -N=O substituting group into the plane of the aromatic ring in the second step may be energetically less favourable for the ortho-substituted compound than the free phenol, which results in a reduction in k_b and hence the overall rate of reaction. Support for the second explanation comes from Zollinger and Snyckers[8], who have recently shown that steric effects in azo coupling reactions arise mainly in the proton-loss step. The observation of a reduced value of the acetate catalytic coefficient, k_{AcO^-}, for the nitrosation of the m-hydroxyphenylacetic acid-methyl ester ($k_{AcO^-} = 1.6 \times 10^{-2}$) compared with that for phenol ($k_{AcO^-} = 4.7 \times 10^{-2}$) is also consistent with this explanation. The efficiency of the

base in assisting removal of the proton in the rate-determining step is reduced in the substituted molecule, since the approach of the base to the proton is hindered by the presence of the bulky neighbouring ester group.

TABLE (6.29) shows that the free acid form of m-hydroxyphenylacetic acid nitrosates at a rate about 2.2X faster than that of the methyl ester. Since there will be certainly very little difference between the electron donating (+I) effect of the ($-CH_2CO_2Me$) and ($-CH_2CO_2H$) groups on the reactivity of the two molecules, this difference in rates is attributed to the difference in steric influence on the reaction rate of these two groups. Thus, the methyl group in the ester group creates a more sterically hindered reaction site compared with the free acid, and hence causes a lower overall rate for the ester as explained previously.

It is evident from the data of TABLE (6.29) that the conjugate base of m-hydroxyphenylacetic acid is nitrosated at a rate 2.5X faster than that of the free acid form of the substrate. In this case, steric influences in the two reactions can be considered identical, since the sizes of the ($-CH_2CO_2H$) and ($-CH_2CO_2^-$) groups are very similar. Although no data is available concerning the relative (+I) effects of these two

substituents, the difference is likely to be very small, the ($-CH_2CO_2^-$) group perhaps being slightly more electron donating than the ($-CH_2CO_2H$) function. Taking into account the possibility of a small increase in tha rate of reaction of the ($-CH_2CO_2^-$) --substituted compound arising from electronic effects of the substituent, the value of 2.5 for the factor k_{2w}(conjugate base) /k_{2w}(free acid) represents the maximum acceleration attributable to intramolecular base catalysis by the neighbouring acetate function.

A true measure of intramolecular base catalysis of a reaction can only be made by comparison of the degree of catalysis with that of the corresponding intermolecular process. A good model for the corresponding intermolecular process in this case is the observed catalysis of the nitrosation of the methyl ester of m-hydroxyphenylacetic acid by added acetate ion. The acetate catalytic coefficient, k_{AcO^-}, for this reaction is $k_{AcO^-} = 1.6 \times 10^{-2}$ $l^2.mole^{-2}.sec^{-1}$. In the kinetic experiments for the determination of k_{2w} for the nitrosation of the free acid and the conjugate base forms of m-hydroxyphenylacetic acid, the total stoicheiometric concentration of the substrate was of the order of 4×10^{-2}M. Thus, the value of k_{2w} for the acid was determined at an effectively zero concentration of the anionic

form of the substrate, while the coefficient k_2w for the conjugate base form of the substrate was determined at a concentration of free base of 4×10^{-2}. Thus, an increase in the rate of $(k_{2HA} - k_{2A^-}) = 0.95 \times 10^{-2}$ l.mole.$^{-1}$sec.$^{-1}$ is achieved by an increase of 4×10^{-2}M in the concentration of the intramolecular acetate ion, which leads to an effective catalytic constant for catalysis by the neighbouring acetate function of $k_A = 0.24$ l.^{2}mole^{-2}.sec^{-1}.

Comparison of this catalytic coefficient for intramolecular catalysis, with that of the intermolecular acetate catalytic coefficient, indicates that the neighbouring group acetate function is about 15 x more effective than external acetate as a base for assisting proton removal in the rate-determining step of the nitrosation of the conjugate base of m-hydroxy--phenylacetic acid. As discussed previously, this factor represents a maximum value, since the relative electronic effects of the substituents on the reaction rate have been neglected in this analysis.

This rather moderate increase in the extent of catalysis of the nitrosation reaction by the neighbouring acetate group is considerably less than that expected of a neighbouring group effect. Many examples of intramolecular nucleophilic

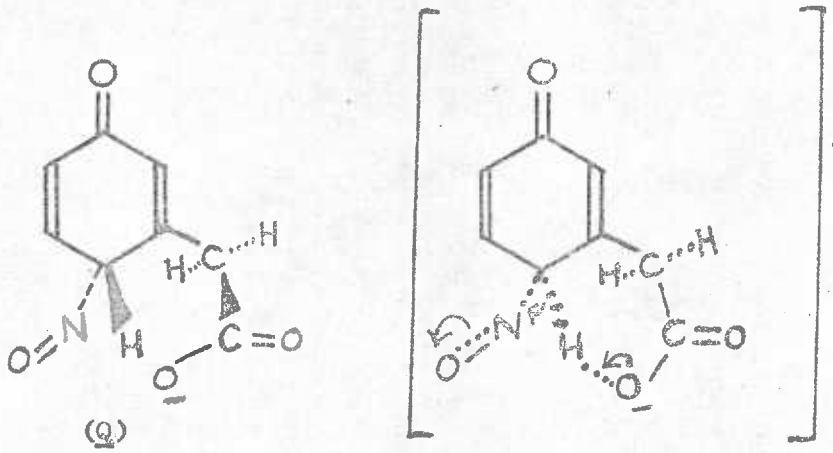
participation in displacement reactions at saturated carbon centres have been described[102], mainly by Winstein and his coworkers[93,103], and such anchimeric assistance has been shown to involve enhancements of the order of 10^3 to 10^6 over similar intermolecular displacements. It is generally held that an increase in rate of at least 5x,and preferably 50x,is necessary for identification of neighbouring group participation through the recognition of anchimeric assistance.[102]

Two factors which must be considered in an explanation of the apparent low effectiveness of the ($-CH_2CO_2^-$) group as an intramolecular base in the nitrosation of m-hydroxyphenylacetic acid are;

1. Can the basic site of the neighbouring group approach the proton closely enough without a large expenditure of energy ?

2. Do they come together frequently enough ?

The answer to the first question is apparent from inspection of a three dimensional model of the intermediate (Q) in the nitrosation reaction, which is drawn in FIGURE (6.9). It is apparent that the intermediate is set up for the formation of a transition state involving participation of the neighbouring acetate function through a six-membered ring



(Q) (T)

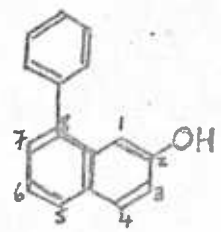
FIGURE (6.9).

as shown, (T). It has been shown previously that neighbouring group participation is most favourable when there is possibility of formation of five and six-membered ring transition states.[102] Thus it would appear that participation of the acetate group in the transition state of the proton removal step is, in principle, energetically favourable.

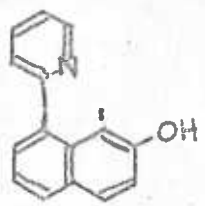
The answer to the second of the above questions may provide the main reason for the decreased activity of the neighbouring base in the nitrosation reaction. The ($-CH_2CO_2^-$) group is in no way fixed in its stereochemistry, and is free to rotate about its C-C bond axis away from the site of substitution. Thus, it is probable that the $-CO_2^-$ group spends little of its time in the transition state of the reaction in close proximity to the leaving proton. This factor, together with the fact that there is only a moderate steric inhibition to the approach of

'external' acetate molecules to the reaction site, is probably responsible for the decreased effectiveness of the neughbouring acetate group as an intramolecular base.

The intramolecular base catalysis in the azo coupling substitution reaction reported by Zollinger and Snyckers[8] arises mainly from steric causes, and these results support the above arguments. The coupling of (I) with ArN_2^+ at the 1-position



(I)



(II)

was reported to proceed with a primary deuterium isotope effect $k_H/k_D = 2.7$, but no base catalysis by pyridine was observed. This demonstrates the effect of the high degree of steric congestion at the reaction site, which in fact totally inhibits the approach of a pyridine molecule in the rate determining step, to the leaving proton. The coupling of (II) under similar conditions shows a kinetic isotope effect of about unity, which was interpreted as evidence for intramolecular catalysis of the proton-loss step by the 2'-pyridyl group, resulting in a change in the rate-determining step. This is consistent

with arguments forwarded earlier, since in (II) the neighbouring base is of a more restricted geometry, and the N atom will be held in close proximity to the leaving proton. An unexplained fact in this work of Zollinger and Snyckers, however, is that the reported rate of coupling of (I) is, in fact, 2.2 x faster than the rate of coupling of the 8-(2'-pyridyl)-compound (II) which is allegedly intramolecularly base-catalysed.

(ii). Nitrosation of 7-Hydroxy-1-Naphthoic Acid.

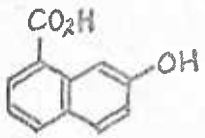
The rate of nitrosation of 7-hydroxy-1-naphthoic acid, at any given pH, is defined by equ.(6.58), in which (7-OH-

$$\text{rate} = \bar{k}_2\left(\text{7-OH-1-napthoic acid}\right)\left[HNO_2\right] \quad . \quad . \quad .(6.58)$$

-1-naphthoic acid) represents the total stoicheiometric concentration of this species in the reaction. The variation of the rate with pH is shown in FIGURE (6.10) ,as a plot of log $\bar{k}_2$ against pH , by the solid line. This plot includes data for the reaction both in $HClO_4$ and in acetic acid buffer solutions, since the data of TABLE (6.27) previously showed that $\bar{k}_2$ was not significantly dependent on buffer concentration. FIGURE (6.10) also includes a plot of the data for the reaction

of the 8-deuterio compound, shown by the broken line, and that for the reaction of 2-naphthol under similar conditions shown by the dotted line.

The variation of the observed deuterium isotope effect with pH for the nitrosation of 7-hydroxy-1-naphthoic acid, (I),



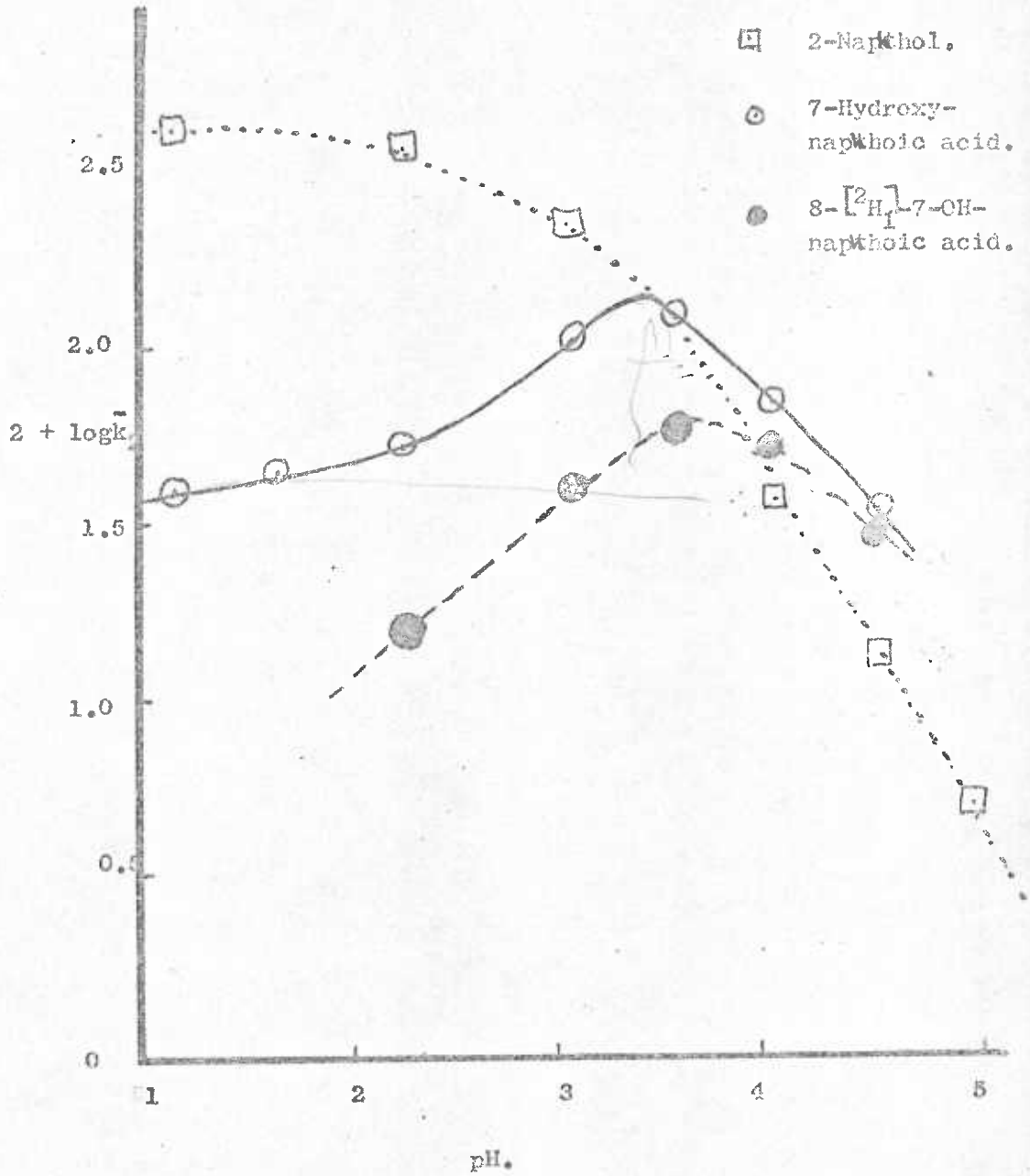
(I)

shows an almost identical trend to that for the reaction of 2-naphthol. Thus the rate-determining step for the reaction at pH $<$ 3.5 is largely C-H bond fission, whilst at pH $>$ 3.5 there is a change in rate-determining step to the initial electrophilic attack.

At pH = 1, the rate of nitrosation of (I) is about 10x slower than that of 2-naphthol, but as the pH is increased to about 3.5, the rate of reaction of the naphthoic acid increases to a maximum value at a pH corresponding to the change in rate determining step as shown by the isotope effect studies. Over the pH range 1 to 3.5, the rate increases with decreasing acidity by a factor of about 4. The decreased rate of nitrosation of the carboxy-substituted compound compared with 2-naphthol at pH = 1 is attributed to a combination of two effects of the

FIGURE (6.10).

Nitrosation of 7-OH-1-Naphthoic Acid at 25°C. Variation of $\bar{k}_2$ (equ.(6.58)) with pH.



carboxy substituent ; (i) the steric influence which tends to decrease k_b and hence the overall rate, (ii) the electronic withdrawing effect of CO_2H on k_a, which also tends to decrease the overall rate, since $\bar{k}_2 = \frac{Kk_ak_b}{k_{-a}}B$. Although the relative magnitudes of these two effects on $\bar{k}_2$ cannot be determmined, the electronic effect is likely to be quite large. The σ_m^+ value for $(-CO_2H)$ of 0.32[33] indicates that the $(-CO_2H)$ group has a large electron withdrawing effect, and this will act on the g-position of (I) resulting in a decreased reactivity and hence overall rate (although σ_m^+ correlations will not apply to the naphthalene system, the value is used as a guide to the effect of the substituent).

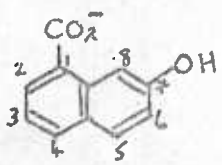
The observed increase in the rate of nitrosation of 7-hydroxy-1-naphthoic acid with decreasing acidity from pH = 1 to 3.3 is consistent with the effect of increasing proportions of the carboxylate anion form of the substrate , for which there is intramolecular catalysis of the k_b step. However, the increase in rate is equally consistent with the electronic effect of the carboxylate anion on the reactivity of the substrate. The σ_m^+ value for the $(-CO_2^-\ K^+)$ is -0.03[33], indicating that this group has an opposite electronic effect to that of the $(-CO_2H)$ function, and might be expected

to increase the reactivity of the 8-position in (I) with respect to 2-naphthol. Thus the increase in rate with decreasing acidity can be attributed to two effects of the increasing proportion of the substrate in the carboxylate form, which are superimposed: (i) the increase in k_b from base catalysis by the neighbouring $-CO_2^-$ group (i) the increase in k_a resulting from the activating electronic effect of the $(-CO_2^-)$.

At pH $>$ 3.5, k_a is largely rate-limiting, and as discussed earlier for 2-naphthol, the rate coefficient is proportional to H_3O^+, since

$$\bar{k}_2 = k_a . K \left[H_3O^+\right] \quad \ldots . \quad (6.59)$$

However, it is apparent from FIGURE (6.10) that $\bar{k}_2$ is much less dependent on H_3O^+ for the nitrosation of the naphthoic acid , than for 2-naphthol, and the rate for the acid is much higher in this pH region than for 2-naphthol. These results are quite consistent with the operation of the superimposed electronic effect of the $(-CO_2^-)$ function on the k_a step. Since $(-CO_2^-)$ is electron donating, the reactivity of the 8--position of the carboxylate-substituted naphthol (II) is



(II)

increased towards electrophilic substitution compared with that of the parent 2-naphthol, and hence k_a is increased for the nitrosation of the carboxylate form of 7-hydroxy-1-naphthoic acid. Similarly, as the pH is raised, the proportion of the carboxylate form of the substrate is increased, resulting in an increase in the overall rate $\bar{k}_2$ which counteracts the opposite 'normal' acidity dependence for the naphthol of equ. (6.59). This accounts very nicely for the reduced acidity dependence observed for the nitrosation of 7-hydroxy-1-naphthoic acid at pH $>$ 3.5, compared to that of 2-naphthol in the same region.

Summary.

The nitrosation of phenol and 2-naphthol in dilute acidic media involves an A-S_E2 mechanism with formation of a steady--state, neutral dienone intermediate (I) (equ.(6.60)) from the interaction of H_2ONO^+ with the molecular form of the substrate.

$$ArOH + H_2ONO^+ \underset{k_{-a}}{\overset{k_a}{\rightleftharpoons}} (I) + H_3O^+ \qquad \ldots(6.60)$$

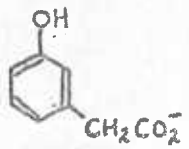
$$(I) + B \xrightarrow{k_b} \text{products.}$$

The overall rate of reaction is given by the expression:

$$\text{Rate} = \frac{k_a k_b K_{H_2ONO^+} [H_3O^+][B][HNO_2][ArOH]}{k_{-a}[H_3O^+] + k_b[B]} \quad \ldots(6.61)$$

Either k_a or k_b can be effectively rate-controlling, the major deciding factor being the pH of the reaction solution. In the nitrosation of 2-napthol, k_{-a}/k_b is of the order of 10^2. Both compounds react via their neutral forms, and the results suggest that phenolate and napthholate ions undergo electrophilic substitution preferentially on oxygen.

Under conditions for which the proton loss from the inter--mediate is rate-determining, only moderate intramolecular base catalysis is observed for the nitrosation of the conjugate base of m-hydroxyphenylacetic acid (II). The lack of any appreciable neighbouring group effect is explained in terms of the high degree of steric freedom of the intramolecular basic site and the site of substitution.



(II)

CHAPTER VII.

SUMMARY OF THE FEATURES OF C-NITROSATION.

C-Nitrosation by the Nitrosonium Ion- Nitrosation in Concentrated Mineral Acids.

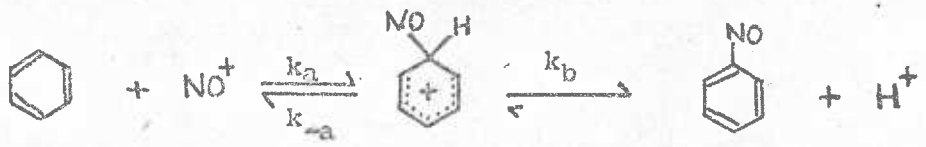
Nitrosation of phenols and aromatic ethers proceed mainly at the most reactive para-position, indicating that NO^+ is a very selective reagent. An assessment of its reactivity can be made by comparison of the rate of its reaction with benzene with the rate of nitration of benzene by the NO_2^+ reagent. In 61.5% $HClO_4$ at 25°C, the nitration of benzene is believed to be encounter-controlled[28], the encounter rate under these conditions being about 2×10^9 $l.mole^{-1}.sec^{-1}$. The rate of nitrosation of benzene by NO^+ in 60% $HClO_4$ at 52.9°C has an overall rate coefficient of 4×10^{-4} $l.mole^{-1}.sec^{-1}$.[37] Direct comparison of these rates suggests that the NO_2^+ ion is at least 10^{13}x more effective than NO^+ in effecting overall reaction. It is also significant that rates of acid-catalysed halogenation by HOBr and HOCl similar to those for the nitrosation of benzene are usually observed in dilute $HClO_4$

of about 0.1 to 1.0 M.[104,105], where the concentrations of positively charged reagents are extremely low. Thus, there is no doubt that the nitrosonium ion is a weak electrophile, although to a lesser extent than previously supposed.

The low reactivity of NO^+ is not reflected by its selectivity towards substrates of differing reactivity. The value of $\rho = -6.2$ for the low temperature nitrosation of p-substituted phenols (supporting the value of $\rho = -6.9$ for nitrosation of mono-substituted benzenes at 53°C[37]) is significantly smaller than those found for other weak electrophiles (e.g. bromination in HOAc $\rho = -12.1$[106,107]). The low ρ value is a natural consequence of a rate-limiting proton transfer from the Wheland intermediate, which has been shown in this work to be characteristic of aromatic C-nitrosation under these conditions, and arises from the opposite electronic demands of Wheland intermediate formation and the rate-limiting proton-loss step. This underlines the danger of assessing reagent reactivities from the magnitude of the ρ -values alone, in the absence of additional direct evidence as to the nature of the rate-determining step in the substitution reaction. Another natural consequence of the rate-limiting step in aromatic C-nitrosation by NO^+ is the catalysis of the reaction

by the anions of strong acids , as observed in the nitrosation of benzene and phenol in concentrated solutions of H_3PO_4 and H_2SO_4.

That the substantial primary deuterium isotope effects persist over a 10^5 fold range of substrate reactivity from benzene to phenol would suggest that slow proton-loss for aromatic nitrosation is unrelated to the acidity of the Wheland intermediate. It seems unlikely, too, that the NO^+ ion is extensively solvated, because the reaction rate in concentrated acids is not strongly dependent on water activity, and this rules out the importance of steric factors in deciding the rate-determining step. Also, the acidifying effect on the leaving proton of the substituting reagent NO^+ cannot be very different to the effect of the NO_2^+ group in nitration, and thus the isotope effect cannot be attributed to a lower acidifying effect of the -N=O function. The NO^+ ion, is, however, a relatively stable species (pK = -6.12 on the H_R scale[108]) compared with other positively charged electrophiles, so that the k_{-a} step in equ.(7.1) should be particularly rapid. This factor would appear to be of overriding importance in deciding the rate-limiting step in aromatic C-nitrosation.



Equ.(7.1). A-S_E2 Mechanism for Aromatic C-Nitrosation at High Acidity.

C-Nitrosation in Dilute Acidic Media.

The H_2ONO^+ and NOCl species have been identified as active electrophiles in aromatic C-nitrosation at low acidities. The nitrosation of extremely reactive compounds becomes a diffusion-controlled process when the basicity of the substrate exceeds a pK_a value of about -3.0. The rate-determining step in these cases is the rate of encounter of the reactant species in solution, which is governed by the viscosity of the reaction medium, and no kinetic isotope effect is therefor observed. The rate-determining step in nitrosation of less reactive compounds ($pK_a < -4$) in dilute acid can be either proton loss from the intermediate or the initial attack of the electrophile, depending on the reaction and conditions:

(i). In the nitrosation of compounds such as 1-nitroazulene ($pK_a = < -4.7$) and the less reactive indoles ($pK_a < -4$), in which the formation of a positively charged Wheland-type inter-mediate is prevalent, proton-loss from the intermediate is

rate-limiting and $k_{-a} \gg k_b$ (equ.(7.2)).

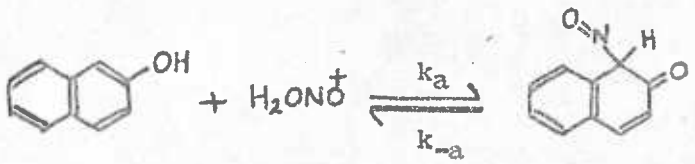
$$ArH + H_2ONO^+ \underset{k_{-a}}{\overset{k_a}{\rightleftharpoons}} Ar\overset{+}{H}NO \qquad \text{.....(7.2).}$$

$$Ar\overset{+}{H}NO \xrightarrow{k_b} ArNO + H^+$$

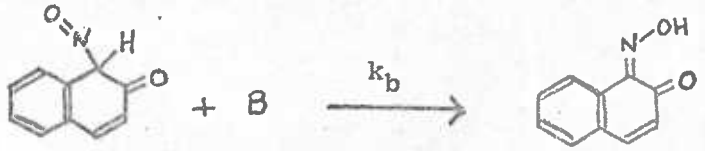
$$\text{rate} = \frac{k_a k_b}{k_{-a}} [ArH][H_2ONO^+] \qquad \text{. . . (7.3)}$$

For these compounds, a primary deuterium isotope effect is observed.

(ii). For the nitrosation of phenols and naphthols in dilute acid 0.1M, the reaction is an S_E-2 process involving the formation of a neutral dienone intermediate in small stationary concentrations. The active electrophile operating at pH 1 to 5 has been identified as the H_2ONO^+ reagent. Since the k_{-a} step (equ.(7.4)) is catalysed by H^+, presumably by protonation on the phenolic oxygen atom, and the second step k_b is catalysed by general bases, the kinetics of the reaction exhibit a variable behaviour dependent on the conditions.



(S) (I) .....(7.4).



(I)

$$\text{Rate} = [S][HNO_2]\frac{k_a k_b [H_3O^+][B]}{k_{-a}[H_3O^+] + k_b[B]} \quad \ldots\ldots (7.5).$$

At very low $[H^+]$, when $k_{-a}[H_3O^+] \ll k_b[B]$, the rate determining step is initial attack of the electrophile, and no primary deuterium isotope effect is observed. When $k_{-a}[H_3O^+] \gg k_b[B]$, proton loss from the intermediate is rate-limiting, the reaction shows linear base catalysis and a substantial primary isotope effect ($k_H/k_D \simeq 4$) is observed. In the intermediate acidity range, the reaction shows a decreasing degree of base catalysis with increasing pH, and a variation of the magnitude of the ratio k_H/k_D with acidity. A value of k_{-a}/k_b of about 10^2 has been obtained for the nitrosation of 2-naphthol in dilute acid. The results for phenol indicate a higher value for k_{-a}/k_b, the difference most likely arising from a higher value of k_b for the reaction of 2-naphthol compared with

phenol, since the rate of nitrosation of 2-naphthol is markedly higher in the acid independent region than that of phenol.

These findings for aromatic C-nitrosation in dilute acidic media have provided conclusive evidence for an S_E-2 mechanism involving formation of a steady-state intermediate. Furthermore, the results eliminate the possibility of an S_E-3 mechanism for aromatic C-nitrosation involving synchronous electrophilic attack and C-H bond fission. Also, the possibility that the nitrosation of phenolic compounds is a special case in which the intermediate has pronounced stability and builds up into non-steady-state concentrations during the reaction can be discounted. Once again , the results for C-nitrosation in dilute acidic media underline the importance of k_{-a} in deciding the rate-controlling step.

PART III.

EXPERIMENTAL.

CHAPTER VIII.

THE EXPERIMENTAL DETAILS.

An account of the experimental methods is given in this chapter, together with examples of typical kinetic runs.

(A). The Kinetic Methods.

1. Method Employing Analysis for Unreacted Nitrous Acid.

The kinetic method used in the majority of this work involved analysis of aliquots of the reaction mixture for unreacted nitrite by a modification[109] of the method first used by Shinn[110].

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

This method involves diazotisation of sulphanilamide by HNO_2 to give a stable diazonium ion, which is then coupled with N-1-naphthylethylenediamine-dihydrochloride to produce an azo dye solution, the optical density of which is directly proportional to the original concentration of HNO_2.

In a typical determination, 5ml of the reaction solution were run into about 25ml of distilled water contained in a 50ml volumetric flask containing 2ml of the sulphanilamide

solution (0.5% in 5M HCl), and the flask shaken thoroughly. After 2 minutes, 2ml of the naphthylethylenediamine solution (0.1% in H_2O) were added, the solution made up to the graduation mark and shaken thoroughly. The time taken for the azo dye to develop fully varies from 15 minutes for analysis of dilute acid solutions, to 45 minutes for strong acidities. After allowing full development of the dye, the optical density of the solution was measured at λ_{max} = 541 n.m. in a spectro--photometric cell of suitable path length, against a reference cell containing only a suitable dilution of the reagent solutions in water.

The light absorption of the dye has been fully investigated[37] and has been shown to obey the Beer-Lambert law (equ.(8.1)) exactly, where the symbols in equ.(8.1) have their usual significance. At 18°C, $\epsilon_{azo} = 5.4 \times 10^4$ l.mole^{-1}.cm^{-1}

$$\log \frac{I_o}{I} = \epsilon_{azo}.[\text{Azo dye}].l \quad \ldots(8.1)$$

$$\propto \epsilon_{azo}.[HNO_2].l.$$

(b), The Kinetic Method.

An account of the general method is given below, followed by a description of the variations in this procedure used in specific cases.

General Method.

The reactions were carried out in volumetric flasks held at constant temperature by immersion in a temperature controlled bath. The required amount of solvent acid or buffer solution was added to water contained in the volumetric flask, followed by the required amount of an aqueous stock solution of the aromatic substrate. The flask was shaken and immersed in the thermostatting bath for 15 minutes. The reaction was initiated by adding a measured quantity of thermally adjusted aqueous stock solution of sodium nitrite. The volume was adjusted by addition of a small quantity of distilled water and the flask shaken thoroughly before immersion in the thermostatting bath. Aliquots of the reaction solution were removed at timed intervals and analysed for nitrous acid by Shinn's method described above.

The gross acidity of the kinetic run was determined by titration against standardised sodium hydroxide solution in the case of the runs performed in mineral acids, or by pH measurement of the runs performed in buffer solutions.

Variations in Procedure.

(i). The acidity of the runs carried out in H_3PO_4 was determined as a weight % H_3PO_4, and so the weight of H_3PO_4 added and the weight of the total reaction solution were measured before

sampling was commenced.

(ii). The runs performed at $0^{o}C$ were held at this temperature by immersion in an ice-water bath.

Side Reactions.

No kinetically significant side reactions other than spontaneous decomposition of nitrous acid were encountered. The initial ortho-nitroso products of the nitrosation of para-substituted phenols are oxidised by the solvent $HClO_4$ immediately on formation, but this process does not interfere with the kinetic analysis. This process is discussed later in the section concerning the products of reaction. All the substrates were completely stable under the reaction conditions.

For the nitrosation of the activated compounds phenol, 7-hydroxy-1-naphthoic acid, naphthol, m-hydroxyphenylacetic acid, and p-cresol, the rate of nitrous acid decomposition is negligible compared with the rate of nitrosation of the aromatic substrate. However, for the reaction of the less reactive p-substituted phenols, this rate of unproductive loss of nitrous acid becomes significant and so it was necessary to fully account for this process in the kinetic analysis. Thus, independent concurrent measurements were made of nitrous acid concentration under identical conditions as for the nitrosation reactions, except

for the absence of aromatic substrate. The decomposition of nitrous acid at the high acidities studied shows an approximate first order dependence of the rate on nitrous acid concentration over a restricted range of concentration[37,108]. By studying both the nitrosation reaction and the spontaneous decomposition with identical initial concentrations of nitrous acid, reasonably reliable and consistent data could be obtained.

Error in Shinn's Analysis.

This method is subject to little error other than the normal volumetric ones. There was no contribution to the absorbance at 541n.m. from any of the substrates or products, and the azo dye solution was quite stable for at least 3 hours after formation. Although slight changes in thr extinction coefficient of the azo dye with acidity have been noted in the past[37], under the pseudo first order conditions employed here, this is kinetically insignificant.

Calculation of Rate Coefficients.

In the presence of excess aromatic substrate over the initial stoicheiometric nitrous acid concentration, the pseudo first order stoicheiometric rate coefficient $\bar{k}_1$ is defined by equ.(8.2), and is calculated according to equ.(8.4).

$$-\frac{d(HNO_2)}{dt} = \bar{k}_1 (HNO_2) \quad \ldots\ldots (8.2)$$

On intergration, equ.(8.2) gives,

$$\bar{k}_1 . t = -2.303 \log (HNO_2) + \text{a constant} \quad \ldots (8.3)$$

and is equivalent to,

$$\bar{k}_1 . t = -2.303 \log A_t + \text{a constant} \quad \ldots (8.4)$$

Thus the rate constants were obtained from the slopes of linear plots of log A_t versus time, where A_t is the absorbance of the Shinn solution, from an aliquot of the reaction extracted at time t.

For the runs in which there is negligible decomposition of nitrous acid over sveral reaction half lives, the measured $\bar{k}_1$ is actually the pseudo first order stoicheiometric rate coefficient for the nitrosation of the aromatic substrate. The second order stoicheiometric rate coefficient ($\bar{k}_2$) for this reaction is calculated directly from the observed pseudo first order coefficient by equ.(8.5) and (8.6).

$$-\frac{d(HNO_2)}{dt} = \bar{k}_2 (HNO_2)(S) \quad \ldots\ldots (8.5)$$

$$\bar{k}_2 = \bar{k}_1 / (S) \quad \ldots\ldots (8.6)$$

In the cases where a correction is applied for nitrous acid decomposition, that is for p-chloro, p-fluoro, p-cyano and p-nitro phenols, the observed first order rate coefficient $\bar{k}_o$ is the sum of the pseudo first order rate coefficient for the nitrosation of the aromatic substrate ($\bar{k}_1$), plus that for nitrous acid decomposition (k'). Thus $\bar{k}_1$ is calculated according to equations (8.7) and (8.8).

$$-\frac{d(HNO_2)}{dt} = \left\{\bar{k}_1 + k'\right\}(HNO_2) \quad \ldots\ldots(8.7).$$

$$= \bar{k}_o\,(HNO_2) \quad \ldots\ldots(8.8)$$

Typical Kinetic Runs.

Five examples of typical kinetic experiments studied by analysis for unreacted nitrous acid are shown in TABLES (8.1) to (8.5). These runs represent the various conditions under which the reactions were studied.

TABLE (8.1).

Nitrosation of p-Cresol followed by Shinn's Method.

Run 145.

$[HClO_4]$ = 4.06M, Initial [p-cresol] = 1.04×10^{-2}M.

t = 0°C., Initial (HNO_2) = 1.0×10^{-4}M.

100% reaction corresponds to an optical density at 541nm of 0.00 in a 1cm. cell.

Time (min)	O.D. at 541nm.	$10^5 \times (HNO_2)$ M.	% reaction	$10^4 \bar{k}_1$ (sec^{-1})
2	0.423	7.83	Taken as t_o --	
13	0.373	6.91	12.1	1.89
38	0.296	5.48	30.3	1.83
56	0.236	4.37	44.2	1.80
73	0.198	3.67	53.5	1.78
103	0.138	2.55	67.2	1.85
138	0.099	1.84	77.4	1.78
223	0.033	0.61	90.5	1.85
∞	0.00	0	100	-

mean value of $\bar{k}_1 = 1.82 \times 10^{-4}$ secs^{-1}.

TABLE (8.2).

Nitrosation of 2-Naphthol in Acetic Acid Buffer Solution Followed by Shinn's Method.

Run 512.

pH = 3.971 Initial $[2\text{-Naphthol}] = 2.84 \times 10^{-3}$M.

$[AcO^-] = 0.02$M. Initial $(NaNO_2) = 8.00 \times 10^{-5}$M.

$t = 25^{\circ}$C.

100% reaction corresponds to an optical density at 541 nm. of 0.00 in a 1cm. cell.

Time mins.	O.D. at 541nm.	$10^5 \times (NaNO_2)$ M.	%reaction	$10^4 \times \bar{k}_1$ $secs.^{-1}$
2	0.821	7.61	taken as t_o	--
12	0.720	6.67	11.0	2.19
39	0.520	4.82	36.6	2.05
57	0.419	3.89	48.9	2.04
77	0.332	3.07	59.7	2.01
102	0.244	2.26	70.3	2.03
137	0.156	1.44	81.1	2.05
172	0.105	0.97	87.3	2.02
202	0.073	0.67	91.2	2.02

mean value of $\bar{k}_1 = 2.05 \times 10^{-4}$ $sec.^{-1}$.

TABLE (8.3).

Nitrosation of Phenol Followed by Shinn's Method.

Run 469.

H_3PO_4 = 52.84% Initial [phenol] = 8.03×10^{-4} M.

t = 0°C. Initial (HNO_2) = 6.5×10^{-5} M.

100% reaction corresponds to an optical density at 541 nm. of 0.00 in a 1cm. cell.

Time (mins.)	O.D. at 541nm.	$10^5 \times (HNO_2)$ M.	% reaction	$10^4 \times \bar{k}_1$ sec^{-1}.
5	0.688	6.37	taken as t_o	--
20	0.595	5.51	13.5	1.61
38	0.498	4.61	27.6	1.64
65	0.381	3.53	44.5	1.64
94	0.287	2.66	58.2	1.64
130	0.204	1.89	70.3	1.62
155	0.159	1.47	76.9	1.63
205	0.098	0.91	85.7	1.63

mean value of $\bar{k}_1$ = 1.63×10^{-4} $secs^{-1}$.

TABLE (8.4).

Nitrosation of p-Chlorophenol Followed by Shinn's Method.

Run 211.

$[HClO_4]$ = 6.8M. $[p\text{-Chlorophenol}] = 1.02 \times 10^{-2}$M.

t = 0°C. Initial $(HNO_2) \simeq 7 \times 10^{-5}$M.

100% reaction corresponds to an optical density at 541nm. of 0.00 in a 1cm. cell.

Time (hours)	O.D. at 541nm.	$10^5 \times (HNO_2)$ M.	% reaction	$10^5 \times \bar{k}_o$ sec^{-1}.
0	0.355	6.57	Taken as t_o	--
1	0.313	5.81	11.6	3.45
2	0.276	5.11	22.2	3.52
3	0.243	4.50	31.5	3.50
4	0.217	4.02	38.8	3.42
5	0.189	3.50	46.8	3.38
6	0.172	3.18	51.6	3.26
7	0.152	2.81	57.2	3.30
∞	0.00	0.0	100	--

Mean value of $\bar{k}_o = 3.39 \times 10^{-5}$ sec^{-1}.

TABLE (8.5).

Decomposition of Nitrous Acid Followed by Shinn's Method.

Run 253.

$[HClO_4]$ = 6.8M.

t = 0°C.

Initial $(HNO_2) \simeq 7 \times 10^{-5}$ M.

100% decomposition corresponds to an optical density at 541nm. of 0.00 in 1cm. cell.

Time (hours)	O.D. at 541nm.	$10^5 \times (HNO_2)$ M.	% reaction	$10^6 \times k'$ sec^{-1}.
0	0.358	6.63	Taken as t_0	-
2	0.345	6.39	3.62	6.25
5	0.322	5.96	10.1	6.19
10	0.287	5.32	19.8	6.14
16	0.251	4.65	29.9	6.17
24	0.212	3.93	40.7	6.06
30	0.188	3.48	47.5	5.97
35	0.169	3.13	52.8	5.86
40	0.153	2.83	57.3	5.80

Mean value of $k' = 6.04 \times 10^{-6}$ sec^{-1}.

Precision of Measured Rate Coefficients in Shinn Method.

The second order rate coefficients ($\bar{k}_2$) for the nitrosation of phenol, m-hydroxyphenylacetic acid, 2-napthol, 7-hydroxy-1-napthoic acid and p-cresol were reproducible to better than 5% in most cases. Rate coefficients for the reactions involving the deactivated p-substituted phenols were subject to much higher error because of the uncertainties introduced by the decomposition - rate of nitrous acid. The error in these rate coefficients is of the order of $\pm$ 10% for p-cyanophenol and $\pm$ 20% for p-nitrophenol.

2. Direct Spectrophotometric Method.

For certain reactions, it proved impractical to measure the rate of nitrosation by determination of unreacted nitrous acid by Shinn's method, either because the rate of reaction was too fast for convenient sampling,as in the reaction of phenol and 2-napthol at high acidities, or because the substrate was nitrosated under the conditions of the Shinn analysis faster than sulphanilamide, as in the case of the very reactive azulene. In these cases, a second method of kinetic study was employed involving direct spectrophotometric monitoring of the reaction

solution at a predetermined wavelength characteristic of either the aromatic substrate, or the product. Thus, the reactions of azulene, phenol in $H_2SO_4 \geq$ 9M and $H_3PO_4 \geq$ 70%, and 2-napthol at pH 3 were followed by direct spectrophotometric measurement of the product concentration at timed intervals. The nitrosation of 1-nitroazulene was followed by monitoring the concentration of starting material in the reaction solution.

These reaction were carried out in thermojacketed silica spectrophotometric cells maintained at constant temperature by water circulating from a temperature controlled bath. In the case of low temperature reactions, the cell faces were continuously swept with nitrogen to prevent condensation from the atmosphere.

The reaction solutions were prepared in volumetric flasks. In a typical run, the required amount of an aqueous stock solution of the aromatic substrate was pipetted into the clean flask containing the calculated amount of aqueous mineral acid, or buffer solution, and the flask shaken and immersed in the thermostatting bath for 20 minutes. The reaction was initiated by adding a small volume of thermally adjusted aqueous stock solution of sodium nitrite, after which the flask contents were made up to the graduation mark with distilled water and shaken thoroughly. For the runs performed in H_3PO_4, the weight

of the reaction solution was determined at this stage, the required amount of concentrated H_3PO_4 having been previously weighed into the flask. In all the runs performed in concentrated mineral acid, the amount of sodium nitrite solution added to initiate the reaction, and the volume of water required to adjust the solution to standard volume were both kept small to minimise temperature changes arising from heat of dilution.

A sample of the reaction solution was quickly transferred to the clean, dry, thermostatted spectrophotometric cell which was then placed in the light beam of a recording spectrophotometer, balanced against a reference cell containing similar solvent concentrations. The reaction was monitored at a predetermined fixed wavelength until no further change in the absorbance of the solution was apparent. For study of the reaction of azulene, 1-nitroazulene and phenol, a Unicam SP 700 recording spectr--photometer was employed, with 1cm and 10cm thermojacketed silica cells. For the study of 2-naphthol, the measurements were made in normal 1cm silica cells set in the thermojacketed cell block of a Unicam SP 1800 machine.

The gross acidity of each run was determined by titration against standard alkali, or by pH measurment, where appropiate.

Background Absorptions.

The reactions of 2-naphthol and phenol were carried out with a large excess (at least 20x) of aromatic substrate over inital stoicheiometric concentration of sodium nitrite, the concentrations of which were very small ($\sim 10^{-4}$). There was negligible contribution to the measured absorbance from nitrous acid at the chosen wavelengths, and the contribution from the aromatic was small and constant throughout the kinetic run. Thus, under the pseudo first order conditions employed, the observed optical densities were used directly for the computing of rate coefficients.

The nitrosation of 1-nitroazulene was studied under conditions of a constant excess of nitrous acid, but at the monitored wavelength, the contribution to the measured optical density from nitrous acid was insignificant. Any background absorption from the product, at the wavelength at which the the concentration of 1-nitroazulene was monitored, can be accounted for by employing equ.(8.9),

$$\left[\text{1-nitroazulene}\right]_t = \frac{\text{O.D.}_t - \text{m.}\epsilon_p}{\epsilon_s - \epsilon_p} \quad \ldots (8.9)$$

where, O.D._t is the measured optical density at time(t), $\text{m.}\epsilon_p$

is equivalent to the optical density at infinite time, and ϵ_s and ϵ_p are the extinction coefficients for 1-nitroazulene and the product, respectively, at the monitored wavelength. Since $\epsilon_s - \epsilon_p$ is constant, then under the pseudo first order conditions employed,

$$\left[\text{1-nitroazulene}\right]_t \propto O.D_t - O.D._\infty \quad \ldots (8.10)$$

and thus the observed optical densities can be used directly to compute the rate coefficients.

Similarly, in the case of the nitrosation of azulene , at the wavelength (λ_{max}) for the nitroso product, the azulene makes a small but measurable contribution to the observed absorbance. The concentration of the product at time (t) is related to the measured optical density by equ.(8.11),

$$\left[\text{Az.NO}\right]_t = \frac{O.D._t - m\epsilon_s}{\epsilon_p - \epsilon_s} \quad \ldots\ldots (8.11)$$

in which, m = initial concentration of azulene, ϵ_s = the extinction coefficient of azulene at the monitored wavelength (λ_{max}) and ϵ_p = the extinction coefficient of the product.

The Ultra-Violet Absorption Spectra.

The U.V. spectra of the 1-nitroso-azulene, and of 1-nitro--azulene in 1M $HClO_4$ have not been previously reported. Details of these spectra are given in TABLES (8.6) and (8.7). Details of the U.V. absorption spectra of all other products are well known and in TABLE (8.8) are summarised the details of absorbing species present in the reaction solutions for all the substrates studied, together with their extinction coefficients at the monitored wavelengths.

TABLE (8.6).

U.V. Absorption Spectrum for 1-Nitroso-Azulene in 10^{-3}M Aqueous $HClO_4$ at 18°C.

λ_{max} (nm.)	280	307	350	400
$\log \epsilon_{max}$	4.08	4.23	4.02	3.66

TABLE (8.7).

U.V. Absorption Spectrum for 1-Nitroazulene in 1M Aqueous $HClO_4$/ /5% Ethanol. at 18°C.

λ_{max} (nm.)	221	235	272.5	310-320	423.7
$\log \epsilon_{max}$	4.33	4.31	4.18	4.17	4.19

TABLE (8.8).

U.V. Absorption of Species Present in Reaction Solutions, for Monitored Wavelength (λ_{max}).

Substrate	[substrate] M.	λ_{max} nm.	ϵ_{sub}	$\epsilon_{prod.}$	$[HNO_2]$ M.	ϵ_{HNO_2} [111,112]
Azulene	10^{-5}	307	2500	17,000	10^{-5}	< 30
1-Nitroazulene	10^{-5}	423.7	15,500	4600	10^{-3}	< 30
Phenol [113]	10^{-3}	385	-	17,000	10^{-5}	< 30
2-Naphthol [114]	5×10^{-3}	380	-	5000	10^{-4}	< 50

Side Reactions.

No kinetically significant side reaction was encountered for any of the reactions studied by this method. The products of the nitrosation of phenol, 2-naphthol and azulene were quite stable under the reaction conditions, and the rate of decomposition of nitrous acid in these experiments was negligible compared with the rate of reaction. The initial product of the nitrosation of 1-nitroazulene is oxidised under the experimental conditions of 100-fold excess of sodium nitrite in 1M $HClO_4$ to 1,3-dinitro-azulene, but since the rate was measured by monitoring the

concentration of 1-nitroazulene, this pathway does not interfere with the kinetic analysis. Also, since the nitrous acid is in 100-fold excess, the order with respect to nitrite is unaffected even if nitrous acid is involved in the oxidation reaction.

In the runs carried out in fairly concentrated mineral acid solutions, there occurs a fast loss of about 5% to 10% of the original nitrite concentration on initial addition to the reaction solution. However, since this loss is known to occur during initial addition and shaking[111], and since there is no significant subsequent loss of nitrous acid during the reaction time, this initial loss is kinetically insignificant under the first order conditions employed.

Calculation of Rate Coefficients.

(i) For 2-napthol, the data refer to the pseudo first order stoicheiometric coefficient ($\bar{k}_1$) defined by equs.(8.12) and (8.13).

$$\text{Rate} = \bar{k}_1^{o} (NaNO_2) \qquad \ldots . (8.12)$$

$$\bar{k}_1 = \bar{k}_2^{o} (\text{2-napthol}) \qquad \ldots . (8.13)$$

Under the pseudo first order conditions employed, the integrated

form of equ.(8.12) can be expressed in terms of the measured optical densities and the data plotted according to equ.(8.14).

$$k_1 t = -2.303 \log (A_\infty - A_t) + \text{a constant} \quad \ldots(8.14)$$

where A_t and A_∞ are the measured optical densities at time (t) and (∞) respectively.

(ii). The data for the reaction of phenol in concentrated acids, refers to the pseudo first order rate coefficient (k_1) defined by equ.(8.15) and equ.(8.16).

$$\text{Rate} = k_1 [HNO_2] \quad \ldots\ldots\ldots(8.15)$$

$$k_1 = k_2[\text{phenol}] \quad \ldots\ldots\ldots(8.16)$$

and k_i is obtained from the integrated form of equ.(8.15) expressed in terms of the optical density as in equ.(8.17).

$$k_i t = -2.303 \log (A_\infty - A_t) + \text{a constant} \quad (8.17).$$

(iii). The data for the nitrosation of 1-nitroazulene refer to the pseudo first order rate coefficient (k_1) defined by equ. (8.18), the integrated form of which can be expressed in

$$\text{Rate} = k_1 [\text{nitroazulene}] \quad \ldots\ldots (8.18)$$

terms of the measured optical density by equ.(8.19)

$$k_1 t = -2.303 \log (A_t - A) + \text{a constant} \quad ..(8.19)$$

and $$k_1 = k_2[HNO_2] \quad ..... (8.20)$$

(iv) The results for the reaction of azulene refer to the second order rate coefficient defined in equ.(8.21), calculated by

$$\text{rate} = k_2 [\text{azulene}][HNO_2] \quad ..... (8.21)$$

by employing the integrated form shown in equ.(8.22), in which

$$k_2 t = \frac{2.303}{(a - b)} \times \log \frac{(a - x)}{(b - x)} + \text{a constant} \quad (8.22).$$

a = initial nitrous acid concentration, b = initial azulene concentration, and x = concentration of product at time t calculated from the measured optical density by equ.(8.11).

In all cases, the rate coefficients were calculated from the slopes of linear plots of the data according to the relevant equation outlined above.

Typical Kinetic Runs.

Four typical kinetic runs followed by the direct spectro--photometric method are detailed in TABLES (8.9) to (8.12); these are representative of the various conditions employed.

TABLE (8.9).

Nitrosation of Azulene Followed by the Direct Spectro-photometric Method.

Run 36.

$HClO_4 = 10^{-3}M$ Initial [azulene] $= 4.64 \times 10^{-5}M.$

$t = 14.5^{o}C.$ Initial $[HNO_2] = 8.00 \times 10^{-5}M.$

100% reaction corresponds to an optical density at 307 nm. of 0.886 in a 1cm. cell.

Time (mins.)	O.D. at 307nm.	10^{5}x[Az.NO] M.	% reaction	k_2 $l.mole^{-1}.sec^{-1}$
1	0.233	0.75	taken as t_o	-
2	0.339	1.38	29	43.0
3	0.423	1.88	40.5	43.1
4	0.490	2.28	49.1	43.4
5	0.556	2.67	54.5	46.5
7	0.635	3.14	67.6	45.8
9	0.693	3.49	75.2	46.1
11	0.731	3.71	80.0	45.1
∞	0.886	4.63	100	-

TABLE (8.10).

Nitrosation of Phenol Followed by the Direct Spectrophotometric Method.

Run 408.

$[H_2SO_4]$ = 10.36M. $[\text{Phenol}] = 1.00 \times 10^{-4}$M.

t = 0°C. Initial $[HNO_2] = 5.0 \times 10^{-6}$M.

100% reaction corresponds to an optical density at 385 nm. of 0.63 in a 10cm. cell.

Time (mins)	O.D. at 385nm.	% reaction	$10^3 \times k_1$ sec^{-1}.
1	0.260	taken as t_o	-
2	0.337	18	3.87
3	0.396	35	3.82
4	0.443	48	3.79
5	0.488	59	3.99
6	0.522	68	4.11
7	0.550	76	4.05
8	0.568	82	4.26

Mean value of $k_1 = 4.0 \times 10^{-3} sec^{-1}$.

TABLE (8.11).

Nitrosation of 2-Naphthol Followed by the Direct Spectro - -photometric Method.

Run 502.

pH = 2.82 $[2\text{-Naphthol}] = 1.78 \times 10^{-3}$ M

$[AcO^-] = 0.02$M Initial $(NaNO_2) = 7 \times 10^{-5}$M.

$t = 25.0^{o}$C.

100% reaction corresponds to an optical density at 380nm. of 0.328 in a 1cm. cell.

Time mins.	O.D. at 380nm.	% reaction	$10^3 \times \bar{k}_1$ sec^{-1}.
2.0	0.080	24.2	taken as t_o
2.5	0.107	32.9	3.92
3.0	0.130	40.4	3.76
3.5	0.150	46.1	3.71
4.0	0.170	51.8	3.76
5.0	0.202	62.3	3.65
6.0	0.225	68.8	3.67
8.0	0.260	81.1	3.60
10.0	0.285	90.2	3.67
∞	0.328	100	-

TABLE (8.12).

Nitrosation of 3-[$^{2}H_{1}$]-1-nitroazulene Followed by the Direct Spectrophotometric Method.

Run 24.

$[HClO_4] = 1.04M$ Initial [1-Nitroazulene] $= 6.0 \times 10^{-5}$ M

$t = 25.0^{o}C.$ $[HNO_2] = 2.90 \times 10^{-3}$ M.

100% reaction corresponds to an optical density at 427.5nm. of 0.276 in a 1cm. cell.

Time (mins)	O.D. at 427.5nm.	10^{5}[nitroazulene] M.	% reaction	$10^{4} \times k_1$ sec^{-1}.
5	0.889	5.60	6.7	taken as t_o
15	0.777	4.58	23.6	3.38
25	0.686	3.75	37.5	3.36
35	0.611	3.06	49.0	3.37
50	0.536	2.38	60.4	3.18
60	0.498	2.03	66.2	3.09
70	0.455	1.64	72.8	3.16
80	0.424	1.35	77.5	3.16
90	0.389	1.03	82.9	3.15
100	0.378	0.93	87.7	3.14
∞	0.276	0.00	100	-

Precision of Rate Coefficients Determined by the Direct Spectrophotometric Method.

The rate coefficients measured by this method were reproducible to better than 5% in all cases.

3.Kinetic Method Employing Sealed Ampoules.

The nitrosation of benzene and its hexadeuterio isomer were carried out in 12M sulphuric acid, at which acidity the nitrous acid is completely converted into the form of NO^+. Since decomposition of nitrous acid probably proceeds by attack of the NO^+ ion on molecular nitrous acid, under these conditions the nitrous acid solutions are therefore quite stable. However, at the elevated temperature used in this investigation, it is necessary to further reduce unproductive loss of nitrous acid by carrying out the reactions in sealed tubes. This also prevents loss of the volatile aromatic substrate during the reaction.

Ampoules of volume approximately equal to 12ml. were prepared by constricting the necks of clean 'Pyrex' test tubes. The reaction solution was prepared in a 100ml graduated flask. A warm mixture of the required amounts of benzene, 98% H_2SO_4

and a small volume of distilled water was shaken thoroughly to ensure complete solution of the benzene, and then cooled to $0^{o}C$ in an ice bath for 30 minutes. A 5ml aliquot of an aqueous stock solution of sodium nitrite at $0^{o}C$ was introduced into the flask and after making the contents up to the graduation mark with water, the flask was shaken thoroughly. A sample of the reaction solution was analysed at this point by U.V. spectroscopy for benzene concentration. 10ml aliquots of the solution were distributed into the ice-cooled ampoules, which were sealed with 'Parafilm' and cooled in liquid nitrogen. The remaining solution was again analysed for benzene to ensure that an equal concentration of reactants had been introduced into each ampoule.

The ampoules were then sealed with a blow-torch and brought to $0^{o}C$ by immersion in an ice-water bath. The tubes were then immersed totally in a temperature controlled bath at $52.9^{o}C$, and after a period of 5 minutes each tube was inspected carefully for homogeneity of the contents. At timed intervals, an ampoule was removed from the bath and opened after cooling to $0^{o}C$, and the contents analysed for nitrous acid by Shinn's method,as described earlier. The U.V. spectrum of the reaction

solution was scanned for analysis for both benzene and product. The acidity was determined by titration of aliquots of the contents of two or three of the ampoules against standard B.D.H. alkali, using methyl red indicator.

Side Reactions.

No evidence was found in the U.V. spectral analysis of the reaction solutions for any kinetically significant side reaction. However, the rate of spontaneous nitrous acid decomposition is significant under the reaction conditions, despite the precautions taken to prevent this unproductive loss. Full account was taken of this process in the kinetic analysis, by independent measurement of the rate of decomposition under identical conditions except for the absence of benzene. The decomposition rate is known to have an approximate first order dependence on nitrous acid concentration[37,108], for at least 70% reaction.

Calculation of Rate Coefficients.

With a large constant excess of benzene over the initial concentration of nitrous acid, the rate of disappearence of nitrous acid to form products follows the rate law in equ.(8.23).

$$-\frac{d[HNO_2]}{dt} = k_1[HNO_2] \quad \ldots\ldots \quad (8.23).$$

However, superimposed on this rate is the spontaneous decomposition process which follows the rate law of equ.(8.24), although the relationship is not exact.

$$-\frac{d[HNO_2]}{dt} = k'[HNO_2] \qquad \ldots\ldots\ldots (8.24)$$

Thus the total observed rate of disappearence of nitrous acid can be expressed as the sum of equs.(8.23) and (8.24) as in equ.(8.25).

$$-\frac{d[HNO_2]}{dt} = \left(k_1 + k'\right)[HNO_2] \qquad \ldots\ldots (8.25).$$

$$= k_o[HNO_2] \qquad \ldots\ldots (8.26)$$

In this way, the pseudo first order rate coefficient (k_1) for the reaction can be computed from the observed coefficients k_o and k'. The second order rate coefficient (k_2) is then calculated from equ.(8.27),

$$k_1 = k_2[\text{benzene}] \qquad \ldots\ldots (8.27)$$

Precision of the Measured Rate Coefficients.

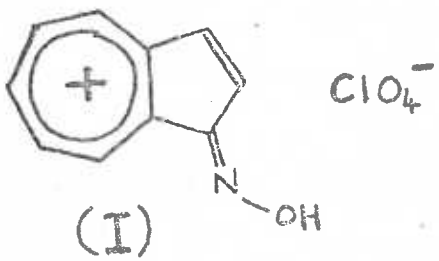
The rate coefficients for reaction of benzene determined

by this method are subject to rather high error due to the non exact nature of the rate of decomposition of nitrous acid. The calculated pseudo first order coefficient (k_1) are accurate to about $\pm$ 20%.

(B). Analysis of the Products of Reaction under the Experimental Conditions.

1. Nitrosation of Azulene.

Nitrosation of azulene at the 1-(or equivalent 3-) position is well known[115] and past workers have isolated 1-oximino-azulenium perchlorate (I) as the exclusive product of the reaction of azulene with nitrosyl perchlorate[116]. However, the free



(I)

1-nitrosoazulene was reported to be too unstable to be purified, and indeed attempts to isolate it in this work were unsuccessful. In the extremely dilute solutions employed here ($\sim 10^{-5}$ M), the

conjugate acid appeared quite stable. Ultra-Violet spectroscopy of the reaction solution showed a good isobestic point at 290nm. and no evidence of any further reaction was seen. Spectral analysis of the product is detailed below, based on the initial stoicheiometry of azulene.

TABLE (8.13).

U.V. Spectrum of 1-nitroso-azulene in 10^{-4} M $HClO_4$, at 18°C.

λ_{max}(n.m.)	280	307	350s	400
$\log \epsilon_{max}$	4.08	4.23	4.02	3.66

2. Nitrosation of 1-Nitroazulene.

Repeated attempts to isolate the product of nitrosation of 1-nitroazulene proved unsuccessful. T.L.C. analysis of an ether extraction of the reaction solution showed a single, yellow highly polar product which darkened to an intractable material on removal from the plate. However, the U.V. spectrum of the reaction solution in 1M $HClO_4$ and excess nitrous acid indicated that the product under these conditions is 1,3-dinitro--azulene. The U.V. spectrum of the reaction solution after several half lives, and after destroying the excess nitrous acid with urea, shows peaks at 240, 300-310 and 380-390 nm. The literature

U.V. spectrum of 1,3-dinitroazulene in ethanol is:[117]

λ_{max}	237	297	306	376	390
$\log \epsilon_{max}$	4.17	4.40	4.47	4.18	4.14

It is therefore assumed that the initial product of nitrosation of 1-nitroazulene is 1-nitro-3-nitrosoazulene, which is oxidised by the excess nitrous acid and $HClO_4$ to the 1,3--dinitroazulene. It is known that the nitration of 1-nitroazulene yields exclusively 1,3-dinitroazulene[73] and this supports the evidence for exclusive nitrosation at the 3-position.

3. Nitrosation of Phenol.

The product of nitrosation of phenol in 0.2M H_2SO_4 has been reported to be at least 95% p-nitrosophenol[118], the few remaining percent arising from ortho substitution. The % para substitution was checked here over the complete acidity range of the kinetic runs. Thin layer chromatography and U.V. spectral analysis and comparison with authentic p-nitrosophenol indicated that the yield of para nitrosophenol is $>$ 90% in all cases.

4. Nitrosation of m-Hydroxyphenylacetic Acid, and the Methyl Ester.

Similar experiments were carried out on m-hydroxy--phenylacetic acid and its methyl ester, as for phenol, and

in both cases, > 95% of one single product was found, with a U.V. spectrum almost identical to that of the p-nitrosophenol. Thus the product in both cases is the expected nitroso - phenol substituted para to the phenolic group. The observed U.V. spectra for both compounds was : λ_{max} 303, $\log \epsilon_{max}$=4.2 at pH = 4.(Literature U.V. for p-nitrosophenol[119] λ_m 302, $\log \epsilon_m$= 4.23 at pH 3.8)

5.Nitrosation of 2-Napthol.

Nitrosation of 2-napthol with nitrous acid in acetic acid has been reported to yield exclusively 1-nitroso-2-napthol[41,120]. This result was confirmed for nitrosation of 2-napthol over the complete range of acidity studied, by t.l.c. analysis and U.V. spectral analysis and comparison with an authentic sample of 1-nitroso-2-napthol. Observed U.V. spectrum of reaction solution at pH 1 to pH 5: λ_{max} 380 nm., $\log \epsilon_{max}$= 3.7, based on stoicheiometry of nitrite. The spectrum of the product isolated from reaction at pH 5 with excess nitrous acid gave; λ_{max}^{EtOH} 270, 370 nm. Literature U.V. for 1-nitroso-2-napthol[114] is: $\lambda_{max}^{H_2O}$ 380(3.7) ; λ_{max}^{EtOH} 260(4.12), 272(4.0), 370(3.7).

6. Nitrosation of 7-Hydroxy-1-Napthoic Acid.

T.l.c. analysis of the reaction solution of 7-hydroxy-

-napthoic acid with nitrous acid in acetic acid buffers, shows the formation of one exclusive product with an ultra-violet spectrum identical to that of 1-nitroso-2-napthol. It is concluded that the sole product is the expected 8-nitroso-7-hydroxy-1-napthoic acid.

7. Nitrosation of Benzene.

With a 100xfold excess of benzene over the initial nitrous acid concentration and in sulphuric acid, as in the kinetic experiments, the product of the nitrosation of benzene was identified as nitrosobenzene by comparison of its U.V. spectrum [121] with that of an authentic sample of nitrosobenzene in 12M H_2SO_4. U.V. maximum for both solutions in 12M H_2SO_4 is λ_{max} 310 nm. That the sole product was nitrosobenzene was confirmed by t.l.c. analysis of an ether extract of a scaled up reaction, and comparison with an authentic sample. With excess nitrous acid in 12M H_2SO_4, appreciable amounts of nitrobenzene were obtained presumably from the oxidation of the initially formed nitrosobenzene by the high concentrations of NO^+ [122] present.

8. Nitrosation of para-Cresol.

U.V. analysis of the kinetic reaction solution after

about 10 half lives showed the presence of 2-nitro-4-methyl-phenol. Thus, the observed spectrum based on the stoicheiometry of added nitrite is:

	In dilute $HClO_4$ at pH=2,		basified with NaOH to pH 14	
λ_{max}	275	370	430	n.m.
$\log \epsilon_{max}$	3.70	3.33	3.45	

(Literature U.V. for ortho-nitro-p-chloro-phenol;[123] $\lambda_{max}^{H_2O}$ 275 (3.72), 370(3.35); λ_{max}^{NaOH} 427(3.50)).

T.l.c. analysis of the reaction carried out with excess p-cresol, excess nitrous acid, and at several acidities between 10^{-2} and 5M $HClO_4$ indicates one single product in all cases. Comparison with an authentic sample of o-nitro-p-cresol confirmed this as the exclusive product under all conditions.

9. Nitrosation of Para-Chloro-and Fluoro- Phenols.

U.V. spectral and t.l.c. analyses of reaction solutions for p-chloro and p-fluoro phenols in $HClO_4$ shows the exclusive product to be the ortho- nitro-para-halophenol, by comparison with authentic sample of o-nitro-p-chlorophenol.

Observed U.V. spectrum for both phenols, based on stoicheiometry of added nitrite: at pH 1 ($HClO_4$), λ_{max} 275 nm.(3.80), 370 nm. (3.46); at pH 14, λ_{max} 430 (3.66).

Literature U.V.spectrum for o-nitro-p-chloro-phenol; $\lambda_{max}^{H_2O}$ 275(3.73)

363(3.43); $\lambda_{max}^{pH\ 12}$ 427 (3,65).

10. Nitrosation of p-Nitrophenol.

The reaction was too slow under the conditions of the kinetic experiments to allow convenient analysis of the product. However, reaction of p-nitrophenol in 7M $HClO_4$ with excess nitrous acid in a sealed tube at 100°C for one month gave appreciable yields of 2,4-dinitrophenol as the sole detectable product. The product was identified by U.V. analysis of the reaction solution;

Observed U.V.spectrum ; pH 1 , λ_{max} 262, 300 nm.

pH 13 λ_{max} 226, 258, 362 nm.

(Lit.[124] for 2,4,-dinitrophenol: $\lambda_{max}^{H_2O}$ 261(4.13), 300(3.97); λ_{max}^{NaOH} 226(4.01), 258(3.86), 358(4.17).).

The product was also confirmed as 2,4-dinitrophenol by t.l.c. analysis of the reaction solution and comparison with an authentic sample.

11. Nitrosation of p-Cyanophenol.

By analogy with all the other p-substituted phenols, the product of nitrosation of p-cyanophenol under the reaction conditions is assumed to be o-nitro-p-cyanophenol. T.l.c.

analysis of the reaction solution established that the p-cyano--phenol was quite stable under the conditions of the kinetic experiments, and that no hydrolysis of the cyano function was occurring.

Concerning the Product of Nitrosation of p-Substituted Phenols.

The observed formation of ortho-nitro products from the nitrosation of p-substituted phenols in aqueous $HClO_4$ solutions is not an unexpected result, since the oxidation of ortho-nitroso phenols is known to be extremely facile[39]. In order to confirm this under the kinetic experimental conditions, authentic samples of ortho-nitroso-p-cresol and ortho-nitroso-p-chloro--phenol were prepared by the method of Cronheim[39]. On dissolution of the former in distilled water, U.V. spectral analysis revealed appreciable oxidation to the nitro counterpart. Both compounds were completely oxidised to their ortho-nitro counterparts on brief contact with very dilute $HClO_4$ solutions. Thus under the kinetic reaction conditions of 6.8M $HClO_4$, the initial nitroso product will be oxidised immediately on formation, by the solvent acid.

The nitrosation of two other p-substituted phenols were briefly studied, but found to be unsatisfactory for kinetic study because of rapid displacement of the para-substituents by

nitrous acid. Thus p-bromophenol on reacting with nitrous acid in 6.8M $HClO_4$ rapidly gives a brown colouration and substantial amounts of p-nitrophenol were isolated from the reaction mixture.

The reaction of p-methoxyphenol with nitrous acid was also observed to result in the displacement of the methoxy group. This reaction has been reported recently to give poor yields (4%) of 4-methoxy-2-nitrophenol and p-benzoquinone[125], but p-benzoquinone formation was much more extensive under conditions used in this work. Thus at $0^{o}C$ in 2 to 5M $HClO_4$, the reaction of p-methoxyphenol with excess nitrous acid yielded quantitative amounts of p-benzoquinone, as seen by U.V. spectral analysis of the reaction solution. At lower acidities (pH = 2 - 3), increasing amounts (up to 30%) of 4-methoxy-2-nitrophenol were detected in the spectra, although p-benzoquinone was still the major product.

(C). Preparation and Purification of Materials.

'Analar' grade phenol was fractionally distilled under reduced pressure, and was dried over P_2O_5 in a vacuum desiccator; f.p. $40.5^{o}C$ (lit.[126] 40.5^{o} - $41.5^{o}C$). 'Analar' benzene and

$[^2H_6]$-benzene (Koch-Light Ltd.) were each fractionally distilled and the middle cut taken; benzene, n_D^{20} = 1.5008 (lit.[127] n_D^{20} = 1.5011); $[^2H_6]$-benzene , n_D^{20} = 1.5013 .

Reagent grade p-cresol and p-chlorophenol were each fractionally distilled twice, and the middle cut vacuum dried over P_2O_5; p-cresol f.p. 34°-34.5°C (lit.[128] 34°C.); p-chlorophenol f.p. 43°C.(lit.[129] 43°C.). Reagent grade p-fluorophenol was recrystallised from petroleum ether (b.p. 40°-60°C.) and dried under vacuum; m.p. 47.5°-48°C.(lit.[130] 48°C.). Reagent grade p-cyanophenol and p-nitrophenol were each recrystallised repeatedly from water and vacuum dried over P_2O_5: p-cyanophenol m.p. 113°C (lit.[131] 113°C.); p-nitrophenol m.p. 113°-114°C.(lit.[132] 114°C.).

Reagent grade 2-naphthol was crystallised repeatedly from water and dried under vacuum over P_2O_5, m.p. 124°C. (lit.[133] 123°-124°C.). 7-hydroxy-1-naphthoic acid was prepared by the method of Royle and Schedler[134] and recrystallised from water with charcoaling, m.p. 253°C (lit.[134] 253° - 254°C.).

Reagent grade azulene was recrystallised from ethanol and dried under vacuum over P_2O_5, m.p. 99°(lit.[135] 98.5°-99°C.) 1-nitroazulene was prepared by the method of Anderson and his coworkers[73] , and recrystallised from dichloromethane/petroleum ether, m.p. 107°C.(lit.[73] 106°-107°C.).

m-Hydroxyphenylacetic acid supplied by Ralph-Emmanuel Ltd. was recrystallised from water, m.p. 132°C (lit.[136] 131°-134°C.). The methyl ester of m-hydroxyphenylacetic acid was prepared by refluxing the acid in anhydrous methanol, with 3% H_2SO_4 as catayst, for 30 minutes followed by neutralisation and ether extraction. The ester was purified by fractional distillation under reduced pressure; b.p. 134°C. at 0.8mm/Hg, n_D^{20} = 1.5311; M^+ = 166. I.R. :- 1720, 1100 cm^{-1}(ester ν -C=O), 3400 cm^{-1} (phenolic -OH).

3-[$^2H_1$]-1-nitroazulene was prepared by stirring a homogeneous mixture of 1-nitroazulene(0.5g), D_2SO_4 (10ml, 100%) D_2O (10ml) and sodium dried ether (10ml.) for 24 hours at room temperature. After neutralisation and extraction with ether, the nitroazulene was purified by crystallisation from dichloromethane/pet.ether, m.p. 109°C. N.m.r. and mass spectral analysis revealed 100% exchange of the 3-proton for deuterium. 1,3-[$^2H_2$]-azulene was prepared in a similar way, again with 100% deuterium incorporation in the 1,3-positions.

The 4-[$^2H_1$]-phenol used was that prepared by A.J.Lawson[37] from p-bromophenol by a Grignard reaction. The compound was 80% pure with respect to isotopic label in the 4-position.

2,6-[$^2H_2$]-p-cresol was prepared by heating the normal

compound dissolved in D_2O (Koch-Light Ltd., 99.7% d) at pH = 9, in a sealed tube at 100°C. for 9 days. After neutralisation and extraction with ether, the $[^2H_2]$-p-cresol was purified as for the normal compound, n_D^{20} = 1.5310. Mass spectral analysis showed 69% incorporation of deuterium in the 2,6-positions.

2,4,6-$[^2H_3]$-3-hydroxyphenylacetic acid was prepared by heating the normal compound in D_2O at pH = 10 in a sealed tube at 100°C for 2 weeks. After normal work up, the product was recrystallised from water. Mass spectral analysis revealed 98% incorporation of deuterium in the 2,4,6-positions. The methyl ester of the 2,4,6-$[^2H_3]$-substituted acid was prepared by esterification of the deuterio-acid as described for the normal compound . Mass spectral analysis revealed no loss of deuterium from the value of 98% for the acid.

1-$[^2H_1]$-2-napthol was prepared by heating the normal compound in D_2O at pH = 12 in a sealed tube at 200°C for 9 days. After neutralisation and filtration of the precipitated napthol, this was recrystallised from boiling water. Mass spectral analysis revealed extensive deuteriation in all four reactive sites of the 2-napthol, but complete absence of the undeuteriated molecular ion. The 1-proton has been reported to exchange exclusively under milder conditions[137], thus it is assumed that

the prepared d-naphthol is 100% deuteriated in the 1-position.

8-[$^{2}H_{1}$]-7-hydroxy-1-naphthoic acid was prepared as for the deuteriated 2-naphthol, but at 100°C. The product was recrystallised from water, m.p.254°C. Mass spectral analysis revealed 88% exchange of the 8-proton for deuterium.

'Analar' grade sodium nitrite, sodium acetate, sodium chloride, and sodium perchlorate were dried in a vacuum desiccator and used without further purification. Perchloric acid (72 wt%), sulphuric acid (98% wt.), phosphoric acid (90 wt.%) and acetic acid were 'Analar' reagents and these were used without further purification. Standard solutions were prepared by dilution.

Deuterium oxide was supplied by Koch-Light Ltd. and Protochem (both 99.7% isotopic purity). That used in the azulene nitrosation study was purified by distillation from a few crystals of potassium permanganate. Otherwise, it was used as supplied.

Deuteriosulphuric acid (D_2SO_4) was prepared by distilling freshly prepared sulphur trioxide into D_2O after the method described by Challis[138].

All other reagents used were of the best available grade.

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