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STUDIES OF THE NITRATION OF PHENOLS AND OTHER
REACTIVE AROMATIC COMPOUNDS AND OF THE BEHAVIOUR
OF CYCLOHEXA-2,5-DIENONE INTERMEDIATES

by

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A thesis submitted in part fulfilment of the
requirements for the degree of Doctor of Philosophy

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ABSTRACT

This thesis is concerned with five aspects of aromatic nitration in aqueous sulphuric acid.

1. The effect of ipso-substitution and encounter control for substrates activated by substituents having an oxygen atom adjacent to the nucleus. The rates for o-cresol, m-cresol and 3,5-dimethylphenol have been determined and these substrates are nitrated at the encounter rate. The proportion of substitution para to hydroxy has been found to increase with increasing acidity from 38 to 55%, 33 to 52% and 30 to 62% respectively and these changes in the product ratios may be due to competition between Wheland intermediate formation, either directly from the hydrogen-bonded encounter pair or subsequent to loss of the hydronium ion.

2-Methyl-6-nitrophenol is established as an important product of nitration of o-methylanisole and a mechanism involving demethoxylation of a Wheland intermediate formed by ipso-substitution at C-Me and a subsequent specific 1,3-rearrangement is proposed.

4-Isopropyl-2-nitrophenol and p-nitrophenol are established as important products of nitration of p-isopropylanisole.

2. The nitrations of substrates having a halogen atom adjacent to the nucleus, namely p-bromophenol, p-chlorophenol, o-bromophenol and 2,4-dibromophenol, are reported and the yields of the products formed have been determined. Nitrodehalogenation was not detected with p-chlorophenol and o-bromophenol, but was the major outcome of the nitration of p-bromophenol and 2,4-dibromophenol, the degree of nitrodebromination decreasing with increasing acidity.

3. The rates of nitration of phloroglucinol at various temperatures have been determined and after correction for C-protonation the rate profile for the nitration of this compound was very close to that for mesitylene, and it is concluded that in as low as 40% sulphuric acid the nitronium ion remains the effective electrophile. The nitration of phenol under the "zeroth-order" conditions has been determined and it has been estimated that a pre-association mechanism should apply to encounter controlled nitrations in below 40% sulphuric acid.

4. Some nitrocyclohexadienones have been synthesised and the rates of rearomatization of 2,4,6-trimethyl- and 4-methyl-4-nitrocyclohexadienones in sulphuric acid have been determined. Above 50% sulphuric acid the rate profiles (vs -Ho) are parallel with slope ~ 0.64 where the oxygen protonated conjugate acid is the reactant and below 50% sulphuric acid the slope decreases gradually to zero and a homolytic dissociation-recombination mechanism is suggested. 3,5-Dimethyl-4-hydroxybenzaldehyde and m-nitromesitol are the main products of reaction of the former dienone, whereas in the latter case 4-methyl-2-nitrophenol is formed quantitatively.

5. The nitration of some molecules having two benzenoid nuclei; For the homogenous nitration of diphenylmethane six nitro products have been identified and the anomalous ratio of mono- to disubstitution is discussed. For the nitration of diphenylether two stages were observed in below 66% sulphuric acid, corresponding to mono- and dinitration and in above 66% sulphuric acid the rate profile for mononitration had zero slope suggesting that the substrate was C-protonated.

Part of the work presented in this thesis has been described in the following publication: R.G. Coombes, J.G. Golding and P. Hadji-georgiou, J. Chem. Soc. Perkin II, 1979, in the press.

CHAPTER 1

GENERAL LITERATURE SURVEY

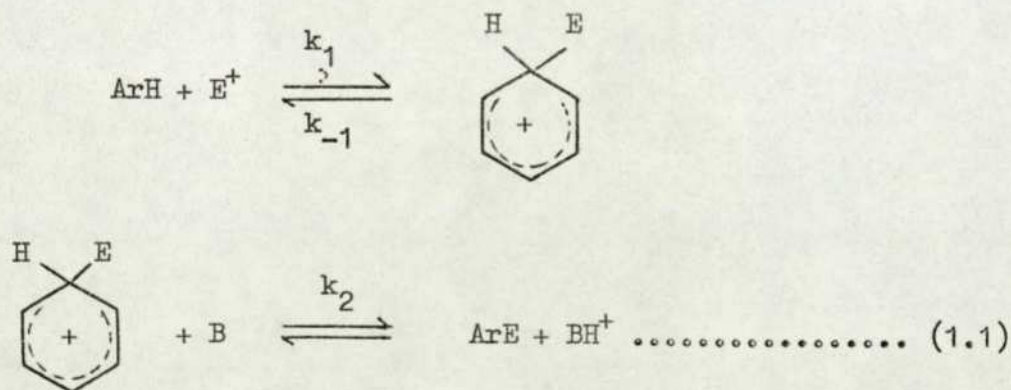
1.1 INTRODUCTION

The first important quantitative studies in aromatic substitution were performed by Holleman¹ who obtained valuable data from which the main generalisations regarding orientation of aromatic substitution could be made. He recognised the connection between orientation and activation and observed that ortho, para directing substituents commonly activate the nucleus, and that meta directing substituents deactivate it.

The study of aromatic nitration reactions is important for two main reasons:

- a) It is the most general process for the preparation of aromatic nitro-compounds.
- b) The basis for development of theoretical organic chemistry has relied heavily on the study of aromatic substitution reactions, and nitration of aromatic compounds is pre-eminent amongst these reactions.

The S_E2 process (Equation 1.1) in which two stages are envisaged, is applicable to electrophilic aromatic substitution^{2,3}. Using the



steady state approximation the rate equation for this process is as follows:-

$$R = \frac{k_1 k_2 [B][ArH][E^+]}{k_{-1} + k_2 [B]} \dots\dots\dots (1.2)$$

If $k_2[B] \gg k_{-1}$ there is no base catalysis, but if $k_2[B] \ll k_{-1}$ then there is a linear relationship between the rate and the concentration of the base. A range of behaviour between these two extremes is possible.

For nitration the effective electrophile is believed to be usually the nitronium ion. The rate limiting first step has been confirmed from



studies of solvent⁴ and isotope⁵ effects, although steric effects may force the second stage to become rate limiting.

Ingold and co-workers⁴ in their classic work, appeared to give a complete picture for nitration, but in the last 12 years, ipso-substitution (see Section 1.51), diffusion control and nitration via nitrosation together with the problems associated with these processes, have led to a renewed interest in this area.

1.2 NITRATING SYSTEMS

Nitration can be achieved under a wide variety of conditions. The reagent used controls the character and kinetics of the reaction, but it is found that under most conditions the nitronium ion is the effective electrophile. Because of this one important effective electrophile, nitration is the most useful model reaction for the study of electrophilic aromatic substitution. It is also of importance that the introduction of one nitro-group generally deactivates the aromatic nucleus to further substitution and clean mono-substitution can be studied.

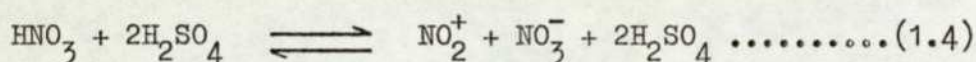
Reagents often employed for nitration are:- (1) concentrated and aqueous nitric acids, (2) nitric acid in concentrated and aqueous

strong acids (e.g. sulphuric acid, perchloric acid, trifluoroacetic acid, methanesulphonic acid), (3) nitric acid in inert organic solvents (e.g. acetic acid), (4) nitric acid in reactive organic solvents (e.g. acetic anhydride), (5) the oxides of nitrogen (e.g. N_2O_4), (6) nitronium salts, (7) nitrous acid (nitration via nitrosation), (8) with transition-metal nitrato-compounds (e.g. $Ti(NO_3)_4$)²³.

1.3 NITRATION IN CONCENTRATED AND AQUEOUS SULPHURIC ACID

1.31 STATE OF NITRIC ACID IN CONCENTRATED AND AQUEOUS SULPHURIC ACID

In concentrated sulphuric acid, nitric acid is completely converted into the nitronium ion, according to the following equilibrium:-



Raman spectroscopy showed that^{6,7,8} the addition of up to 10% of water does not affect the concentration of the nitronium ion, but that further dilution reduces the concentration of this species, which is not detectable in solutions containing less than 85% sulphuric acid. The introduction of water generates bisulphate ions and hydroxonium ions which tend to repress the formation of nitronium ions, but the equilibrium so much favours the nitronium ion that even moderate quantities of water have a negligible effect on its concentration. Figure 1.1 shows the Raman spectroscopy results obtained by measuring⁸ the areas of the bands due to NO_2^+ and HNO_3 .

The UV spectra of solutions of potassium nitrate in various concentrations of sulphuric acid have been studied⁹ and absorptions arising from the nitrate ion, molecular nitric acid and the nitronium ion have been identified. The results show that in less than 15% sulphuric acid the nitrate ion is the main species present. In the range 15 - 70% sulphuric acid, molecular nitric acid and the nitrate

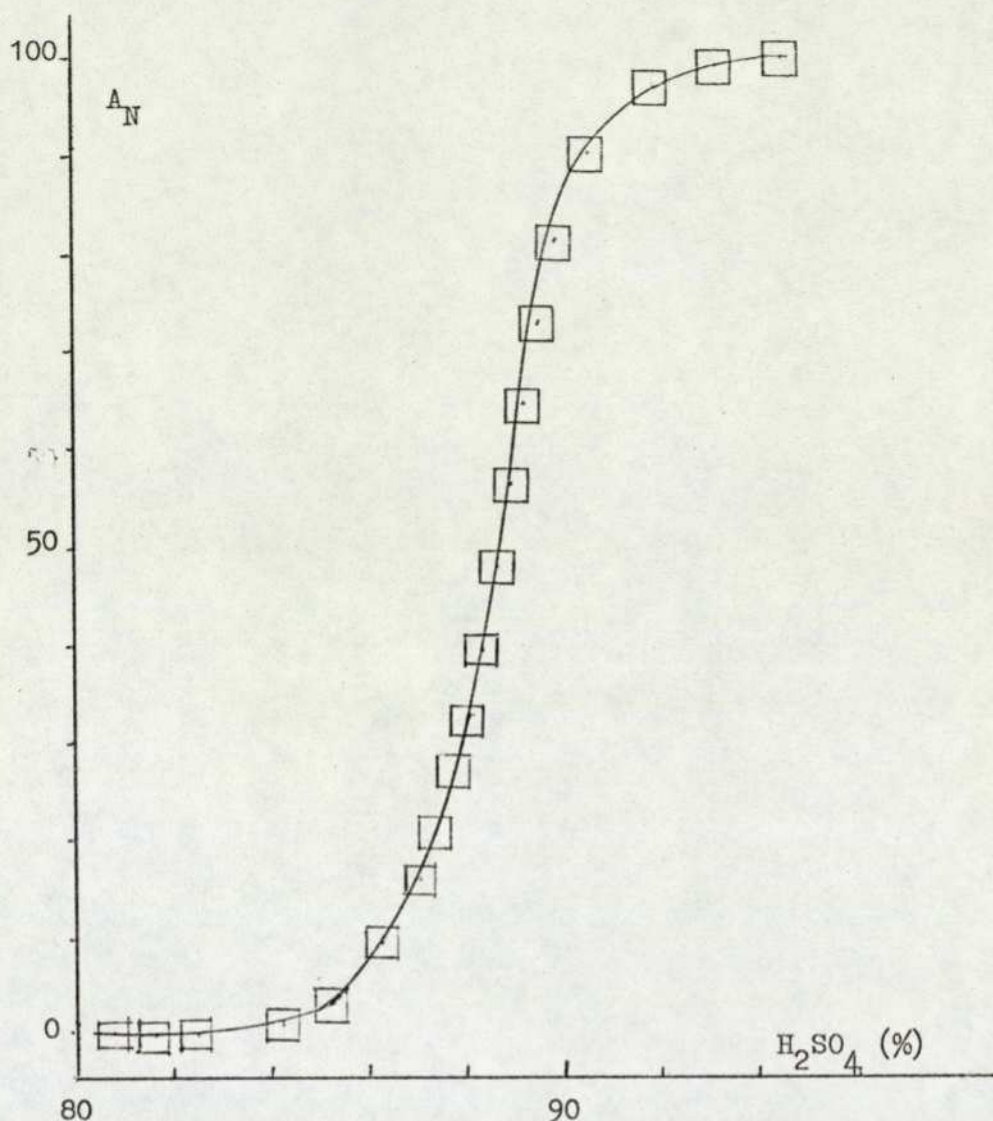


Fig. 1.1 Study of the protonation equilibrium of HNO_3 in 80 - 96% sulphuric acid by Raman spectroscopy.

A_N : normalised areas of the NO_2^+ band.

ion coexist in measurable quantities, with the proportion of nitric acid increasing with acidity. Between 72 and 82% sulphuric acid, molecular nitric acid is the species in major amount and in 89% sulphuric acid the ionisation to the nitronium ion is complete.

1.32 NITRATION IN CONCENTRATED SULPHURIC ACID

A simple kinetic order for the nitration of aromatic compounds was first established by Martinsen¹⁰. The rate of nitration of nitrobenzene was found to obey a second-order rate law. Although

$$R = k_2(\text{obs}) [\text{ArH}] [\text{HNO}_3] \dots\dots\dots (1.5)$$

the concentration of the nitronium ion does not change between 90 - 100% sulphuric acid the rate constants for nitration of most compounds decrease over this acidity range. Many aromatic compounds are sufficiently basic to be protonated in concentrated sulphuric acid and the nitration occurs through attack on the free base, as the reactivity of the conjugate acid is negligible. Thus by increasing the acidity of the medium, the proportion of the free base will be less, reducing the rate of reaction. This explanation is only partially satisfactory because a fall in rate is found with substrates (usually aromatic nitro-compounds and heteroaromatics) that are not appreciably protonated. This behaviour can be explained in terms of the changes in the activity coefficients, which are known to occur in strongly acidic media. From the transition state theory the rate should be given by:-

$$R = k_2 [\text{NO}_2^+] [\text{ArH}] (f_{\text{NO}_2^+} f_{\text{ArH}} / f^\ddagger) \dots\dots\dots (1.6)$$

The nitrations of p-nitrotoluene, p-chloronitrobenzene and o-chloronitrobenzene have been studied over a wide range of concentrations of sulphuric acid^{11a,b}, and it has been shown that if corrections are made for the decrease in activity coefficients, which have been determined, the corrected rate coefficients $k_2(\text{obs}) / f_{\text{ArH}}$ vary only slightly between 90 - 100% sulphuric acid. In contrast to the behaviour of these compounds the rate of nitration of p-dichlorobenzene¹² does

not vary over the range of acidity represented by 90 - 98% sulphuric acid.

1.33 NITRATION IN AQUEOUS SULPHURIC ACID

The addition of water to nitric acid solutions in 90% sulphuric acid reduces the rate of nitration. The fall in rate of nitration has been shown ¹³ to be parallel to the fall of the concentration of nitronium ions in the region 90 - 85% sulphuric acid. At concentrations of sulphuric acid where the nitronium ion is ~~most~~ detectable the second-order rate coefficient ($k_2(\text{obs})$) is found to decrease by a factor of about 10^4 for each 10% decrease in sulphuric acid concentration. Under these conditions the effective electrophile is not molecular nitric acid, because the variation in rates is not similar to the corresponding change in concentration of molecular nitric acid, determined by UV spectroscopy or vapour pressure measurements^{9,14}. Under these conditions the continued effectiveness of the nitronium ion has been indicated by comparing the dependence of these rates on the concentration of sulphuric acid, with the acidity dependence of the ionisation of model compounds. (This is discussed fully in Section 4.1).

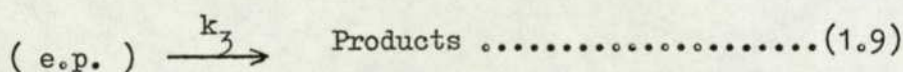
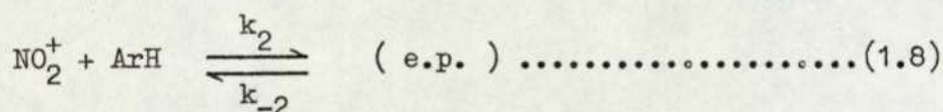
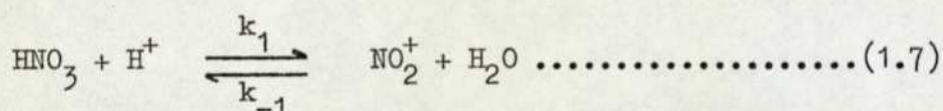
1.34 NITRATION AT THE ENCOUNTER RATE IN AQUEOUS STRONG ACIDS

Consideration of the fall in rate with decreasing sulphuric acid concentration and of the fact that in 90% sulphuric acid nitric acid is completely ionized to the nitronium ion, suggests that in 68% sulphuric acid the concentration of the nitronium ion is only 10^{-8} times the concentration of the nitric acid present. Thus the rate coefficient for reaction between the substrate and the nitronium ion ($k_2 = \text{rate} / [\text{ArH}] [\text{NO}_2^+]$) at 25 °C in 68% sulphuric acid is about 10^8 times the stoichiometric rate coefficient, ($k_2(\text{obs}) = \text{rate} / [\text{ArH}] [\text{HNO}_3]$). The value of $k_2(\text{obs})$ for nitration of benzene¹⁵ in 68% sulphuric acid at 25 °C is $4.2 \times 10^{-2} \text{ dm}^3 \text{ mole}^{-1} \text{ s}^{-1}$ giving

$k_2 = 4.2 \times 10^6 \text{ dm}^3 \text{ mole}^{-1} \text{ s}^{-1}$. Now it is believed that for reaction in solution, two reacting species remain in proximity for a finite time and the encounter pair (e.p.) formed can be considered as a transient intermediate. The theoretical value of the rate coefficient for encounter between two species in 68% sulphuric acid at 25°C is given by $k_2 = 8RT/3\eta^{16}$ (where R = Gas constant; T = Temperature; η = Viscosity of sulphuric acid) and is found to be $6 \times 10^8 \text{ dm}^3 \text{ mole}^{-1} \text{ s}^{-1}$. Thus the value found for the nitration of benzene in 68% sulphuric acid approaches the theoretically estimated encounter limit.

This consideration prompted the investigation of the nitration of benzene and some more reactive substrates in aqueous strong acids to establish to what extent the reactions of these compounds were affected by the rate of diffusion of the two active species¹⁷.

Considering the encounter pair as a reaction intermediate the overall reaction scheme can be written as follows:-



For a series of compounds studied, a limiting maximum rate of nitration by the nitronium ion was reached in sulphuric acid (Table 1.1), perchloric acid (Table 1.2), trifluoroacetic acid (Table 1.3) and methanesulphonic acid (Table 1.4). From the fact that in all cases the reaction was found to be first order in aromatic substrate, the assumption was made that nitric acid and

Table 1.1

Rate coefficients¹⁷ for nitration in 68.3% sulphuric acid
at 25.0°

Substrate	$k_2(\text{obs})/$ $\text{dm}^3 \text{ mole}^{-1} \text{ s}^{-1}$	Estimated relative rate ^a
Benzene	5.8×10^{-2}	1
Toluene	1	23 ^b
<u>o</u> -Xylene	2.2	60 ^c
<u>m</u> -Xylene	2.2	400 ^c
<u>p</u> -Xylene	2.2	50 ^c
Mesitylene	2.1	16000
1-Methoxynaphthalene	2.0	-

a) Relative to that of benzene

b) Ref. 18 and 19

c) Calculated from the observed value for toluene
and the known isomer ratios by assuming the
additivity principle.

Table 1.2

Rate coefficients¹⁷ for nitration 61.1% perchloric acid
at 25.0°

Substrate	$k_2(\text{obs})/$ $\text{dm}^3 \text{ mole}^{-1} \text{ s}^{-1}$	Estimated relative rate ^a
Benzene	8.3×10^{-2}	1
Toluene	1.6	23
<u>p</u> -Xylene	7.0	50
Mesitylene	6.5	16000
Naphthalene	2.2	300
1-Methoxynaphthalene	7.3	-
1-Naphthol	7.0	-

a) see Table 1.1

Table 1.3

Rate coefficients²⁰ for nitration in trifluoroacetic
acid ($\text{H}_2\text{O} = 0.50 \text{ M}$) at 25.0°

Substrate	$k_2(\text{obs}) /$ $\text{dm}^3 \text{ mole}^{-1} \text{ s}^{-1}$	Estimated relative rate ^a
Benzene	0.13	1
Toluene	5.7	23
<u>o</u> -Xylene	11.5	60
<u>m</u> -Xylene	13.4	400
<u>p</u> -Xylene	15.2	50
Mesitylene	11.3	16000
1,2,3-Trimethyl- benzene	16.6	-

a) see Table 1.1

Table 1.4

Rate coefficients²¹ for nitration in 87.4% methane-
sulphonic acid at 25.0°

Substrate	$k_2(\text{obs})/$ $\text{dm}^3 \text{ mole}^{-1} \text{ s}^{-1}$	Estimated relative rate ^a
Benzene	1.2×10^{-2}	1
Toluene	7.2×10^{-2}	23
<u>o</u> -Xylene	4.3×10^{-1}	60
<u>m</u> -Xylene	5.8×10^{-1}	400
<u>p</u> -Xylene	3.3×10^{-1}	50
Mesitylene	8.7×10^{-1}	16000
Naphthalene	1.3×10^{-1}	300
2-Methoxynaphthalene	4.2×10^{-1}	-

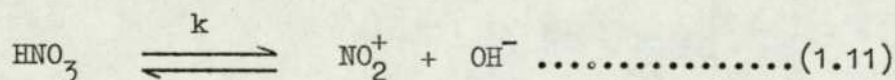
a) see Table 1.1

nitronium ion are effectively in equilibrium, and reactions (1.7 - 1.9) lead by the steady state treatment to the following expression:-

$$k_2(\text{obs}) = \frac{[\text{NO}_2^+]}{[\text{HNO}_3]} \frac{k_2 k_3}{(k_{-2} + k_3)} \dots\dots\dots(1.10)$$

for the second-order rate coefficient, $k_2(\text{obs})$, in terms of the ratio of the equilibrium concentration of nitronium ion to the stoichiometric concentration of nitric acid. The relative magnitude of k_{-2} and k_3 will determine whether a particular rate of nitration is limited by the encounter rate, k_3 will have little dependence on the medium whereas k_{-2} will depend on the viscosity of the medium, and should decrease with increasing viscosity. Thus the less viscous the medium the greater must be the reactivity of the substrate to be limited by the encounter rate. The varying viscosity of the medium is presumably the explanation for the fact that the rate profile for mesitylene, a typical encounter rate substrate, has a lower slope than substrates that are not encounter controlled, such as benzene at lower acidities.

Table 1.5 gives the activation energies of some encounter-controlled reactions in 67.1% sulphuric acid and if the above considerations are correct the activation energy determined must result almost entirely from the high endothermicity of the dissociation of nitric acid to the nitronium ion. This has been investigated²² and the enthalpy change for the following ionization in 68.3% sulphuric acid has been determined.



The value obtained is not in conflict with the theory of encounter control for the nitration of reactive aromatic compounds in aqueous sulphuric acid.

Table 1.5

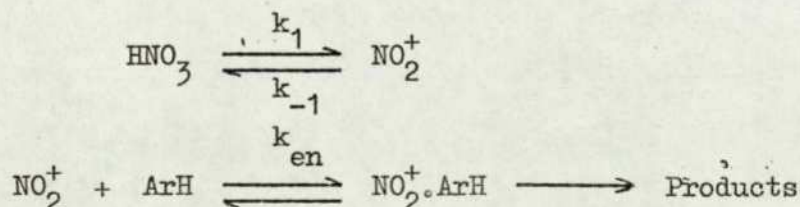
Activation parameters for nitration in sulphuric acid¹⁷

Substrate	H ₂ SO ₄ (%)	Temp. range (°C)	E/kJ mole ⁻¹
Benzene	67.1	25 - 44	75.6
Benzene	73.2	2 - 25	57.5
Mesitylene	67.1	25 - 53	75.6
Naphthalene	67.1	25 - 44	65.1

The fact that in 68% sulphuric acid the toluene : benzene rate ratio is close to that observed in other less viscous media¹⁸ and that the rate of nitration of benzene is less than the fortieth of the limit set by the encounter rate, suggests that benzene is not reacting at the encounter rate and comparison of reactivity with other substrates less reactive than benzene can be made. The acidity plot of $\log_{10} k_2(\text{obs})$ vs $-(H_R + \log_{10} a_{H_2O})$ (see Section 4.1) is unity for benzene in this region. However at higher acidities the slope becomes 1.2 and the profile is thus no longer parallel to similar plots for a number of deactivated substrates¹⁵. Furthermore the rate profile for benzene approaches closely the rate of encounter and thus in the acidity range 68 - 82% sulphuric acid, comparison must be made with care because the observed relative rates, particularly at the higher acidities, may not be true measures of relative reactivity.

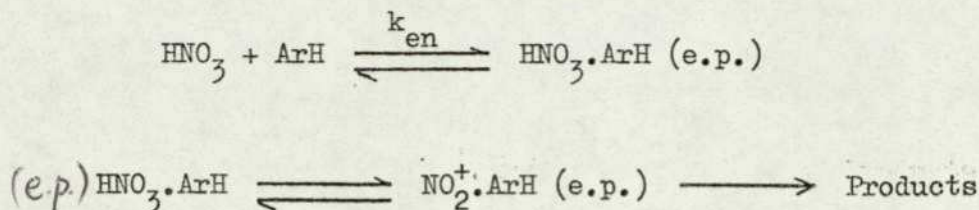
1.341 PRE-ASSOCIATION

It has been recently suggested¹⁰¹ that as the lifetime of the nitronium ion becomes less, it becomes increasingly difficult to visualise the reaction with a reactive aromatic substrate as a diffusion controlled process (Scheme 1.1) and so called pre-association mechanisms have to be considered, in which the nitronium ion is



Scheme 1.1

formed from its precursor, presumably nitric acid, within an already existing encounter pair containing the aromatic substrate and the precursor (Scheme 1.2).

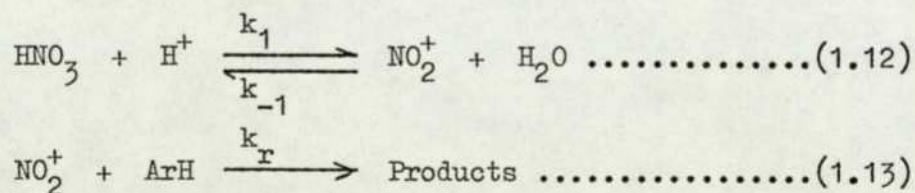


Scheme 1.2

Approximate calculations suggest that if the half-life of the nitronium ion is less than 10^{-10} seconds the nitronium ion does not live long enough to form an encounter pair with the substrate (scheme 1.1).

1.342 "ZEROOTH ORDER" NITRATION

It is well known from studies of the kinetics of nitration of aromatic compounds in various media²³, that the order of the reaction in the aromatic compound can change from unity to zero as either the concentration of the substrate or its reactivity are increased or the water content of the medium is decreased. The rate of nitration of aromatic compounds under the "zeroth order" conditions is controlled by the rate of formation of the nitronium ion (1.12) and not by the rate of attack on the substrate (1.13). Each of the three factors make it more likely that $k_r[\text{ArH}]$ will be $> k_{-1}[\text{H}_2\text{O}]$.

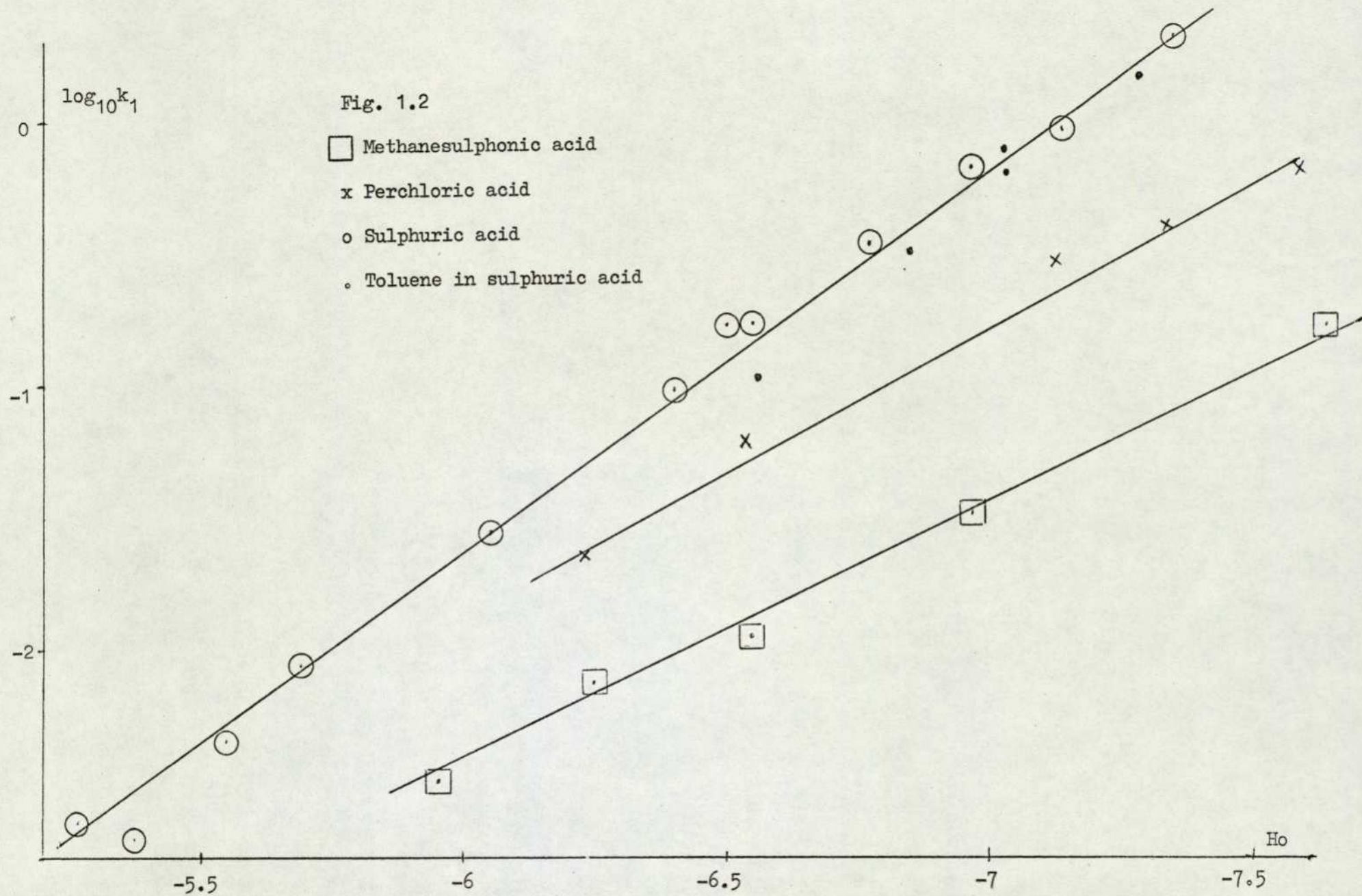


Plots of the logarithms of the second-order rate coefficients for the nitration under the "zeroth order" conditions of anisole and toluene²⁴ against the acidity function $-H_0$ in sulphuric acid, perchloric acid and methanesulphonic acid are shown in Fig. 1.2 and have slopes 1.5, 1.1 and 1.0 respectively. These coefficients are indeed independent

Fig. 1.2

- Methanesulphonic acid
- x Perchloric acid
- Sulphuric acid
- Toluene in sulphuric acid

16



of the nature and concentration of the substrate. Earlier work by Strachan ¹²⁶ on the nitration of toluene under "zeroth order" conditions in sulphuric acid gave a quite similar plot but with a lower slope (1.0). These results are now regarded as inaccurate.

In considering the mechanism of the ionisation of nitric acid it was convenient to focus attention on the reverse step of equation 1.12, the hydration of the nitronium ion. This was done by combining the data obtained ²³ with the observed second-order rate constants for the nitration of benzene, ^{17,53} k_2^{bz} . The second-order rate coefficient can be determined from equation (1.14) which is derived from equations (1.12) and (1.13) under first order conditions.

$$k_2 = k_r k_1/k_{-1} \dots\dots\dots(1.14)$$

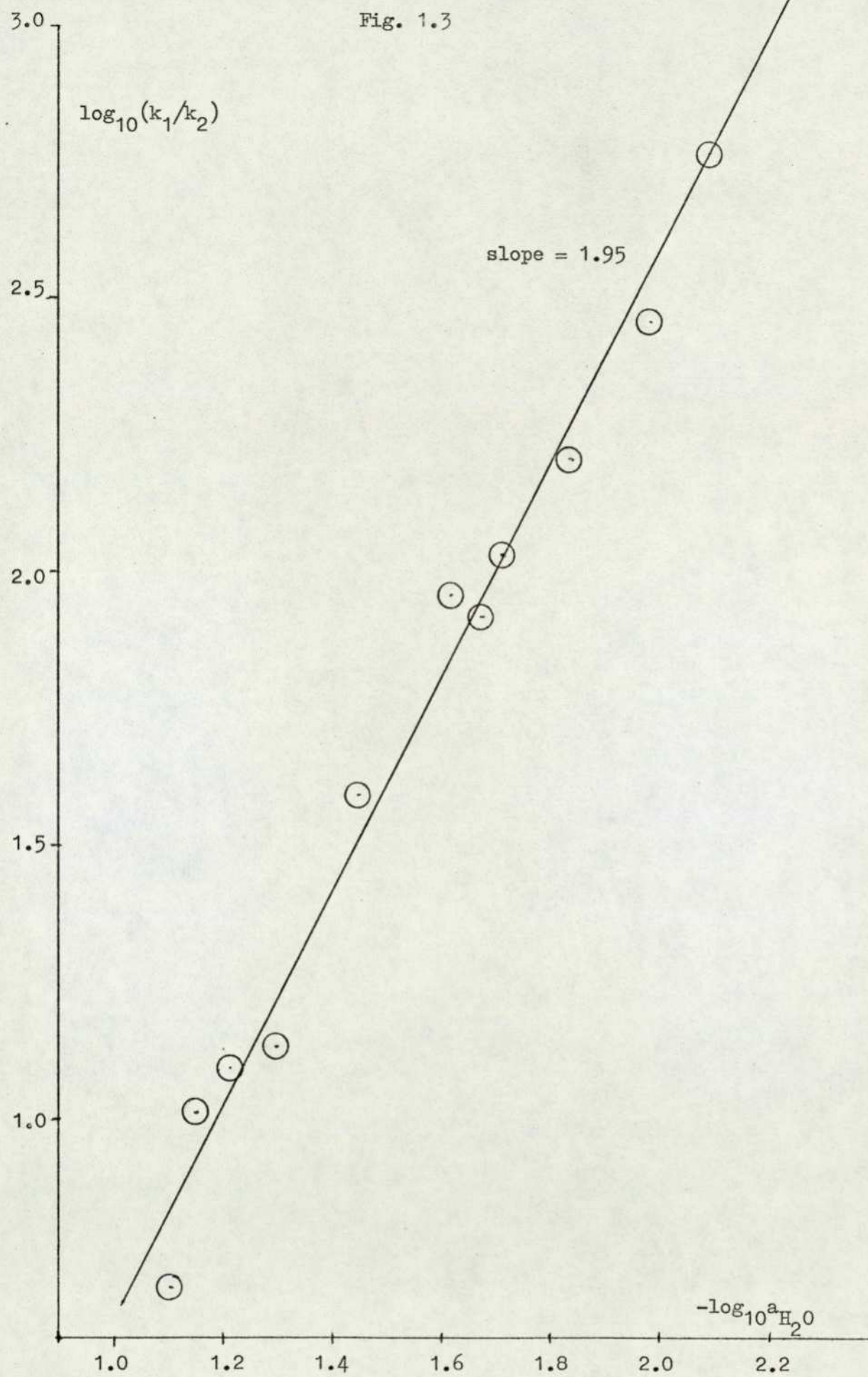
For benzene

$$k_2^{bz} = k_r^{bz} k_1/k_{-1}$$

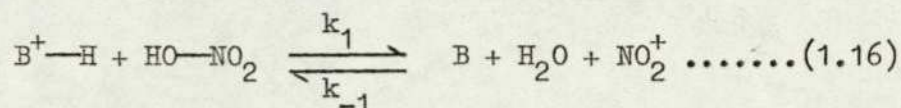
$$\text{or } k_1/k_2^{bz} = k_{-1}/k_r^{bz} \dots\dots\dots(1.15)$$

In (1.15) k_r^{bz} is the specific rate constant for the reaction of benzene with the nitronium ion. Since the reaction is not diffusion controlled ¹⁷, k_r^{bz} will be independent of viscosity and can be expected to vary little with acidity. Variation of k_1/k_2^{bz} then indicates the medium dependence of k_{-1} , the rate constant for the hydration of the nitronium ion. A plot of $\log (k_1/k_2^{bz})$ vs $-\log(\text{activity of water})$ for the data relating to sulphuric acid (Fig. 1.3) is linear with slope of 1.95. It was therefore concluded that two water molecules are needed to hydrate the nitronium ion and a satisfactory picture of the reaction is (1.16), in which BH^+ and B are hydronium ion and water respectively.

Fig. 1.3



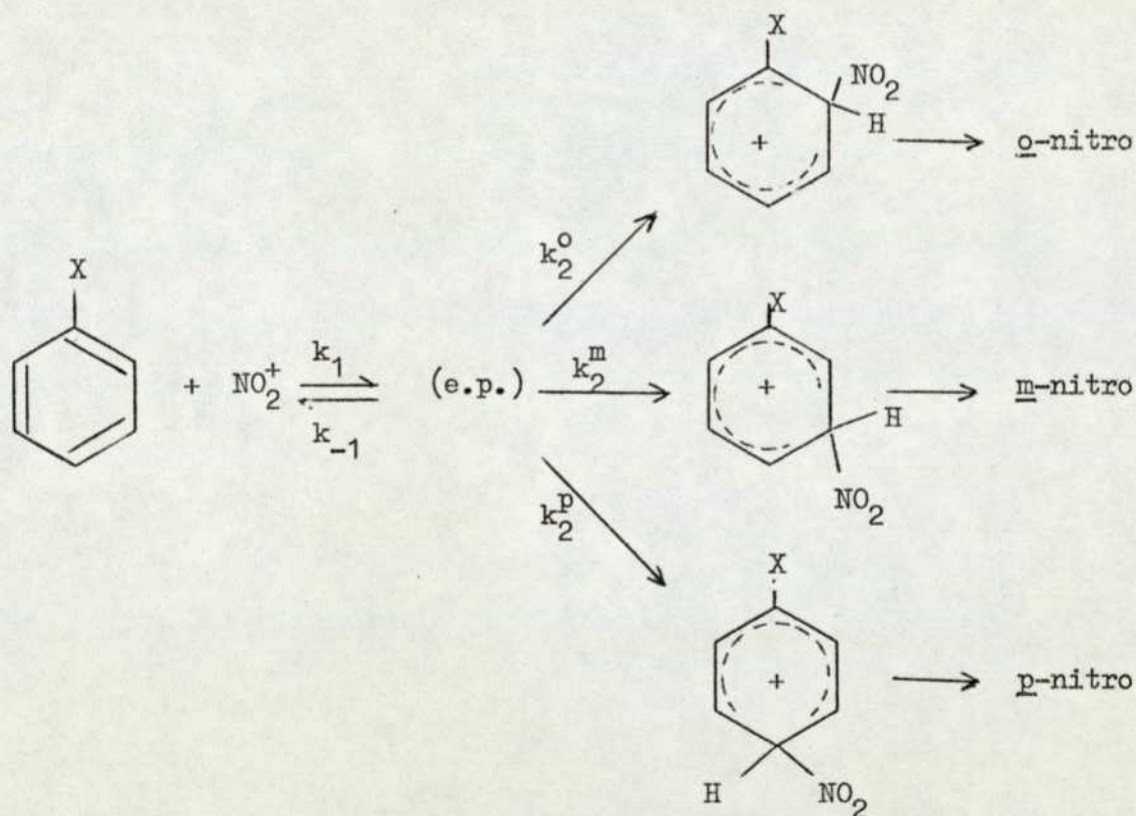
The role of the second water molecule B in the hydration step is that of a general-base catalyst¹⁰. There are several other cases in which



attack of water on an electrophilic centre in aqueous solution is thought to be subject to general base catalysis by water or other species^{127,128}.

1.343 SELECTIVITY IN ENCOUNTER CONTROLLED NITRATIONS

For nitration in sulphuric acid it is suggested that at the limit the rate-determining step changes to one in which the encounter pair is formed (Scheme 1.3).



Scheme 1.3

By analogy to literature discussions²⁵ of diffusion-controlled processes it was implied that there was no interaction within the encounter pair. If this were the case, as k_{-1} can be estimated²⁶ as about $10^9 - 10^{10} \text{ s}^{-1}$ and k_2 can in the limit approach $10^{12} - 10^{13} \text{ s}^{-1}$, it would be possible for considerable intramolecular selectivity to remain between positions in a substrate which is sufficiently reactive to be nitrated at the limiting rate.

Another suggestion^{27,28} has been that the existence of a limiting rate might be explained by what has been called the Hammond effect. As the reactivity increases along a series of suitable substrates the transition state will become progressively earlier, bonding from the electrophile to the carbon atom increasingly less developed and the activation energy lower until differences might have effectively disappeared. It has been envisaged that these transition states might be positionally oriented²⁸ and in this circumstance selectivity between sufficiently reactive positions should disappear at the limiting rate. This would also be the situation if there existed separate encounter pairs for different positions of substitution in a molecule³⁰. If these early transition states are not positionally oriented the existence of a common discrete intermediate, prior to formation of Wheland intermediates, seems obligatory and therefore the suggestion would be of a change in rate-determining step to that of formation of this intermediate.

Expressions²⁹ of these ideas suggest that the intermediate has in fact an orientated π -complex type of structure. For it to be necessary to postulate a change of rate-determining stage to one in which a common intermediate which involves attractive interaction is formed, an intramolecular selectivity greater than that possible for a non-interacting encounter pair would have to be observed.

On the other occasions²⁹ the oriented π -complex type of structure has been drawn as a representation of early transition states of the positionally oriented type to which the previous arguments would apply.

Present evidence on these points comes from the work of Schofield and co-workers³¹ who studied the nitration of 1,2,4-trimethylbenzene and have shown that there is about 9:1 selectivity of attack on positions 5 and 6 provided that one makes the reasonable assumption that any ipso-attack is not followed by rearrangement under the chosen conditions. Both positions are reactive enough to achieve the limiting rate and have similar steric requirements. This deduction rules out the explanation in terms of early transition states of the positionally orientated type and of the possibility of positionally orientated intermediates prior to the Wheland intermediates. It means that there must be a common intermediate prior to Wheland intermediate formation, but the extent of intramolecular selectivity is certainly not sufficient to make it necessary to postulate any attractive interaction in this intermediate. The nitrations of 2-methoxy-6-methylnaphthalene and of 1-(3,5-dimethoxyphenyl)-2-(3',5'-dimethylphenyl)ethane in methanesulphonic acid have also been studied²¹. 2-Methoxy-methylnaphthalene provides an intermediate case with regard to the distance between the positions undergoing nitration. C-1 and C-5 in 2-methoxy-6-methylnaphthalene are sufficiently activated to allow 2-methoxy-6-methylnaphthalene to react upon encounter. The selectivity observed between these positions was found to be 6.5 to 1 which suggested a situation like that of 1,2,4-trimethylbenzene. The encounter process between nitronium ion and 2-methoxy-6-methylnaphthalene is therefore best viewed as one in which nitronium ion and aromatic form irreversibly one encounter pair (or indistinguishably several rapidly interconverting encounter pairs)

in which there is sufficient mobility and longevity for selection between positions of different intrinsic reactivity to occur.

If there are two separate aromatic rings of different intrinsic reactivity reacting upon encounter, two separate encounter pairs can be formed and no selectivity between the rings would be expected. As the rings are brought and held close together as for example in the case of diphenylmethanes or ethanes it is conceivable that one encounter pair for the pair of rings could be formed and if the two rings were of different intrinsic reactivity, selectivity between the rings would be expected. In the case of 1-(3,5-dimethoxyphenyl)-2-(3',5'-dimethylphenyl)ethane the ratio of reactivities of the methoxylated and the methylated rings (1.8) was found to be close to the ratio of reactivities of the corresponding mononuclear compounds (1.5) and it was concluded that two different encounter pairs could be formed in the rate-controlling step and that the same step also controlled the product distribution between the rings. The subsequent step of σ -complex formation was thought probably to control the product distribution within each ring.

However, the two rings involved with this substrate are expected to be very activated and it is possible that in this case the k_2 values approach or reach the limit of $10^{12} - 10^{13} \text{ s}^{-1}$ in which case the results could indeed be the result of the formation of one common encounter pair.

1.344 MEDIUM EFFECTS IN ENCOUNTER CONTROLLED NITRATIONS

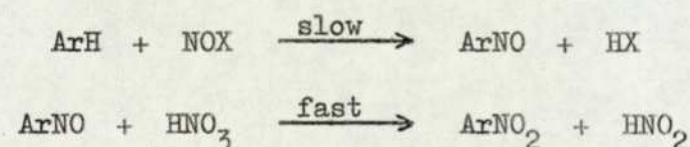
Several previous studies on electrophilic aromatic substitution have drawn attention to the existence of medium effects on the ratio of the relative rates of attack of the nitronium ion at the various nuclear positions in the mononitration of aromatic compounds by nitric acid in aqueous sulphuric acid. Some such effects of alkylbenzenes

acidity at which equal amounts of the two detected products are formed was however lower (by ca 6% by w/w) for 3,5-dimethylanisole.

The nitration of o-methylanisole⁵⁰ in sulphuric acid led to a mixture of 2-methyl-4- and 2-methyl-6-nitroanisoles and the overall yield of mononitro-products increased from 65 to 100% in the region 62 -68% sulphuric acid (see Fig. 2.20). The drop in yield below 68% sulphuric acid was thought to be due to the nucleophilic capture of the ipso-Wheland intermediate formed at C-Me by water at the lower acidities.

1.4 NITRATION VIA NITROSATION

Nitrous acid has been found to catalyse the nitration of some very reactive substrates and in particular amines and phenols. Oxidation was found to occur to some of these compounds under the reaction conditions and the formation of more nitrous acid led to autocatalysis. The following mechanism for nitration via nitrosation and subsequent oxidation has been suggested,



where NOX represents the nitrosating species. The above scheme accounts for the constant concentration of nitrous acid throughout the reaction. Nitric acid is thought to account for the oxidation of the nitroso-compound but evidence was obtained³² to suggest that dinitrogen tetroxide may function as both nitrosating and oxidising agent in carbon tetrachloride.

If the possibility of nitrosation is ignored many misleading results can be obtained for certain reactive compounds. In the nitration of naphthalene^{27,33} it was found that the relative

reactivity of naphthalene to that of benzene is 62 whereas that for 1-methylnaphthalene was found to be 20600 which suggested an unreasonable activating effect of the methyl group. The concentration of nitrous acid was low in both cases but the result was wholly ascribed to the effect of nitrosation.

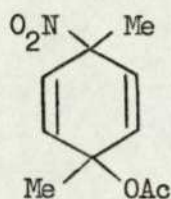
Nitrosation is also an important factor affecting positional selectivity for certain reactive aromatic compounds such as phenol and anisole where nitration via nitrosation gives predominantly para-substitution. It has been suggested that the less reactive nitrosating electrophile gives a late transition state more like a Wheland intermediate in character. The catalytic effect of nitrous acid can be removed by the addition to the reaction mixture of compounds which react rapidly with nitrous acid. Urea, sulphamic acid and sulphanilic acid are examples of such compounds which have been widely used.

However the idea that nitration via nitrosation involves an initial electrophilic nitrosation is certainly not a complete picture. The nitration of N,N-dimethylanilinium ion in 85% sulphuric acid¹²⁹ was shown to be catalysed by nitrous acid but this catalysis was shown not to occur through the formation and oxidation of the C-nitroso derivative. The catalysed reaction was shown to be first order with respect to the N,N-dimethylanilinium ion and the nitrosonium ion but zeroth order with respect to nitric acid. This kinetic form and rate are the same as those for the nitrous acid catalysed mechanism for hydrogen isotope exchange at the nitrogen pole of the amine. These observations were interpreted as involving the rate determining formation of the $\text{PhNMe}_2^+\text{NO}^\bullet$ radical pair followed by the fast reactions of this species with the nitronium ions. It may be that mechanisms of this type are more general.

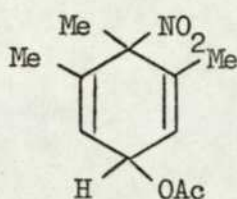
1.5 IPSO NITRATION

1.51 ADDUCTS

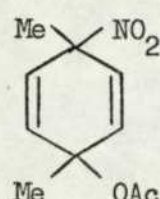
Fischer and his co-workers^{34,35} have studied the nitration of polymethylbenzenes in acetic anhydride and the following intermediates were isolated and characterised:-



I



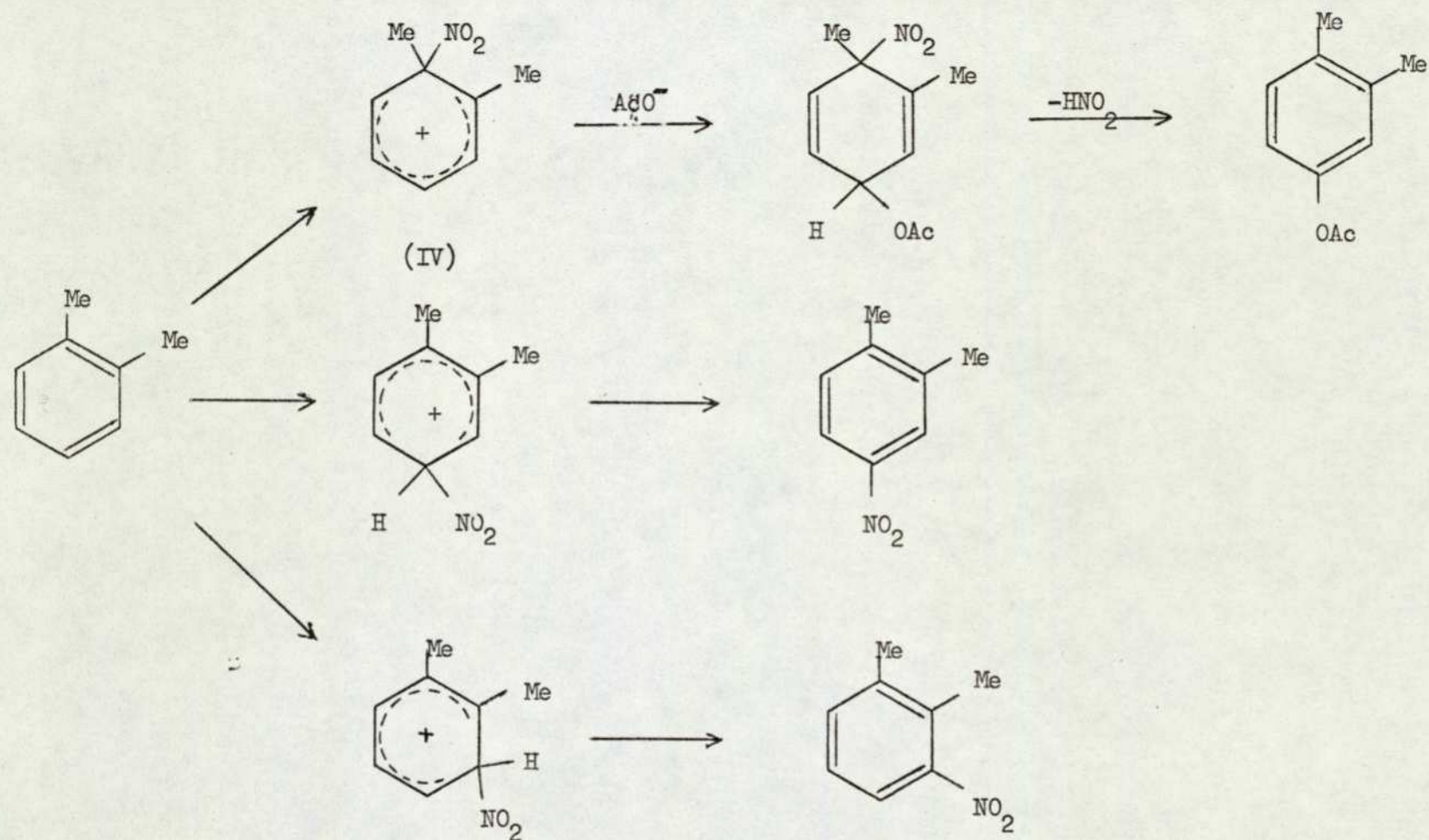
II



III

This verified a suggestion by Ridd¹⁸, that these addition products were intermediates in the acetoxylation reaction which often accompanied nitration and therefore that the acetoxylation occurs by an addition-elimination process (Scheme 1.5) and not by a direct electrophilic substitution mechanism as previously suggested³⁶.

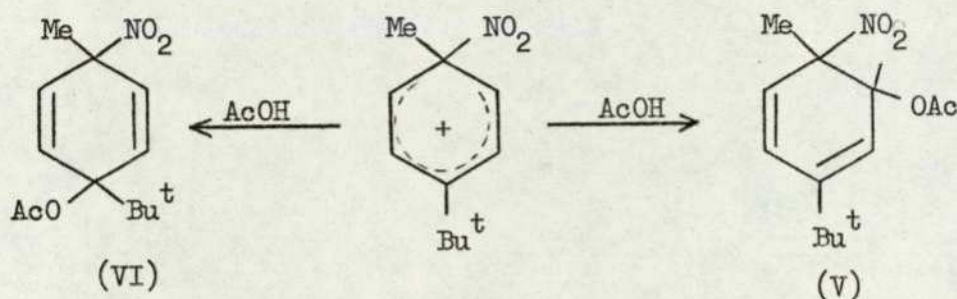
Attack by the electrophile at a ring position bearing a hydrogen atom leads to normal nitration (via a Wheland intermediate), but attack at a position bearing a substituent other than hydrogen (ipso-position) leads to the formation of an ipso-Wheland intermediate (e.g. IV) followed by nucleophilic attack, or trapping, by AcO^- . The extent of acetoxylation accompanying nitration depends upon the structure of the substrate³⁷. Appreciable adduct formation occurs with substrates such as o-xylene, p-xylene and hemimellitene where the ipso-positions are sufficiently activated, but if the ipso-positions are not sufficiently activated (e.g. toluene, m-xylene) very little or no adduct formation occurs. If nucleophilic trapping is complete the amount of non-conventional product will depend on the formation of the ipso-Wheland intermediate, (e.g. IV, Scheme 1.5).



Scheme 1.5

A large number of 1,4-adducts have now been isolated from nitrations and a few of them are shown in Table 1.6.

1,2-Capture of nitro-ipso-Wheland intermediates is uncommon, but not unknown. Thus, in the nitration of *p*-*t*-butyltoluene both the 1,2- (V) and 1,4-adducts (VI) are formed¹³⁰:-



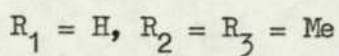
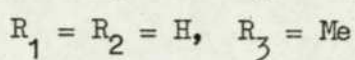
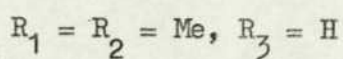
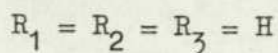
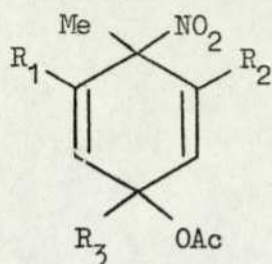
1.52 IPSO-NITRATION IN SULPHURIC ACID

The observation of ipso-substitution in some reactions in acetic anhydride led to the reinterpretation of some unexplained results obtained in other media.

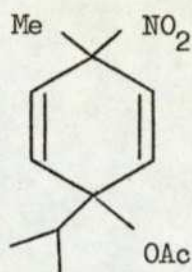
o-Xylene was nitrated³⁰ in various concentrations of aqueous sulphuric acid and the isomer ratio of 1,2-dimethyl-3-nitrobenzene to 1,2-dimethyl-4-nitrobenzene was found to vary from 0.44 at 49% sulphuric acid to 1.5 at 72% sulphuric acid and above 72% sulphuric acid the ratio was constant within experimental error. The change in ratio was accounted⁴⁵ for by the formation of the 1,2-dimethyl-1-nitrocyclohexadienyl cation (IV) which is competitive with the formation of the isomeric cyclohexadienyl cations as shown in Scheme 1.6. The isomer ratio change with acidity can be associated with a change in the dominant reaction pathway of (IV) which is suggested to undergo 1,2-shift of the nitro-group thus enhancing the 3-nitro product. At low acidities nucleophilic capture of the ipso-Wheland intermediate (IV) leading to formation of a phenol is more

Table 1.6

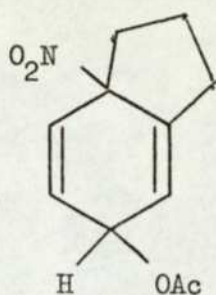
Some 1,4-adducts isolated from nitrations in acetic
anhydride



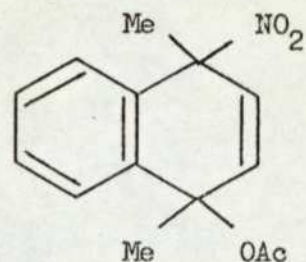
Ref. 38



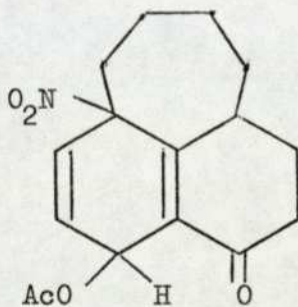
Ref. 39



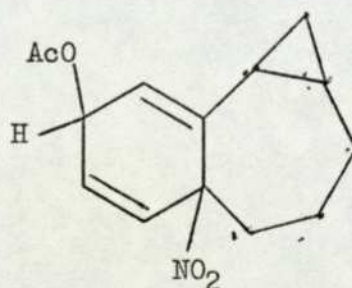
Ref. 40



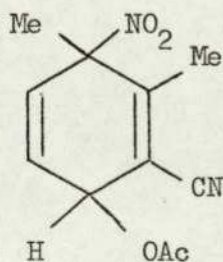
Ref. 41



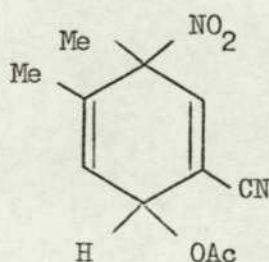
Ref. 42



Ref. 43



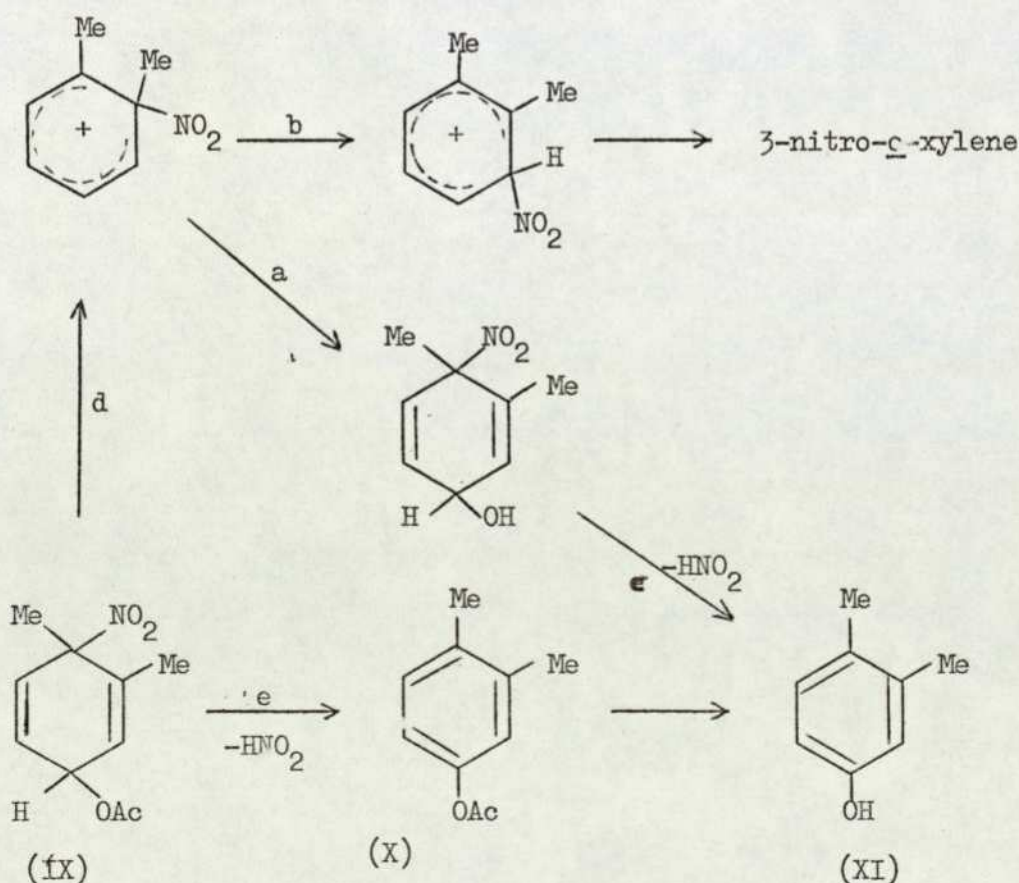
Ref. 44



Ref. 44

likely to occur owing to the larger amount of water present but above 72% sulphuric acid the 1,2-shift of the nitro group is preferred. Myhre tested this theory by studying the solvolysis of the adduct 3,4-dimethyl-4-nitrocyclohexa-2,5-dienyl acetate in 50 - 85% aqueous sulphuric acid and 3-nitro-o-xylene was isolated in yields of 2 to 93% respectively but no 4-nitro-o-xylene was found.

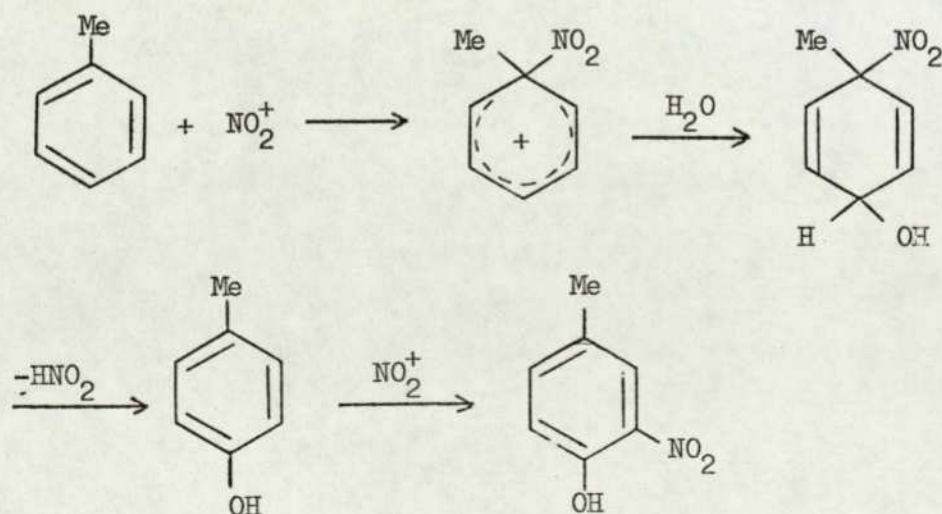
Moodie and co-workers⁴⁶ have shown that the rate of solvolysis of 3,4-dimethyl-4-nitrocyclohexa-2,5-dienyl acetate is too rapid to follow and occurs in two competing pathways (Scheme 1.7): elimination of nitrous acid to give X which is then hydrolysed to XI and hydrolysis (step d) to give XI and 3-nitro-o-xylene. Step d becomes increasingly important with increasing acidity and is the important pathway above 55% sulphuric acid. Above that acidity data from the acetolysis of the acetate reflects the competition between paths a and b and is relevant to studies of the nitration of o-xylene.



Scheme 1.7

Similar studies were made⁴⁷ on the solvolysis of 4-nitro-3,4,5-trimethylcyclohexa-2,5-dienyl acetate where 4-nitrohemimellitene was formed in nearly quantitative yields in sulphuric acid solutions in the 75 - 85% range, but the yield fell off rapidly through the 65 - 55% region and became zero below 50% sulphuric acid. No 5-nitrohemimellitene was detected under any of the solvolytic conditions

The nitration of toluene, o-, m- and p-xylenes, pseudocumene and hemimellitene has been carried out by Moodie et al⁴⁸ to determine the yields of the mononitro products formed in a range of acidities in aqueous sulphuric acid. The results showed that the yields of nitrotoluenes and nitro-m-xylenes varied relatively little with acidity and accounted for virtually 100% of the products and the yields of products for o- and p-xylenes, pseudocumene and hemimellitene increased with increasing acidity. These results agree with the previous observations and indicate considerable ipso-substitution in o- and p-xylenes, pseudocumene and hemimellitene. Small amounts of a side product were detected and isolated as 4-methyl-2-nitrophenol in the nitration of toluene in less than 55% sulphuric acid and the following Scheme was suggested:-



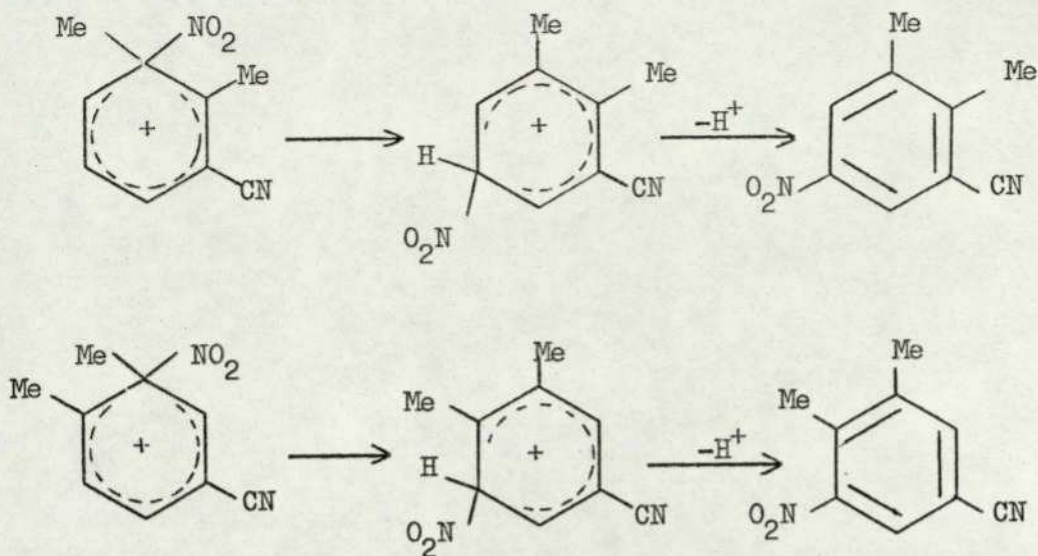
Scheme 1.8

It was concluded that the isomer yields can vary with the acidity of the medium in two distinct ways: the variation with acidity of the relative reactivities of all nuclear positions (the general-medium effect) and the medium-dependent partitioning of the ipso-Wheland intermediate between rearrangement and nucleophilic capture. In the case of o-xylene the proportion of attack at the 3-, 4- and ipso-positions varied considerably with acidity and these changes have been attributed to a strong medium dependence of the relative reactivities of the various substituted and unsubstituted positions of the molecule. The nucleophilic capture of ipso-Wheland intermediates by H_2O at low acidities in sulphuric acid seems to correlate with the extent of AcO^- capture in acetic anhydride suggesting perhaps that both are complete.

Nitration of p-cumene at 0° in acetic anhydride in the presence of urea gave amongst other products up to 40% adducts involving ipso-substitution at C-Me and 10% p-nitrotoluene. The isolation of p-nitrotoluene indicates that ipso-attack at the isopropyl position occurs, but that displacement of the isopropyl group is a significant pathway. Ipso-group displacement has also been observed in the nitration of halogenoaromatics. (This is fully discussed in Section 3.1).

1.53 1,3-SHIFTS

1,3-Nitro shifts have been shown⁴⁴ to occur in the nitrations of 2,3- and 3,4-dimethylbenzonitriles (Scheme 1.9) where the following rearrangements took place.



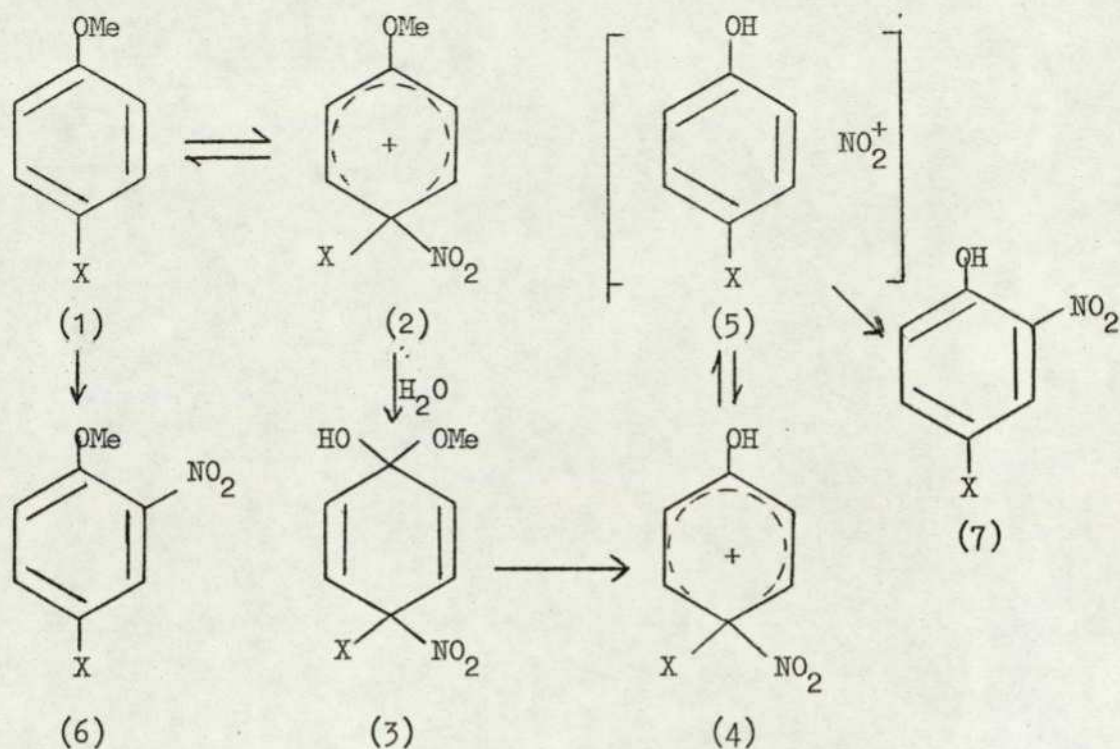
Scheme 1.9

It was suggested that 1,2-shifts in these cases would result in Wheland intermediates with an sp^3 carbon atom ortho- or para- to the cyano group and therefore it would be energetically unfavourable.

It was concluded that the 1,3-nitro shifts were intramolecular processes, since firstly, there was no evidence for the formation of other products and secondly, the product obtained from the 1,3-nitro shift was not suppressed in the presence of reactive arenes.

In studies of the nitration of p-chloroanisole⁴⁹ in acetic acid a 1,3-shift was postulated to explain the formation of 4-chloro-2-nitrophenol and it was also suggested that ipso-substitution and 1,3-migration is responsible for some of the 4-chloro-2-nitroanisole which was the major product.

Similar results were obtained in the nitration of p-methylanisole⁵⁰ and p-chloroanisole⁵¹ in aqueous sulphuric acid. The nitration of p-methylanisole (1; X=Me, Scheme 1.10) in 50 - 75% sulphuric acid gives (6; X=Me) (60%) and (7; X=Me) (40%). Similarly p-chloroanisole (1; X=Cl) gives (6; X=Cl) (60%) and (7; X=Cl) (40%) in 58-62% sulphuric acid.

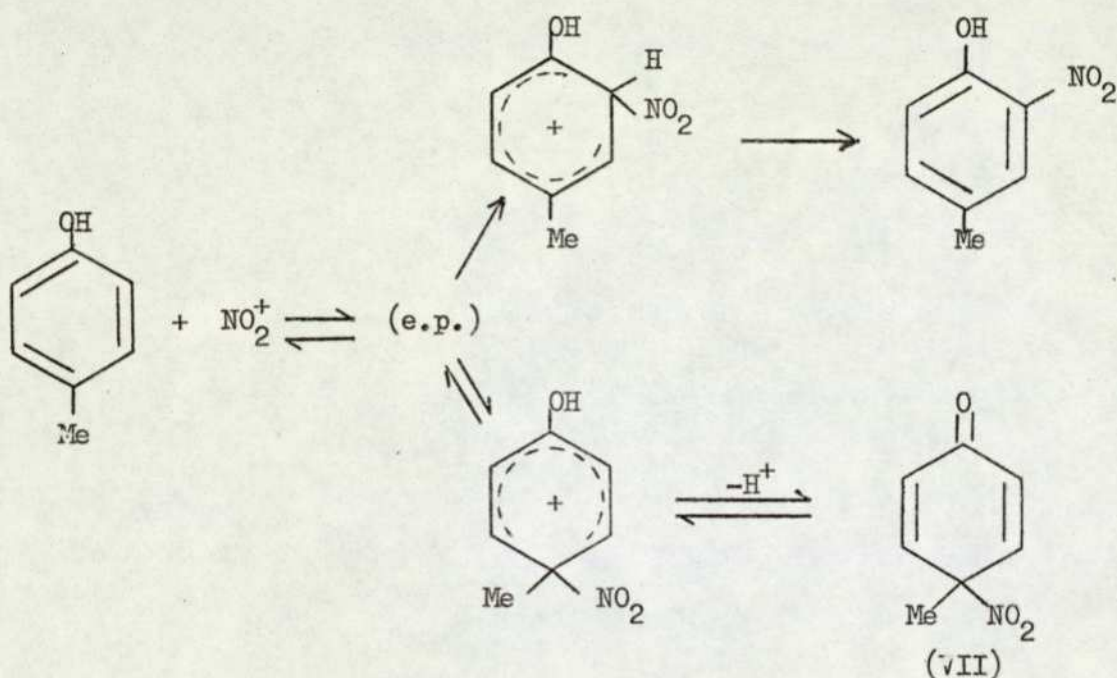


Scheme 1.10

It has been concluded⁵⁰ that (7) is formed via the ipso-Wheland intermediate (2) and it has been confirmed by labelling experiments⁵¹ that demethoxylation occurs via (3) rather than by S_N2 demethylation of (2) and that nitro-group migration proceeds through the encounter pair (5).

In the nitration of *p*-cresol in aqueous sulphuric acid⁸¹ an intermediate species absorbing at $\lambda_{\text{max}} = 240 \text{ nm}$ was observed during the course of reactions in 68 - 73% sulphuric acid which was formed transiently during the course of a reaction. This absorption is in the region expected for that of a cyclohexa-2,5-dien-1-one and in view of other studies¹⁰⁶, is clearly due to the formation of 4-methyl-4-nitrocyclohexa-2,5-dien-1-one, which is formed via the ipso-Wheland intermediate shown in the Scheme 1.11. Suitable increase of the nitric acid concentration allowed the first-order rate coefficient for the

acid catalysed conversion of (VII) into 4-methyl-2-nitrophenol to be studied as a function of the acidity of the medium. A plot of $\log_{10} k_1$ vs $-H_0$ gave a straight line with slope 0.9 indicating that (VII) behaves quite like a Hammett base and that the rate limiting step in the rearrangement involves the protonated cyclohexadienone. It was suggested that here and also for the same process (path (4) — (7)) in Scheme 1.10, rate limiting reversion to the encounter pair was involved.



Scheme 1.11

Hahn and Groen⁴³ have reported a 1,3-nitro shift involving two consecutive 1,2-nitro shifts. Olah and co-workers⁵² have reported a study of the nitrohexamethylbenzenium ion in which the nitro-group is shown to migrate around the ring by a series of 1,2-shifts.

1.54 LOW YIELDS ABOVE 82% SULPHURIC ACID

A drop in total yield in above about 82% sulphuric acid has been found to occur for most of the hydroxy and methoxy substituted compounds which have been studied in this region of acidity. In the case of anisole, dinitration was shown to be only partly responsible for this⁵⁰ and in the case of phenol where the mononitration products are less

reactive than those of anisole it was deduced this is presumably also the case. 4-Methyl-2-nitrophenol was, however, nitrated about ten times faster than the nitro-anisoles and so dinitration may be more important with this substrate. The redetermined "zeroth-order" rates of nitration for reactive compounds at high acidities²³ do not alter significantly the calculations⁵⁰ which suggest that nitration is very much faster than sulphonation under the reaction conditions. Some of the lowered yields at high acidity therefore remain unaccounted for.

1.6 OBJECTIVES OF THE PRESENT STUDY

The work described in this thesis is concerned with some aspects of the nitration of reactive aromatic compounds by nitric acid in aqueous sulphuric acid. In most cases the activation of the aromatic ring to electrophilic attack is due to the presence of an oxygen atom in the substituent adjacent to the aromatic nucleus.

In Chapter 2 the nitrations of o-cresol, m-cresol and 3,5-dimethylphenol are investigated in order to examine the generality of the medium effect on hydroxy and methoxy compounds mentioned in 1.342. These studies led to the reinvestigation of the nitration of o-methylanisole. A brief study of p-isopropylanisole, where some displacement of the substituent may be expected, is also reported.

In Chapter 3 these studies are extended to some less reactive halogenophenols and the complications of ipso-substitution and nitrodehalogenation are reported.

Chapter 4 is concerned with nitrations at low acidities, where the intervention of another electrophile is more likely. Details of the nitrations of 1,3,5-trimethoxybenzene and phloroglucinol are reported and studies of the "zeroth-order" nitration of phenol extend the range of acidities for which rates of nitronium ion formation are available, and enable some comment to be made about

the possibility of a pre-association mechanism for nitration reactions at low acidities.

Chapter 5 describes the independent isolation and study of some cyclohexa-2,5-dienones, which are also intermediates in some nitration reactions.

Chapter 6 is concerned with the study of diphenylmethane and diphenylether. This is a preliminary study of compounds which contain two aromatic rings which will be extended in the future to such compounds with differently activated rings which should provide information concerning the detailed structure of encounter pairs.

CHAPTER 2

THE NITRATIONS OF o-CRESOL, m-CRESOL, 3,5-DIMETHYLPHENOL,
o-METHYLANSOLE AND p-ISOPROPYLANISOLE

2.1 INTRODUCTION

o-Cresol and m-cresol have been previously nitrated⁵⁷ by aqueous mixtures of nitrous and nitric acids at various concentrations of nitric acid (ca 1-3M) at 25 °C. These investigations showed that in the nitration of o-cresol the 6- and 4-nitro derivatives were obtained in about the ratio 1:1. This ratio seemed to increase slightly with increasing concentration of nitric acid. In the nitration of m-cresol the ratio of the yields of 6-nitro and 2-nitro to 4-nitro derivatives was 2:3 and was not influenced by changes in the concentration of the nitrous acid and nitric acid. The nitration of m-cresol in sulphuric acid, nitric acid and nitrous acid mixtures yielded 87% of 3-methyl-4-nitrophenol. This compound was also the main product on nitration in a sulphuric acid, nitric acid and sodium nitrite mixture. One must presume that these results reflect the effect of nitration via nitrosation which would be expected to give enhanced nitration para to the hydroxy group. High yields of p-nitroanisole and p-nitrophenol were also observed in the nitration of anisole⁵⁸ and phenol⁵⁹ respectively under conditions where nitrosation might be expected to be important.

3,5-Dimethylphenol has been nitrated in an aqueous sodium nitrate and sulphuric acid mixture and the ratio of the 2-nitro isomer to the 4-nitro isomer was found to be 6. For nitration by nitric acid in acetic acid this ratio was found to be 1.6.

2.2 EXPERIMENTAL

2.21 MATERIALS

These were as described in Section 7.2 with the addition of the following. o-Cresol, m-cresol, o-methyl-anisole, 3,5-dimethylphenol, 2-methyl-3-nitrophenol, 2-methyl-5-nitrophenol, 3-methyl-2-, 4-, -5- and -6-nitrophenols, p-nitroanisole, m-nitrophenol, p-nitrophenol and

m-nitroanisole were commercial reagents redistilled or recrystallized as necessary. These compounds had physical properties corresponding to those in the literature. 2-Methyl-4- and -6-nitroanisoles have been described previously⁵⁰ and they were the gift of Professor K. Schofield, as were p-isopropylanisole, 4-isopropyl-2-nitroanisole and 4-isopropyl-2-nitrophenol. The donated sample of 4-isopropyl-2-nitroanisole was impure and was only used for the determination of its retention time on the h.p.l.c. chromatogram since the amount given was too small to be purified.

2.211 2-METHYL-4-NITROPHENOL.

A solution of sodium nitrite (5g) in water (20 ml) was slowly added to a suspension of 2-methyl-4-nitroaniline (10g) in 10% sulphuric acid at 0°. The resulting clear solution was warmed on a water-bath. A solution of 90% sulphuric acid (100 ml) and water (200 ml) was then added in portions until the evolution of nitrogen had ceased. The product separated out on cooling, was filtered off under vacuum and was then recrystallized twice from a benzene-petroleum ether (80-100) mixture. The final product was obtained as brown-yellow coloured crystals; m.p. 117-118 °C (lit.⁶² 119 °C).

2.212 2-METHYL-6-NITROPHENOL

o-Toluidine (5.75g) was dissolved in concentrated sulphuric acid (10 ml) and water (40 ml). The solution was cooled to 15 °C and a solution of sodium nitrite (15g) in water (50 ml) was added gradually with cooling. The reaction mixture was poured at once into an excess of sulphuric acid (50%) contained in a large dish heated on a water-bath. After the vigorous evolution of nitrogen had subsided the mixture was steam distilled. The steam distillate contained 2-methyl-6-nitrophenol (80%) and 2-methyl-4,6-dinitrophenol (20%), which were separated by preparative thin layer chromatography (silica gel, 20% ethyl

acetate/cyclohexane) and identified by $^1\text{H.n.m.r.}$ spectroscopy (see Section 2.324). The former had m.p. 62-63 °C (lit.⁶³ 65 °C).

2.213 3,5-DIMETHYL-2-NITROPHENOL

3,5-Dimethylphenol (1g) was dissolved in 70% sulphuric acid (400 ml) and 0.1g of sulphanilic acid was added. A solution of nitric acid (1 ml, $d=1.42$) in 70% sulphuric acid (25 ml) was added dropwise with continuous stirring over half an hour and the temperature was not allowed to rise above 30 °C. The reaction mixture was stirred for another hour and then diluted with 750g of ice. The mixture was extracted with chloroform, the extract evaporated under vacuum leaving a dark-brown residue. 200 ml of water was added and the solution was steam distilled. The steam distillate contained 3,5-dimethyl-2-nitrophenol which was recrystallized from methanol to yield yellow needles m.p. 64-65 °C (lit.⁶⁰ 65°C).

$^1\text{H.n.m.r.}$ (CDCl_3): τ 7.67 (s, 3H), 7.38 (s, 3H), 3.32 (s, 1H)
3.20 (s, 1H).

2.214 3,5-DIMETHYL-4-NITROPHENOL.

The remaining solution from the above steam distillation was left overnight when pale yellow needles crystallized out. The crystals were filtered and then recrystallized from dil. HCl to yield pale yellow needles; m.p. 107 °C (lit.⁶⁰ 107 °C).

$^1\text{H.n.m.r.}$ (CDCl_3): τ 7.68 (s, 6H), 3.04 (s, 2H).

2.22 KINETIC MEASUREMENTS

The methods used for o-cresol, m-cresol and 3,5-dimethylphenol are described in Section 7.3.

2.23 PRODUCT ANALYSIS

2.231 o-CRESOL

Two methods were used to ascertain the isomer distribution from the nitration of o-cresol.

a) The conventional h.p.l.c. method as described in Sections 7.4(i) and 7.4(ii) was used. Table 2.1 gives the details for the h.p.l.c. procedure.

b) The UV spectrophotometric method as described by Dewar and Urch⁶⁴. Consider a solution containing substances 1,2,3,...,i at unknown concentrations $x_1, x_2, x_3, \dots, x_i$ mole dm^{-3} . Standard solutions of 1,2,3,...,i have known concentrations of $c_1, c_2, c_3, \dots, c_i$ mole dm^{-3} and give rise to absorptions (measured as $\log_{10} I_0/I$) of $A_1, A_2, A_3, \dots, A_i$ at wavelength λ . If R is the observed value of $\log_{10}(I_0/I)$ for the unknown solution and Beer's Law is obeyed, then:-

$$R = x_1 \cdot A_1 / c_1 + x_2 \cdot A_2 / c_2 + \dots + x_i \cdot A_i / c_i \dots\dots\dots 1$$

where all measurements refer to the same value of λ .

Dividing through by A_1 gives:-

$$R/A_1 = x_1/c_1 + x_2 \cdot A_2/c_2 \cdot A_1 + \dots + x_i \cdot A_i/c_i \cdot A_1 \dots\dots\dots 2$$

For a two component system, R, A_1, A_2, c_1 and c_2 are known experimentally. If the values of R/A_1 for various wavelengths are plotted against the corresponding values of A_2/A_1 the points should lie on a straight line of slope x_2/c_2 and the intercept on the R/A_1 axis gives x_1/c_1 . Any deviation from a straight line indicates the presence of other absorbing components.

Solutions were prepared in the same manner as for the kinetic studies, i.e. 25 ml of aqueous sulphuric acid containing approximately 0.05 mole dm^{-3} sulphamic acid, 1.61×10^{-4} mole dm^{-3} of o-cresol and the appropriate concentration of nitric acid at 25°. The reaction was allowed to proceed for ten half-lives (determined from the kinetic measurements) and the UV extinction curve was then determined in the range 250 - 390 nm. Extinction curves were also determined

Table 2.1

H.p.l.c. conditions for the separation of
2-methyl-3-, -4-, -5- and -6-nitrophenols

Column : 25cm x 1/4" Merkosorb SI60

Solvent : 10% AcOEt/cyclohexane

Flow rate : 2 ml/min

Wavelength : 320 nm

Detector : Cecil 272

Pump : Waters Associates, model 6000A

Temperature : Ambient

Compound	Retention times/s
2-methyl-3-nitrophenol	596
2-methyl-4-nitrophenol	700
2-methyl-5-nitrophenol	360
2-methyl-6-nitrophenol	142
<u>m</u> -nitroanisoie (reference standard)	220

for a known concentration of 2-methyl-4-nitrophenol (7.97×10^{-5} mole dm^{-3}), of 2-methyl-6-nitrophenol (8.34×10^{-5} mole dm^{-3}) and of the appropriate concentration of nitric acid in the same concentration of aqueous sulphuric acid. The method of calculation described above was applied to obtain values for the yields of 2-methyl-4- and 2-methyl-6-nitrophenols.

2.232 - 2.235 m-CRESOL, 3,5-DIMETHYLPHENOL, o-METHYLANISOLE
AND p-ISOPROPYLANISOLE

The conventional h.p.l.c. method as described in Sections 7.4(i) and 7.4(ii) was used to determine the isomer distributions from the nitration of these compounds. Details of the h.p.l.c. procedures for mcresol, 3,5-dimethylphenol, o-methylanisole and p-isopropylanisole are given in Tables 2.2, 2.3, 2.4 and 2.5 respectively.

2.3 RESULTS

2.31 KINETICS

2.311 o-CRESOL

The results and subsequent calculations required for a typical determination of a rate coefficient for the nitration of o-cresol are given below:-

Concentration of sulphuric acid	: 66.6% w/w
Concentration of nitric acid	: 8.98×10^{-4} mole dm^{-3}
Concentration of <u>o</u> -cresol	: 1.25×10^{-4} mole dm^{-3}
Concentration of sulphamic acid <u>ca</u>	0.05 mole dm^{-3}
Temperature	: $25.0 \pm 0.02^{\circ}$
Wavelength of measurement	: 310 nm

Fig. 2.1 shows the extinction curve obtained, Table 2.6 shows

Table 2.2

H.p.l.c. conditions for the separation of
3-methyl-2-, 4-, 5- and 6-nitrophenols

Column : 25cm x 1/4" Merkosorb SI60
Solvent : 10% EtOAc/cyclohexane
Flow rate : 2 ml/min
Wavelength : 300 nm
Detector : Cecil 272
Pump : Waters Associates, model 6000A
Temperature : Ambient

Compound	Retention times /s
3-methyl-2-nitrophenol	252
3-methyl-4-nitrophenol	870
3-methyl-5-nitrophenol	600
3-methyl-6-nitrophenol	162
2-methyl-3-nitrophenol (reference standard)	690

Table 2.3

H.p.l.c. conditions for the separation of
3,5-dimethyl-2-nitrophenol and 3,5-dimethyl-4-nitrophenol

Column : 25cm x 1/4" Merkosorb SI60
Solvent : 13% AcOEt/cyclohexane
Flow rate : 2 ml/min
Wavelength : 320 nm
Detector : Cecil 272
Pump : Waters Associates, model 6000A
Temperature: Ambient

Compound	Retention times /s
3,5-dimethyl-2-nitrophenol	157
3,5-dimethyl-4-nitrophenol	560
p-nitroanisole (reference standard)	260

Table 2.4

H.p.l.c. conditions for the separation of
2-methyl-4- and 6-nitroanisole and
2-methyl-4- and 6-nitrophenol.

Column : 25cm x 1/4" Merkosorb SI60
Solvent : 10% AcOEt/cyclohexane
Flow rate : 2 ml/min
Wavelength : 300 nm
Detector : Cecil 272
Pump : Waters Associates, model 6000A
Temperature : Ambient

Compound	Retention times /s
2-methyl-4-nitrophenol	664
2-methyl-6-nitrophenol	144
2-methyl-4-nitroanisole	255
2-methyl-6-nitroanisole	195
<u>m</u> -nitrophenol (reference standard)	535

Table 2.5

H.p.l.c. conditions for the separation of
4-isopropyl-2-nitroanisole, 4-isopropyl-2-nitrophenol,
p-nitroanisole and p-nitrophenol

Column : 25cm x 1/4" Merkosorb SI60
Solvent : 13% AcOEt/cyclohexane
Flow rate : 2 ml/min
Wavelength : 300 nm
Detector : Cecil 272
Pump : Waters Associates, model 6000A
Temperature : Ambient

Compound	Retention times /s
4-isopropyl-2-nitrophenol	150
4-isopropyl-2-nitroanisole	224
p-nitrophenol	760
p-nitroanisole	260
2-methyl-3-nitrophenol (reference standard)	510

the data obtained therefrom and Fig. 2.2 shows a plot of $\log_{10}(A_{\infty} - A_t)$ vs t .

$$k_2(\text{obs}) = -2.303 \times \text{slope} / [\text{HNO}_3] \text{ dm}^3 \text{ mole}^{-1} \text{ s}^{-1}$$

$$k_2(\text{obs}) = 2.303 \times 2.51 \times 10^{-4} / 8.98 \times 10^{-4} \text{ dm}^3 \text{ mole}^{-1} \text{ s}^{-1}$$

$$k_2(\text{obs}) = 0.58 \text{ dm}^3 \text{ mole}^{-1} \text{ s}^{-1}$$

Second-order rate coefficients for the nitration of o-cresol, 2-methyl-4-nitrophenol and 2-methyl-6-nitrophenol in various concentrations of sulphuric acid are given in Table 2.7. A rate profile ($\log_{10} k_2(\text{obs})$ vs %H₂SO₄) is shown in Fig. 2.3 in which data for mesitylene and benzene are also shown for comparison.

2.312 m-CRESOL

A typical determination of a rate coefficient:-

Concentration of sulphuric acid : 66.3% w/w

Concentration of nitric acid : $8.98 \times 10^{-4} \text{ mole dm}^{-3}$

Concentration of m-cresol : $1.37 \times 10^{-4} \text{ mole dm}^{-3}$

Concentration of sulphamic acid ca $0.05 \text{ mole dm}^{-3}$

Temperature : $25.0 \pm 0.2^\circ$

Wavelength of measurement : 310 nm

Fig. 2.4 shows the extinction curve, Table 2.8 the data obtained therefrom and Fig. 2.5 the plot of $\log_{10}(A_{\infty} - A_t)$ vs time.

$$k_2(\text{obs}) = -2.303 \times \text{slope} / [\text{HNO}_3] \text{ dm}^3 \text{ mole}^{-1} \text{ s}^{-1}$$

$$k_2(\text{obs}) = 0.60 \text{ dm}^3 \text{ mole}^{-1} \text{ s}^{-1}$$

Second-order rate coefficients for the nitration of m-cresol, 3-methyl-2-nitrophenol, 3-methyl-4-nitrophenol and 3-methyl-6-nitrophenol at various concentrations of aqueous sulphuric acid are given in Table 2.9. A rate profile ($\log_{10} k_2(\text{obs})$ vs % H₂SO₄) is shown in Fig. 2.6 in which data for mesitylene and benzene are shown for comparison.

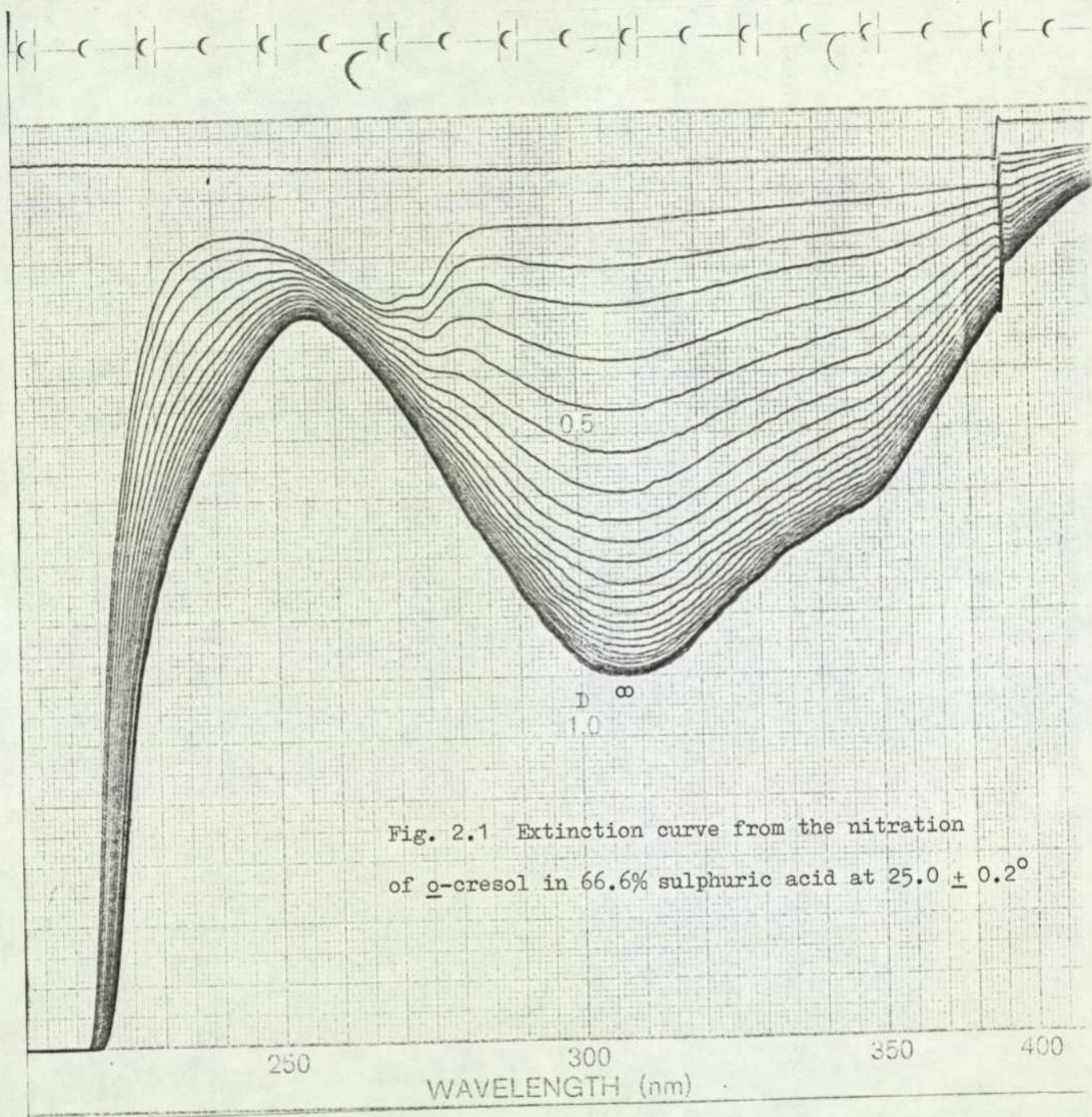


Table 2.6

Data from a typical determination of the rate
of nitration of o-cresol in 66.5% sulphuric acid
at $25.0 \pm 0.2^\circ$

Time (t) /s	Absorbance (A_t)	$\log_{10}(A_\infty - A_t)$
60	0.140	-0.12
180	0.220	-0.17
300	0.286	-0.21
473	0.379	-0.28
674	0.460	-0.35
878	0.530	-0.43
1083	0.597	-0.52
1289	0.640	-0.58
1495	0.679	-0.65
1701	0.712	-0.72
1907	0.748	-0.81
2113	0.770	-0.88
t_∞	0.903	

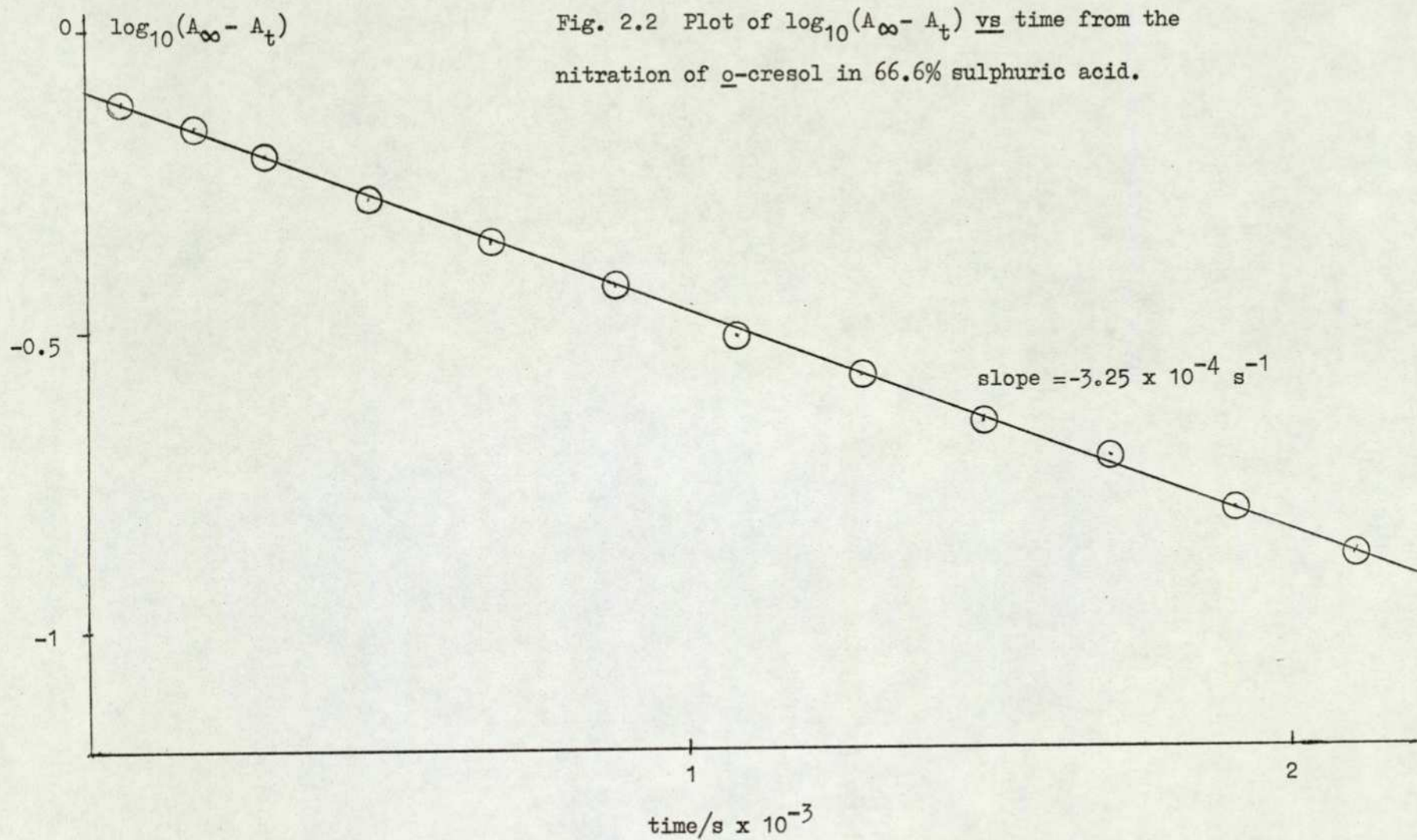


Table 2.7

Second-order rate coefficients for nitration

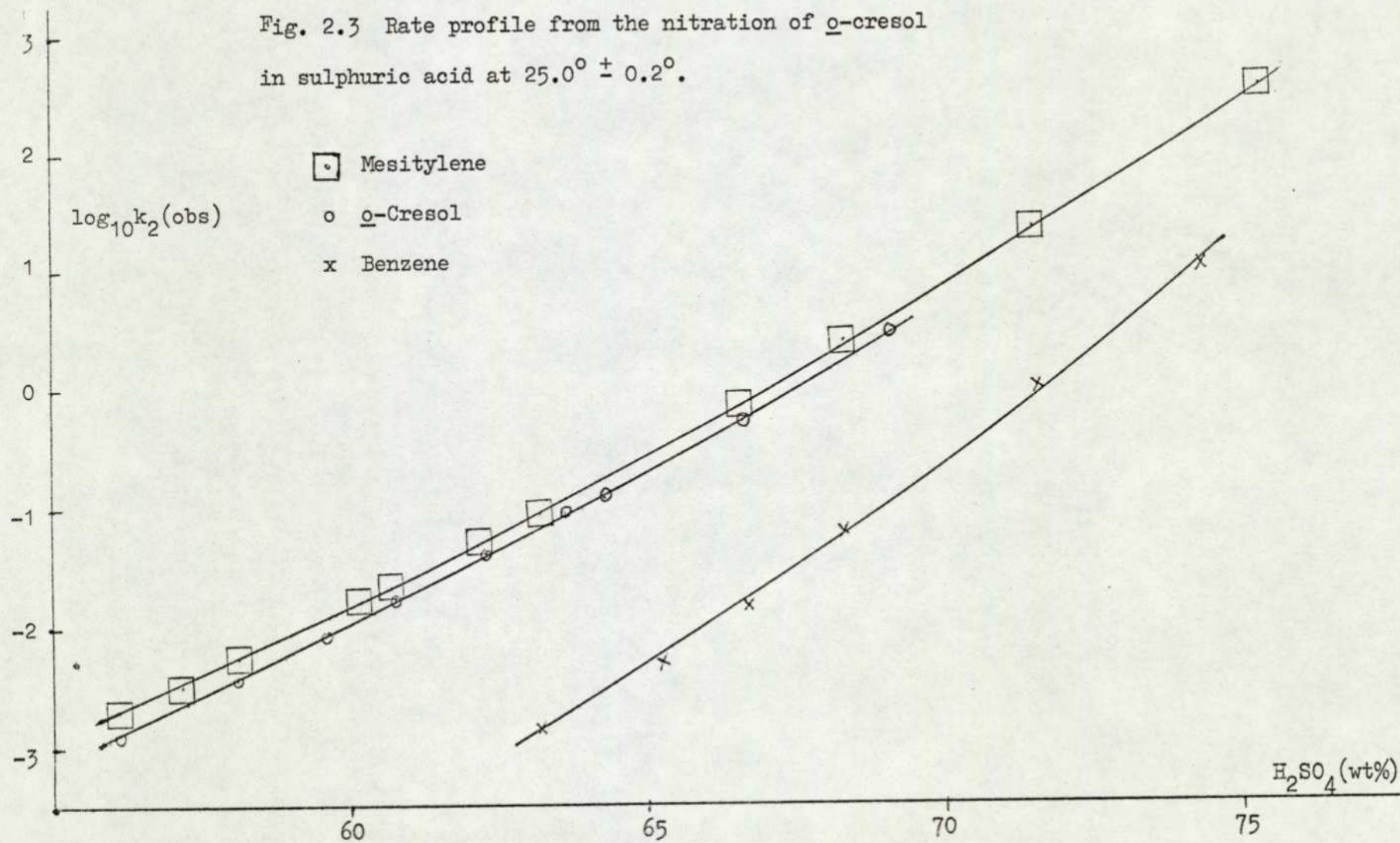
in sulphuric acid at $25.0 \pm 0.2^\circ$

H_2SO_4 (%) ^a	$10^2[\text{HNO}_3]$ /mole dm ⁻³	$k_2(\text{obs})$ /dm ³ mole ⁻¹ s ⁻¹
<u>o</u> -Cresol ^{b,c,d}		
56.1	5.5	1.2×10^{-3}
58.1	5.5	3.6×10^{-3}
59.6	2.3	8.5×10^{-3}
60.8	0.67	1.7×10^{-2}
62.3	0.25	4.1×10^{-2}
63.6	0.25	9.9×10^{-2}
64.3	0.09	1.2×10^{-1}
66.6	0.09	5.8×10^{-1}
69.1	0.09	2.8
2-Methyl-4-nitrophenol ^{e,f}		
80.8	5.5	2.5
2-Methyl-6-nitrophenol ^{e,g}		
80.8	5.5	2.5

Table 2.7 (continued)

- a) $\pm 0.1\%$ w/w
- b) $[\text{ArH}] = 1.25 \times 10^{-4} \text{ mole dm}^{-3}$
- c) $[\text{Sulphamic acid}] \text{ ca } 0.05 \text{ mole dm}^{-3}$
- d) Measurement at 305 or 310 nm
- e) Measurement at 280 nm
- f) $[\text{ArH}] = 1.12 \times 10^{-4} \text{ mole dm}^{-3}$
- g) $[\text{ArH}] = 1.09 \times 10^{-4} \text{ mole dm}^{-3}$

Fig. 2.3 Rate profile from the nitration of o-cresol
in sulphuric acid at $25.0^\circ \pm 0.2^\circ$.



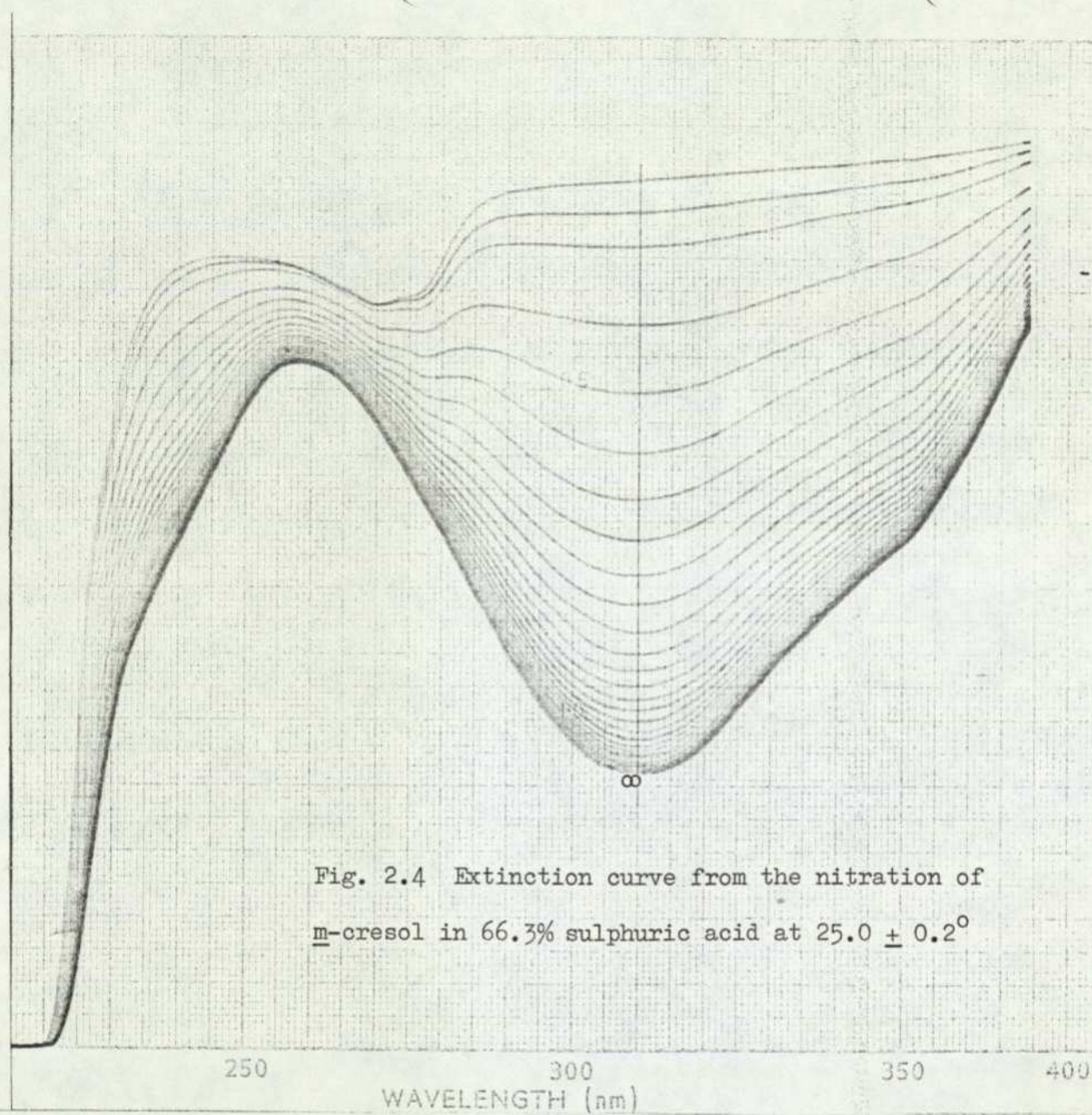


Fig. 2.4 Extinction curve from the nitration of m-cresol in 66.3% sulphuric acid at $25.0 \pm 0.2^\circ$

Table 2.8

Data from a typical determination of the rate
Coefficient of m-cresol in 66.3% sulphuric acid
at $25.0 \pm 0.2^\circ$

Time (t) /mins	Absorbance (A_t)	$\log_{10} (A_\infty - A_t)$
1	0.183	-0.05
5	0.283	-0.09
10	0.401	-0.17
15	0.506	-0.24
20	0.594	-0.39
25	0.677	-0.45
30	0.729	-0.52
35	0.782	-0.59
40	0.827	-0.67
45	0.868	-0.74
t_∞	1.083	

Fig. 2.5 Plot of $\log_{10}(A_{\infty} - A_t)$ vs time from the nitration of m-cresol in 66.3% sulphuric acid.

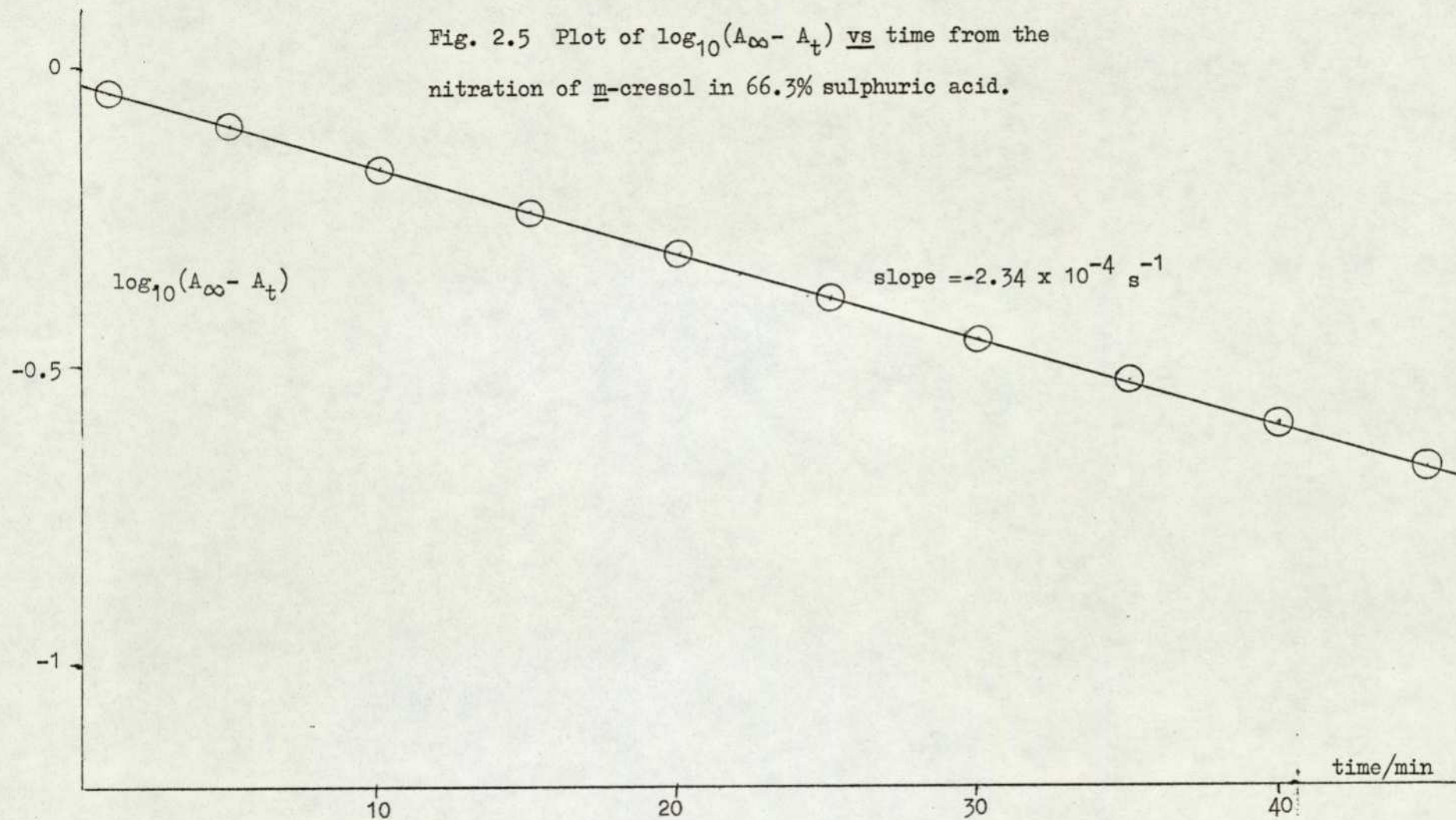


Table 2.9

Second-order rate coefficients for nitration

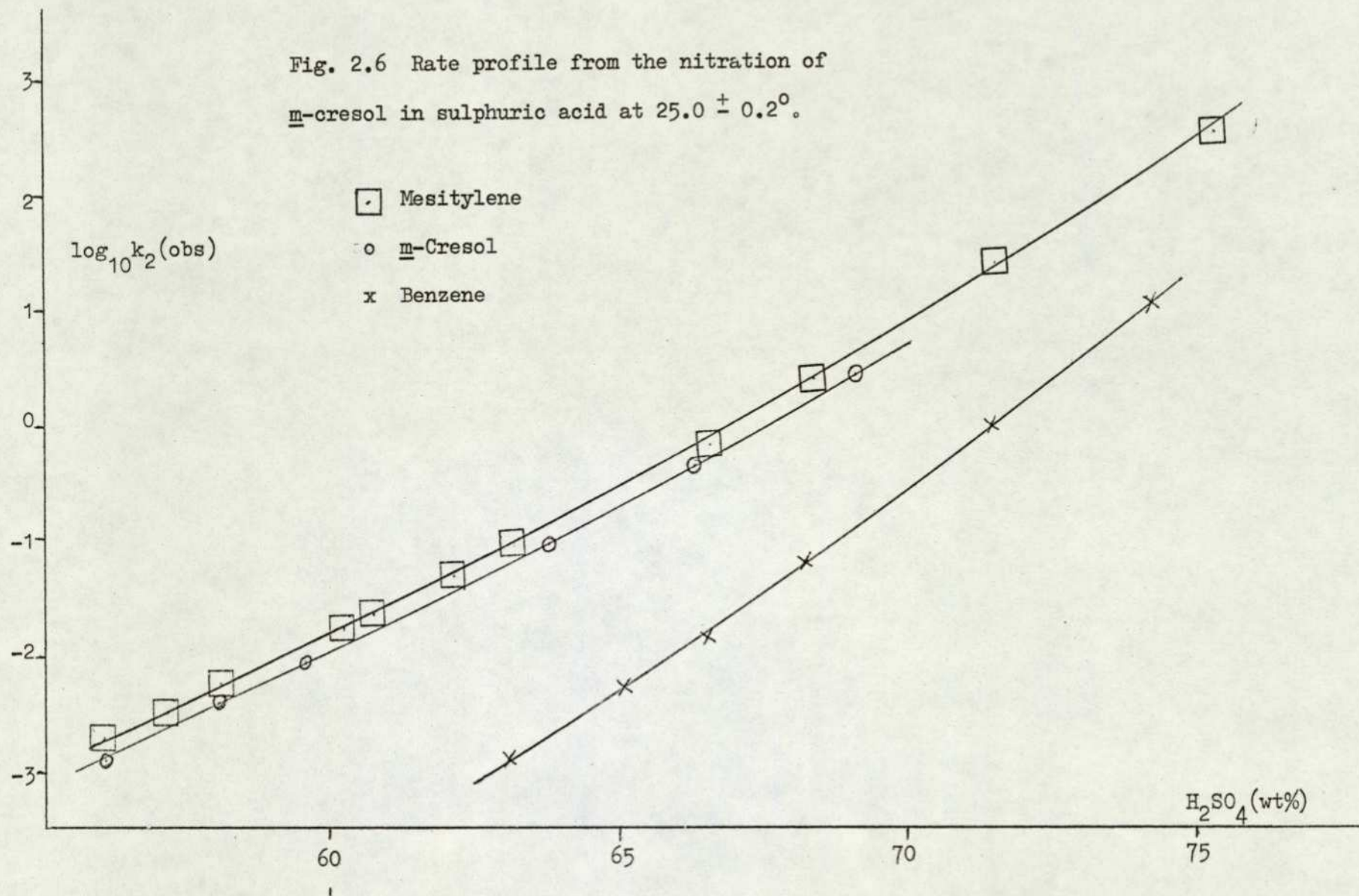
in sulphuric acid at $25.0 \pm 0.2^\circ$

H_2SO_4 (%) ^a	$10^2 [\text{HNO}_3]$ /mole dm ⁻³	$k_2(\text{obs})$ /dm ³ mole ⁻¹ s ⁻¹
<u>m</u> -Cresol ^{b,c,d}		
56.1	5.5	1.1×10^{-3}
58.1	5.5	4.0×10^{-3}
59.6	2.3	1.1×10^{-2}
62.2	2.3	3.8×10^{-2}
63.8	2.3	9.1×10^{-2}
66.3	0.09	6.0×10^{-1}
69.1	0.09	2.5
3-Methyl-2-nitrophenol ^{e,f}		
80.8	5.5	2.7
3-Methyl-4-nitrophenol ^{g,h}		
80.8	5.5	3.0
3-Methyl-6-nitrophenol ^{i,j}		
80.8	5.5.	2.9

Table 2.9 (continued)

- a) $\pm 0.1\%$ w/w
- b) $[\text{ArH}] = 1.37 \times 10^{-4} \text{ mole dm}^{-3}$
- c) $[\text{Sulphamic acid}] \text{ ca } 0.05 \text{ mole dm}^{-3}$
- d) Measurement at 300, 305 or 310 nm
- e) $[\text{ArH}] = 1.21 \times 10^{-4} \text{ mole dm}^{-3}$
- f) Measurement at 273 nm
- g) $[\text{ArH}] = 1.27 \times 10^{-4} \text{ mole dm}^{-3}$
- h) Measurement at 278 nm
- i) $[\text{ArH}] = 1.09 \times 10^{-4} \text{ mole dm}^{-3}$
- j) Measurement at 286 nm

Fig. 2.6 Rate profile from the nitration of
m-cresol in sulphuric acid at $25.0 \pm 0.2^\circ$.



2.313 3,5-DIMETHYLPHENOL

A typical determination of a rate coefficient:-

Concentration of sulphuric acid	: 62.2% w/w
Concentration of nitric acid	: 2.33×10^{-2} mole dm^{-3}
Concentration of 3,5-dimethylphenol	: 1.22×10^{-4} mole dm^{-3}
Concentration of sulphanilic acid	<u>ca</u> 0.05 mole dm^{-3}
Temperature	: $25.0 \pm 0.2^\circ$
Wavelength of measurement	: 305 nm

Fig. 2.7 shows the extinction curve, Table 2.10 the data obtained therefrom and Fig. 2.8 the plot of $\log_{10}(A_\infty - A_t)$ vs time.

$$k_2(\text{obs}) = -2.303 \times \text{slope} / [\text{HNO}_3] \text{ dm}^3 \text{ mole}^{-1} \text{ s}^{-1}$$

$$k_2(\text{obs}) = 5.6 \times 10^{-2} \text{ dm}^3 \text{ mole}^{-1} \text{ s}^{-1}$$

Second-order rate coefficients for the nitration of 3,5-dimethylphenol, 3,5-dimethyl-2-nitrophenol and 3,5-dimethyl-4-nitrophenol at various concentrations of sulphuric acid are given in Table 2.11.

A rate profile ($\log_{10} k_2(\text{obs})$ vs % H_2SO_4) is shown in Fig. 2.9 in which data for mesitylene and benzene are shown for comparison.

2.32 YIELDS OF NITRO-COMPOUNDS

2.321 o-CRESOL

2.3211 UV SPECTROPHOTOMETRIC METHOD

An example of the method of Dewar and Urch for calculating the yields of nitro-products from the nitration of o-cresol is given below:-

Concentration of sulphuric acid	: 75.2% w/w
Concentration of nitric acid	: 1.65×10^{-4} mole dm^{-3}
Concentration of <u>o</u> -cresol	: 1.52×10^{-4} mole dm^{-3}
2-Methyl-4-nitrophenol	: 7.97×10^{-5} mole dm^{-3}
2-Methyl-6-nitrophenol	: 8.38×10^{-5} mole dm^{-3}

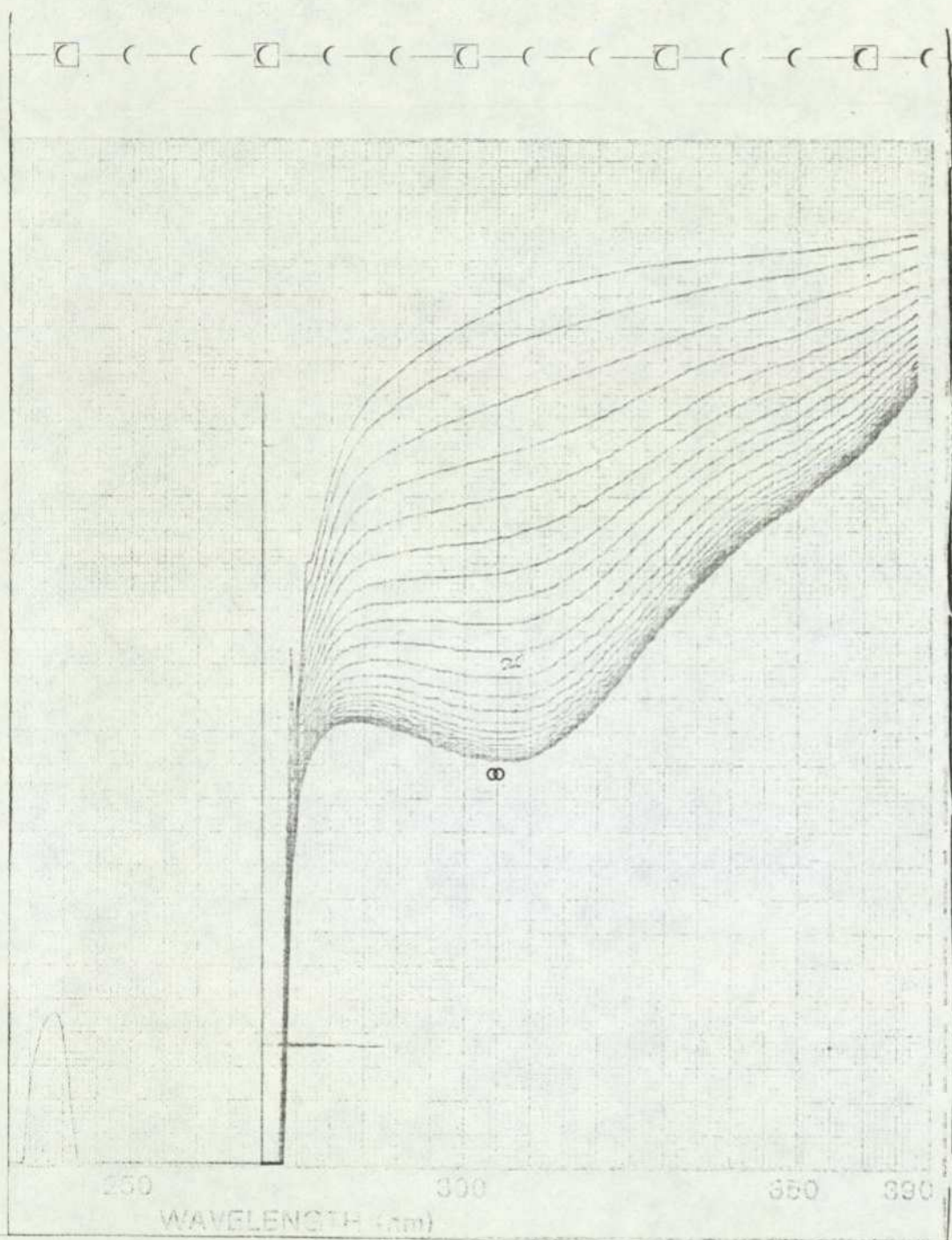


Fig. 2.7 Extinction curve from the nitration of 3,5-dimethylphenol in 62.2% sulphuric acid at $25.0 \pm 0.2^{\circ}$

Table 2.10

Data from a typical determination of the rate
coefficient of 3,5-dimethylphenol in 62.2%
sulphuric acid at $25.0 \pm 0.2^\circ$

Time (t) /min	Absorbance (A_t)	$\log_{10}(A_\infty - A_t)$
3	0.280	-0.21
7	0.439	-0.34
11	0.562	-0.47
15	0.658	-0.62
17	0.690	-0.68
20	0.731	-0.77
23	0.770	-0.89
26	0.798	-0.99
29	0.820	-1.09
32	0.838	-1.21
35	0.850	-1.30
38	0.860	-1.41
t_∞	0.900	

Fig. 2.8 Plot of $\log_{10}(A_{\infty} - A_t)$ vs time from the nitration of 3,5-dimethylphenol in 62.2% sulphuric acid.

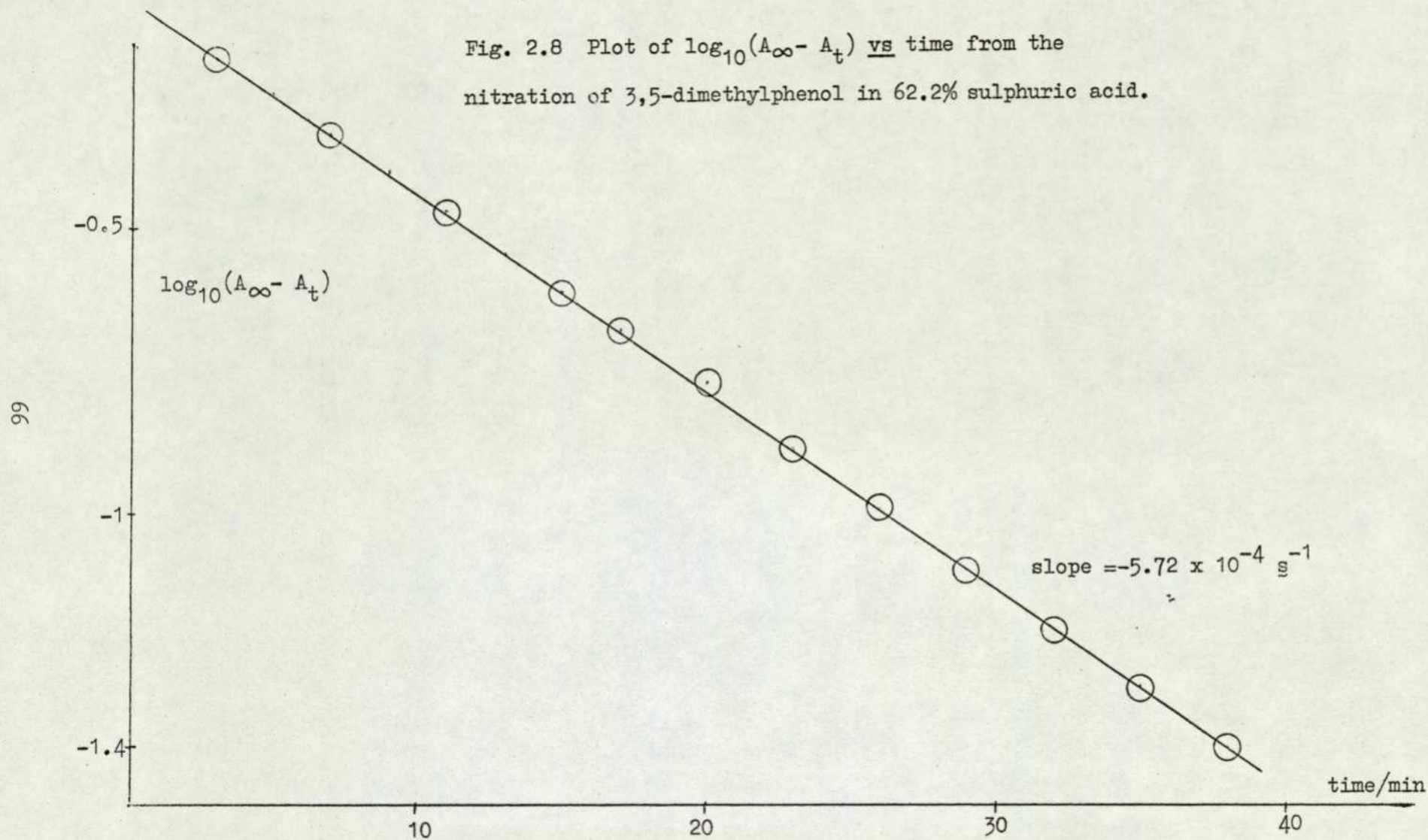


Table 2.11

Second-order rate coefficients for nitration
in sulphuric acid at $25.0 \pm 0.2^\circ$

H_2SO_4 (%) ^a	$10^2[\text{HNO}_3]$ /mole dm ⁻³	$k_2(\text{obs})$ /dm ³ mole ⁻¹ s ⁻¹
3,5-Dimethylphenol ^{b,c,d}		
56.1	5.5	1.8×10^{-3}
58.1	5.5	4.7×10^{-3}
59.6	2.3	1.1×10^{-2}
62.2	2.3	5.6×10^{-2}
63.8	2.3	1.2×10^{-1}
66.3	2.3	0.5
68.4	0.09	2.3
70.6	0.09	9.9
3,5-Dimethyl-2-nitrophenol ^{e,f}		
74.3	5.5	3.5×10^{-2}
3,5-Dimethyl-4-nitrophenol ^{g,h}		
74.3	5.5	4.9×10^{-2}

Table 2.11 (continued)

- a) $\pm 0.1\%$ w/w
- b) $[\text{ArH}] = 1.22 \times 10^{-4} \text{ mole dm}^{-3}$
- c) $[\text{Sulphamic acid}] \text{ ca } 0.05 \text{ mole dm}^{-3}$
- d) Measurement at 305 or 310 nm
- e) $[\text{ArH}] = 1.13 \times 10^{-4} \text{ mole dm}^{-3}$
- f) Measurement at 270 nm
- g) $[\text{ArH}] = 1.03 \times 10^{-4} \text{ mole dm}^{-3}$
- h) Measurement at 280 nm

Fig. 2.9 Rate profile from the nitration of
3,5-dimethylphenol in sulphuric acid at $25.0 \pm 0.2^\circ$.

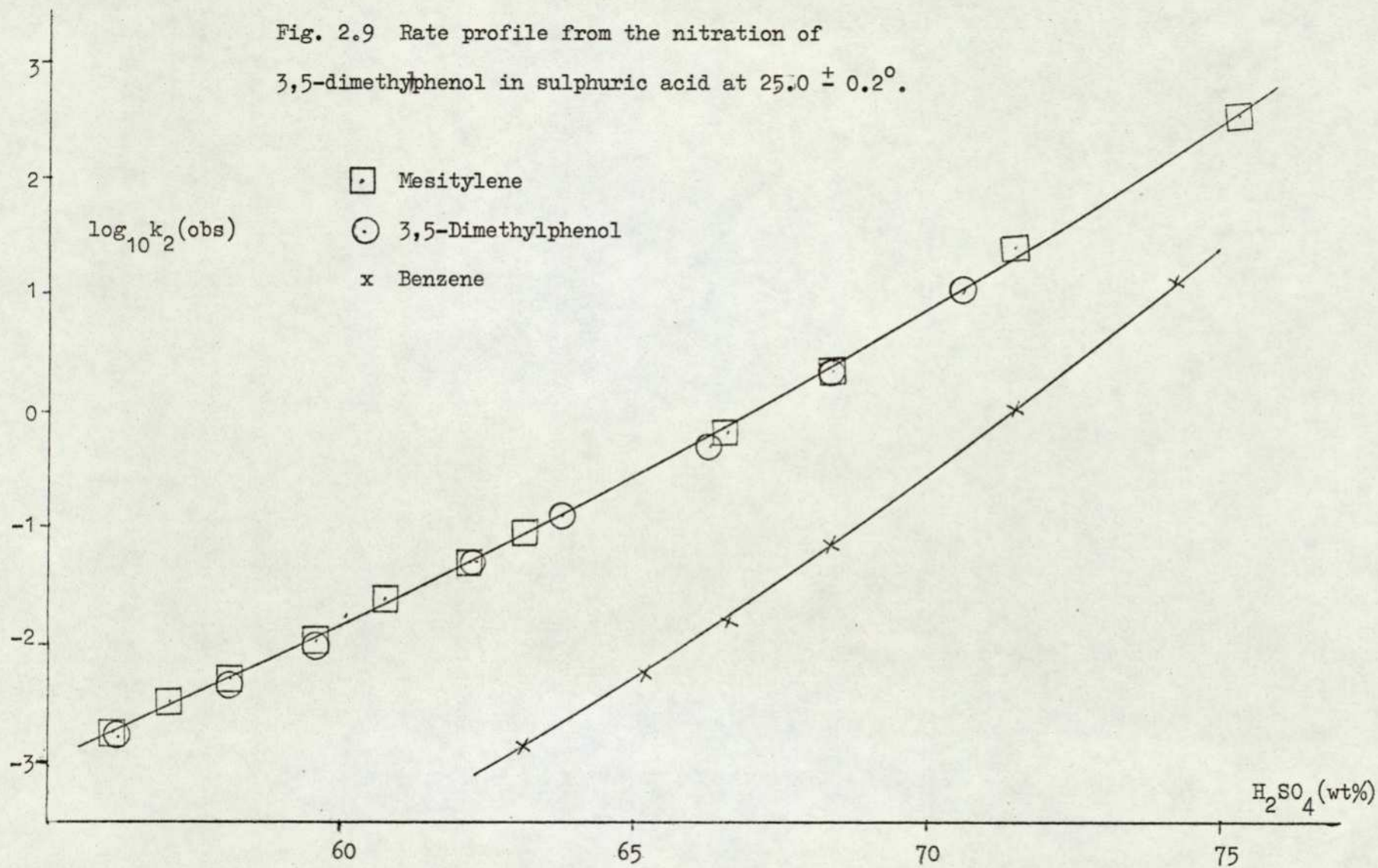


Fig. 2.10 shows the extinction curve obtained from the nitration of o-cresol (A), the extinction curves for 2-methyl-4-nitrophenol (B), for 2-methyl-6-nitrophenol (C) and for nitric acid (D) solutions in 75.2% sulphuric acid respectively. Table 2.12 shows the data obtained from the extinction curves and Fig. 2.11 shows the plot of R/A_1 vs A_2/A_1 where:-

R : observed value of $\log_{10} I_0/I$ for the unknown mixture

A_1 : observed value of $\log_{10} I_0/I$ for 2-methyl-6-nitrophenol

A_2 : observed value of $\log_{10} I_0/I$ for 2-methyl-4-nitrophenol

The intercept is x_6/c_6 and the slope is x_4/c_4 where:-

x_6 : concentration of 2-methyl-6-nitrophenol in the unknown

x_4 : concentration of 2-methyl-4-nitrophenol in the unknown

c_6 : concentration of 2-methyl-6-nitrophenol in the standard

c_4 : concentration of 2-methyl-4-nitrophenol in the standard

$$\text{Intercept} = 0.90, \quad c_6 = 8.38 \times 10^{-5} \text{ mole dm}^{-3}$$

$$\therefore x_6 = 7.51 \times 10^{-5} \text{ mole dm}^{-3}$$

$$\text{Slope} = 0.92, \quad c_4 = 7.97 \times 10^{-5} \text{ mole dm}^{-3}$$

$$\therefore x_4 = 7.33 \times 10^{-5} \text{ mole dm}^{-3}$$

$$\therefore \text{Total yield} = 1.484 \times 10^{-4} \text{ mole dm}^{-3}$$

$$\% \text{ 2-methyl-6-nitrophenol} = 52.5\%$$

$$\% \text{ 2-methyl-4-nitrophenol} = 45.5\%$$

Table 2.13 and Fig. 2.12 give the yields of nitro-compounds from the nitration of o-cresol in various concentrations of aqueous sulphuric acid using the Dewar and Urch method.

Fig. 2.10 Extinction curves from the nitration of *o*-cresol (A), for 2-methyl-4-nitrophenol (B), for 2-methyl-6-nitrophenol (C) and for nitric acid (D) solutions in 75.2% sulphuric acid.

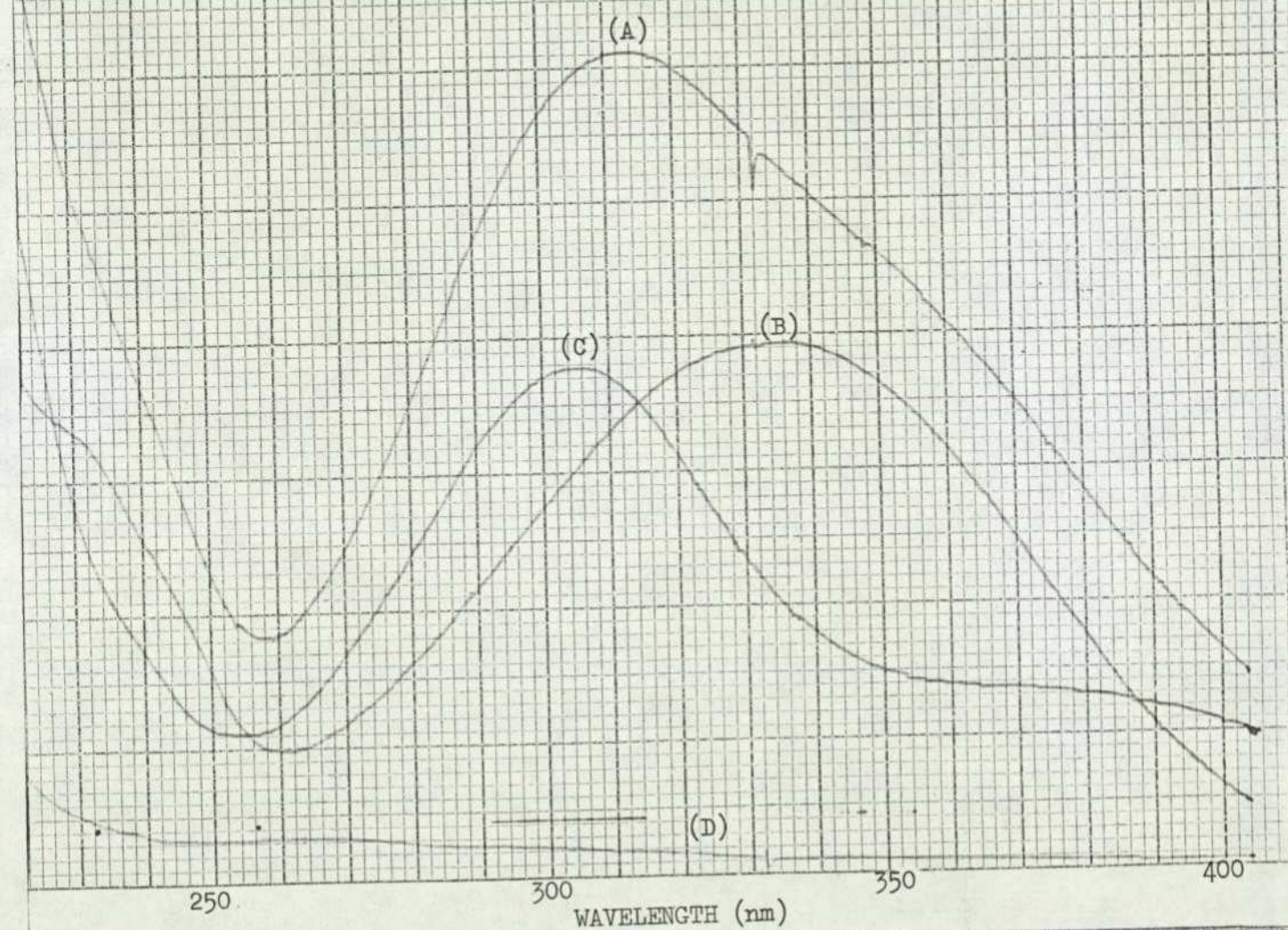


Table 2.12

Data from a typical Dewar and Urch calculation from
the nitration of o-cresol in 75.2% sulphuric acid

Wavelength	R	A_1	A_2	R/A_1	A_2/A_1
280	0.65	0.43	0.27	1.51	0.63
290	0.89	0.59	0.38	1.51	0.63
300	1.08	0.70	0.50	1.54	0.71
310	1.18	0.70	0.62	1.68	0.88
320	1.17	0.59	0.72	1.98	1.20
330	1.09	0.45	0.76	2.42	1.69
340	0.99	0.34	0.76	2.91	2.23
350	0.90	0.28	0.71	3.21	2.53
360	0.80	0.26	0.61	3.07	2.35
370	0.68	0.26	0.48	2.61	1.85
380	0.55	0.24	0.33	2.24	1.37

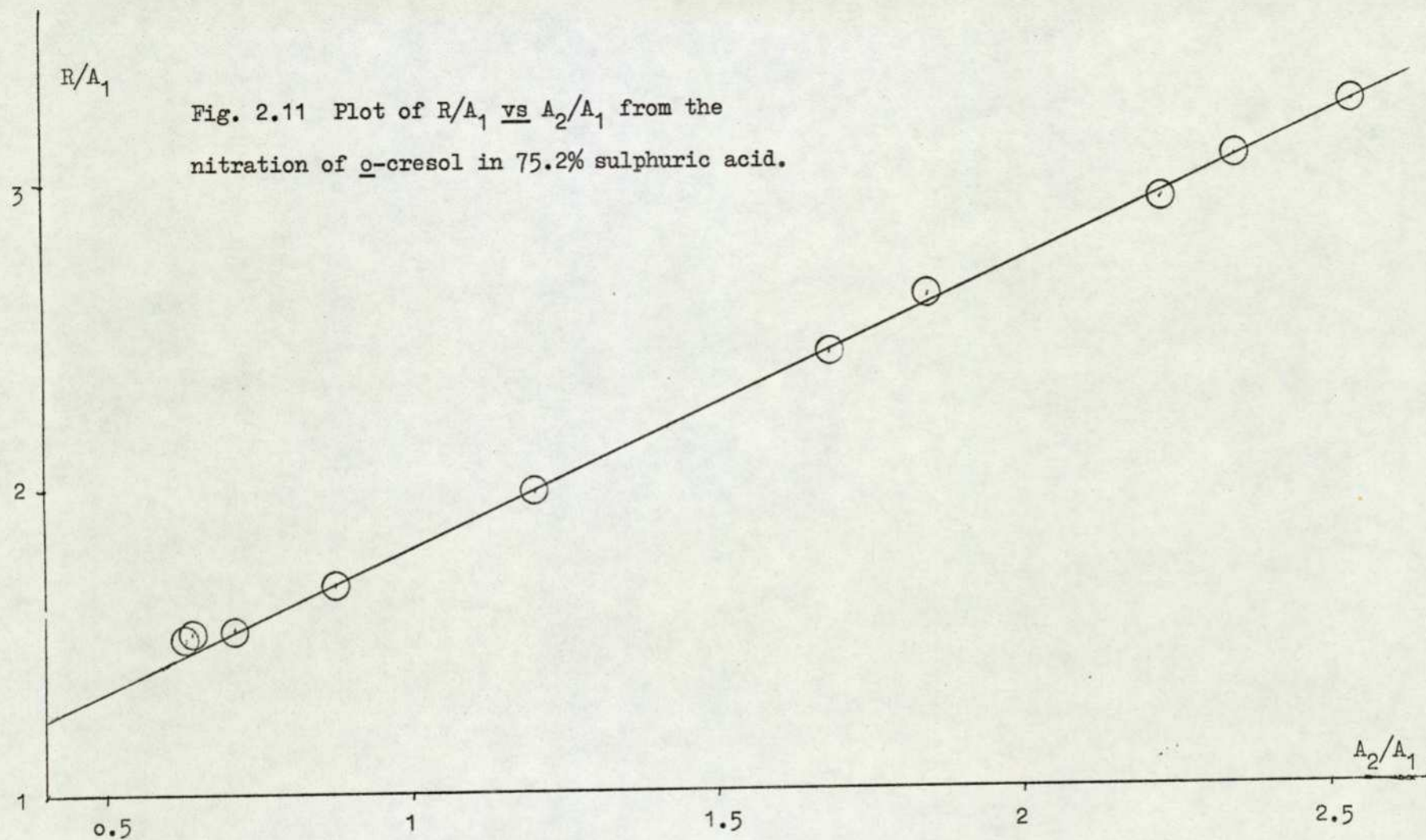


Table 2.13

Yields of nitro-compounds from the nitration of o-cresol
in sulphuric acid by the UV spectrophotometric method

H_2SO_4 (%) ^{a,d}	2-methyl-6-nitro- phenol (%)	2-methyl-4-nitro- phenol (%)	Mass balance (%)
58.1 ^b	64.7	35.2	99.9
62.8 ^b	62.6	36.5	99.1
63.6 ^b	64.5	35.4	99.9
69.1 ^{b,c}	61.7	36.1	97.8
70.8 ^{b,c}	57.5	42.3	99.8
73.5 ^{b,c}	53.6	42.7	96.3
75.2 ^{b,c}	52.5	45.5	98.3
76.6 ^{b,c}	51.4	44.1	95.5
78.3	49.6	49.2	98.8

a) $\pm 0.1\%$ w/w

b) $[\text{ArH}] = 1.52 \times 10^{-4} \text{ mole dm}^{-3}$

c) $[\text{HNO}_3] = 1.65 \times 10^{-4} \text{ mole dm}^{-3}$

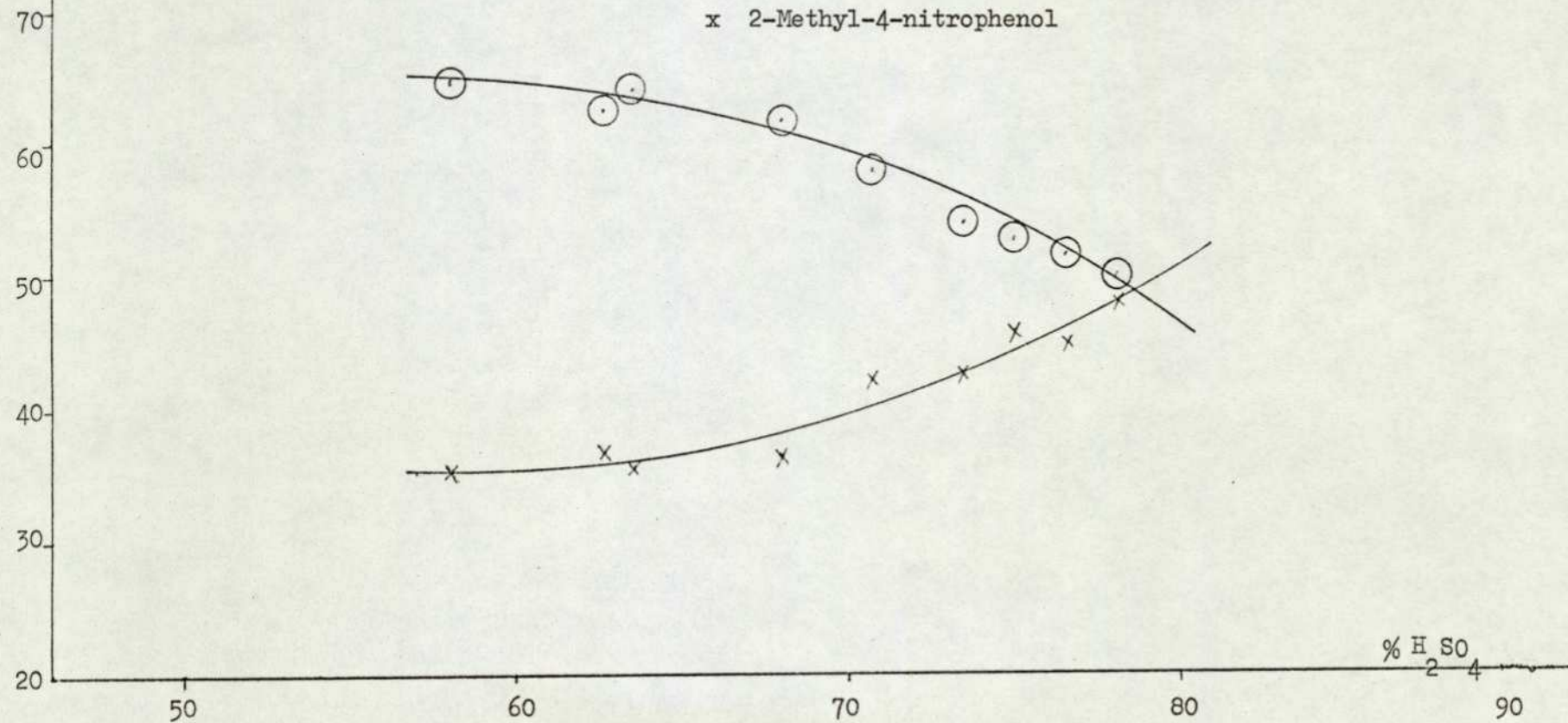
d) $[\text{Sulphamic acid}] \text{ ca } 0.05 \text{ mole dm}^{-3}$

Fig. 2.12 Yields of the nitro-compounds from the nitration of o-cresol in aqueous sulphuric acid at $25.0 \pm 1^\circ$

% yield

o 2-Methyl-6-nitrophenol

x 2-Methyl-4-nitrophenol



2.3212 H.P.L.C. METHOD

An example of the calculation of the yields of the nitro compounds by the h.p.l.c. method from the nitration of o-cresol in aqueous sulphuric acid is given below:-

Sulphuric acid	: 53.9% w/w
Amount of nitric acid	: 1.38×10^{-3} moles
Amount of <u>o</u> -cresol	: 1.01×10^{-4} moles
Amount of <u>m</u> -nitroanisole (reference standard) added	: 6.0×10^{-5} moles

Fig. 2.13 shows the chromatogram obtained (h.p.l.c. conditions as in Table 2.1).

Peak weights from chromatogram (Fig. 2.13)

Compound	Weight/g
2-methyl-6-nitrophenol	0.0186
2-methyl-4-nitrophenol	0.0502
<u>m</u> -nitroanisole (reference standard)	0.0253

The method of relative response factors as described in Section 7.5 was used.

$$c_x/c_s = A_x/A_s \times f$$

Factor f for 2-methyl-4-nitrophenol : 0.33

Factor f for 2-methyl-6-nitrophenol : 1.39

∴ Amount of 2-methyl-4-nitrophenol

$$= \frac{0.0502}{0.0253} \times 6.0 \times 10^{-5} \times 0.33 \text{ moles}$$

$$= 3.98 \times 10^{-5} \text{ moles}$$

$$\% \text{ of 2-methyl-4-nitrophenol} = \frac{3.98 \times 10^{-5}}{1.01 \times 10^{-4}} \times 100$$

$$= 39.5 \%$$

Fig. 2.13 Chromatogram of the products from the nitration of o-cresol in 53.9% sulphuric acid

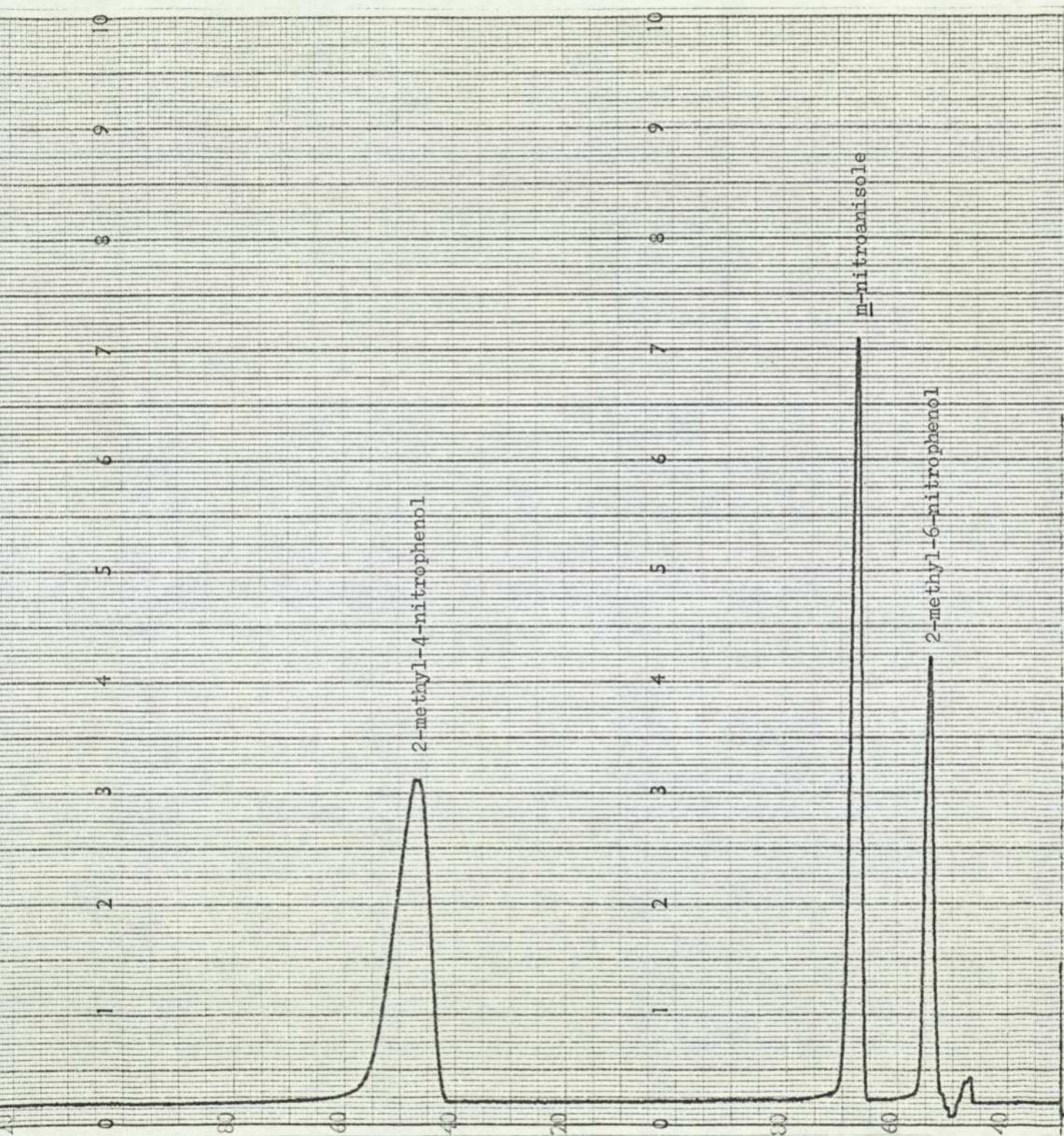


Table 2.14

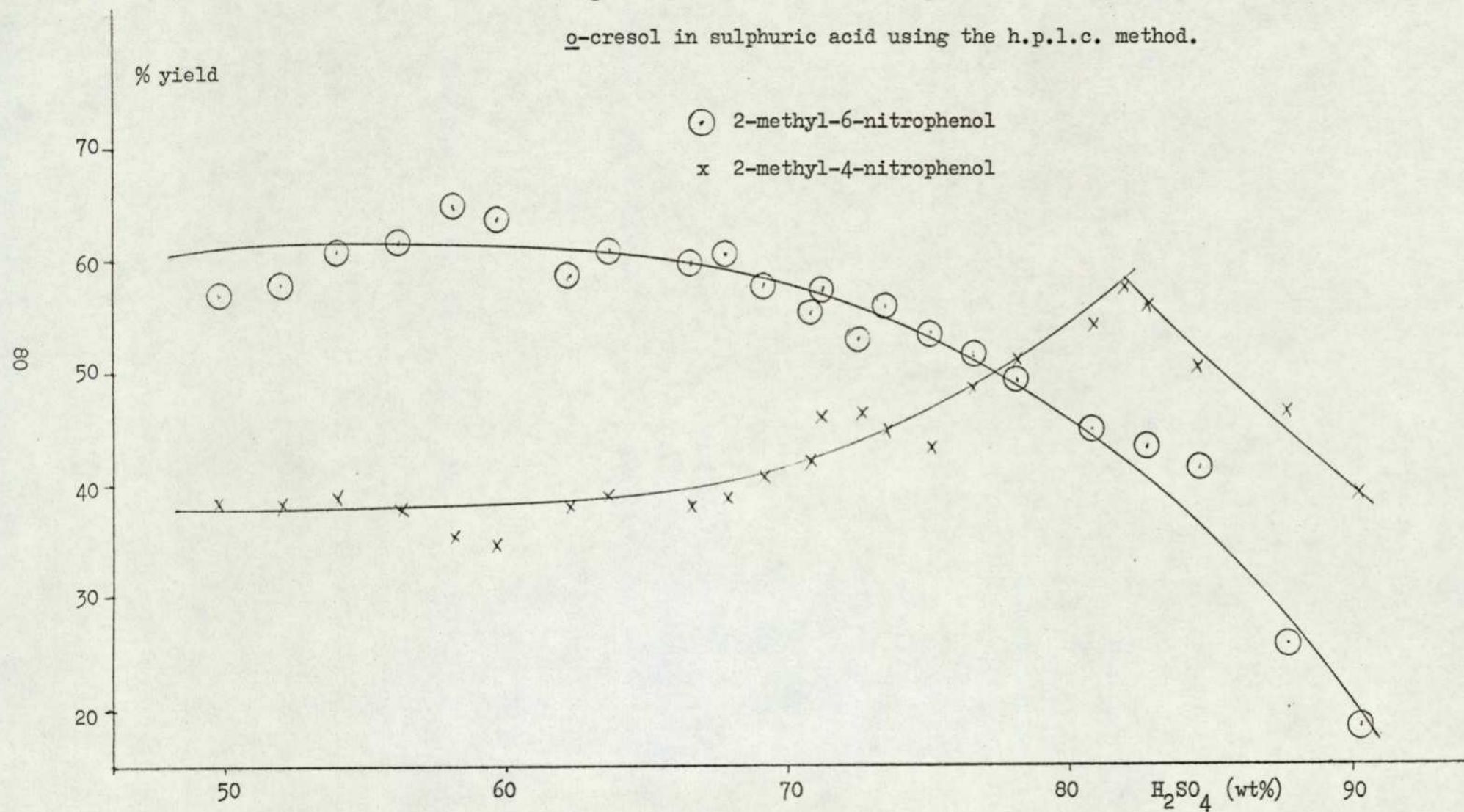
Yields of nitro-compounds^e from the nitration of
o-cresol in sulphuric acid by the h.p.l.c. method

H ₂ SO ₄ (%) ^{a,d}	2-methyl-6-nitro- phenol (%)	2-methyl-4-nitro- phenol (%)	Mass balance (%) ^f
49.8 ^b	56.2	38.3	94.5
52.0 ^b	57.3	38.2	95.5
53.9 ^b	60.8	39.6	100.4
56.1 ^b	61.5	37.8	99.3
58.1 ^b	63.3	37.2	100.5
59.6 ^b	63.5	34.7	98.2
62.4 ^b	58.4	38.2	96.6
63.6 ^b	60.7	40.3	101.0
66.6 ^b	59.7	38.2	97.9
69.1 ^{b,c}	57.7	40.3	98.0
70.8 ^{b,c}	55.3	41.9	97.2
71.2 ^{b,c}	57.5	45.8	103.3
72.5 ^{b,c}	52.5	46.2	98.7
73.4 ^{b,c}	55.2	44.8	100.0
75.2 ^{b,c}	53.4	42.9	96.3
76.6 ^{b,c}	51.4	48.5	99.9
78.2 ^{b,c}	50.5	49.4	99.9
80.8 ^{b,c}	45.1	53.9	99.0
82.8 ^{b,c}	53.3	55.1	98.4
84.6 ^{b,c}	41.4	50.2	91.6
87.8 ^{b,c}	25.8	46.6	72.4
91.3 ^{b,c}	18.1	38.9	57.0

Table 2.14 (continued)

- a) $\pm 0.1\%$ w/w
- b) $[\text{ArH}] = 1.01 \times 10^{-4} \text{ mole dm}^{-3}$
- c) $[\text{HNO}_3] = 1.02 \times 10^{-4} \text{ mole dm}^{-3}$
- d) $[\text{Sulphamic acid}] \text{ ca } 0.05 \text{ mole dm}^{-3}$
- e) 2-Methyl-3-nitrophenol ($< 0.2\%$) and 2-methyl-5-nitrophenol ($< 0.2\%$) were not found.
- f) $\pm 2\%$

Fig. 2.14 Yields of nitro-compounds from the nitration of o-cresol in sulphuric acid using the h.p.l.c. method.



Smilarly : % of 2-methyl-6-nitrophenol = 60.8 %

Table 2.14 and Fig. 2.14 give the yields of nitro-compounds from the nitration of o-cresol in various concentrations of aqueous sulphuric acid using the h.p.l.c. method.

2.322 m-CRESOL

Typical calculation of the yields by h.p.l.c. :-

Sulphuric acid	: 66.3% w/w
Amount of nitric acid	: 1.48×10^{-4} moles
Amount of <u>m</u> -cresol	: 1.47×10^{-4} moles
Amount of reference standard	
2-methyl-3-nitrophenol	: 1.09×10^{-4} moles

Fig. 2.15 shows the chromatogram obtained (h.p.l.c. conditions as in Table 2.2).

Peak weights from chromatogram (Fig. 2.15)

Compound	Weight/g
3-methyl-2-nitrophenol	0.0160
3-methyl-4-nitrophenol	0.1010
3-methyl-6-nitrophenol	0.0830
2-methyl-3-nitrophenol (reference standard)	0.0350

The method of relative response factors (Section 7.5) was used.

$$c_x/c_s = A_x/A_s \times f$$

Factor f for 3-methyl-2-nitrophenol : 0.57

Factor f for 3-methyl-4-nitrophenol : 0.17

Factor f for 3-methyl-6-nitrophenol : 0.26

∴ Amount of 3-methyl-2-nitrophenol =

$$= \frac{0.0160}{0.0350} \times 1.09 \times 10^{-4} \times 0.57 \text{ moles}$$

$$= 2.81 \times 10^{-5} \text{ moles}$$

Fig. 2.15 Chromatogram of the products from the nitration of m-cresol in 66.3% sulphuric acid

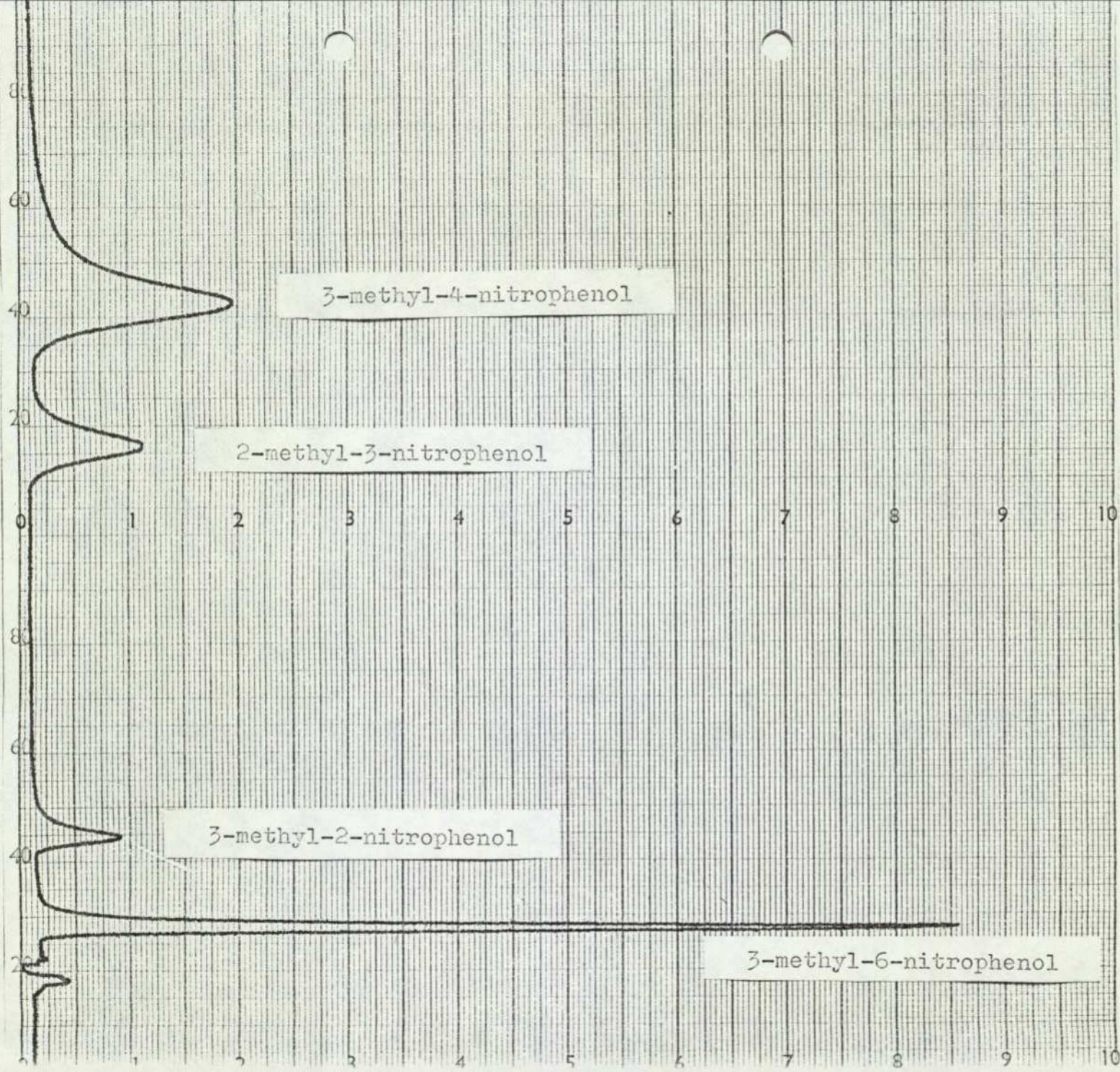


Table 2.15

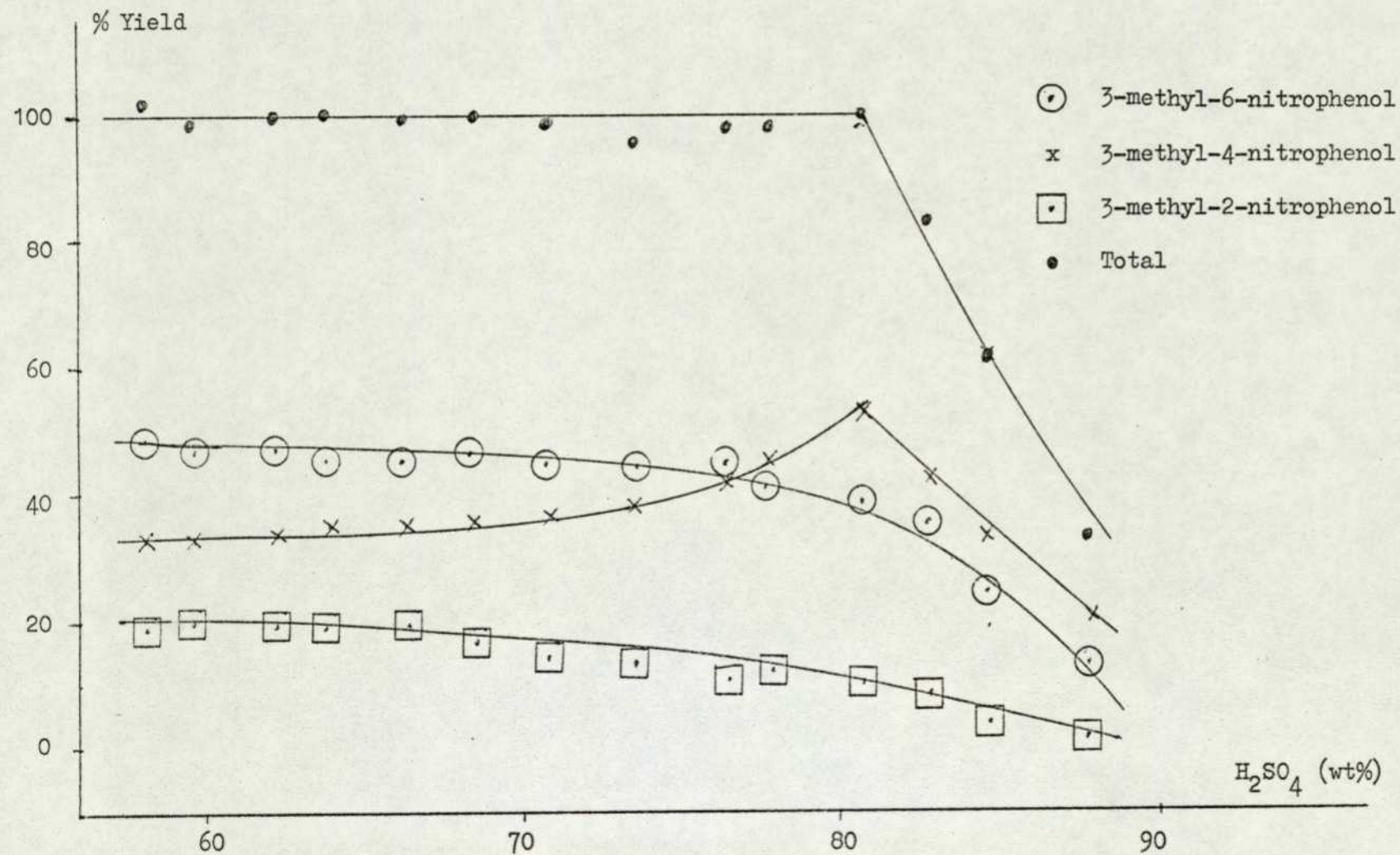
Yields of nitro-compounds^e from the nitration
of o-cresol^{b,c} in sulphuric acid at $25.0 \pm 0.2^{\circ}$

H_2SO_4 (%) ^a	3-methyl- 2-nitro- phenol	3-methyl- 4-nitro- phenol	3-methyl- 6-nitro- phenol	Mass balance (%) ^f
58.1	18.5	33.0	48.8	100
59.6	19.5	33.1	46.6	99
62.2	19.6	33.9	46.6	101
63.8	18.9	33.2	46.3	100
66.3 ^d	19.0	35.4	45.0	99
68.5 ^d	15.4	35.9	46.7	100
70.8 ^d	14.2	36.3	44.0	98
73.4 ^d	13.3	38.1	43.8	95
76.5 ^d	10.6	42.3	44.7	98
77.6 ^d	12.8	44.5	39.9	97
80.8 ^d	9.7	52.3	37.9	100
82.8 ^d	8.0	40.6	35.2	83
84.6 ^d	3.0	33.1	25.0	61
87.7 ^d	1.6	18.2	12.4	32

Table 2.15 (continued)

- a) $\pm 0.1\%$ w/w
- b) $[\text{ArH}] = 5.88 \times 10^{-3} \text{ mole dm}^{-3}$
- c) $[\text{Sulphanilic acid}] \underline{\text{ca}} 0.05 \text{ mole dm}^{-3}$
- d) $[\text{HNO}_3] = 5.92 \times 10^{-3} \text{ mole dm}^{-3}$
- e) No 3-methyl-5-nitrophenol was detected ($< 0.3\%$)
- f) $\pm 2\%$

Fig. 2.16 Yields of nitro-compounds from
the nitration of m-cresol in sulphuric acid



$$\begin{aligned}\% \text{ of 3-methyl-2-nitrophenol} &= \frac{2.81 \times 10^{-5}}{1.47 \times 10^{-4}} \times 100 \\ &= 19.0 \%\end{aligned}$$

Similarly :

$$\% \text{ of 3-methyl-4-nitrophenol} = 35.4 \%$$

$$\% \text{ of 3-methyl-6-nitrophenol} = 45.0 \%$$

Table 2.15 and Fig. 2.16 give the yields of the nitro-products from the nitration of m-cresol in various concentrations of aqueous sulphuric acid.

2.323 3,5-DIMETHYLPHENOL

Typical calculation of the yields by h.p.l.c. :-

Sulphuric acid	: 62.2% w/w
Amount of 3,5-dimethylphenol	: 5.21×10^{-5} moles
Amount of nitric acid	: 5.82×10^{-4} moles
Amount of reference standard	
<u>p</u> -nitroanisole	: 2.55×10^{-5} moles

Fig. 2.17 shows the chromatogram obtained (h.p.l.c. conditions as in Table 2.3).

Peak weights from chromatogram

Compound	Weight/g
3,5-dimethyl-2-nitrophenol	0.0199
3,5-dimethyl-4-nitrophenol	0.0037
<u>p</u> -nitroanisole	0.0305

The method of relative response factors (Section 7.5) was used.

$$c_x/c_s = A_x/A_s \times f$$

$$\text{Factor } f \text{ for 3,5-dimethyl-2-nitrophenol} : 1.85$$

$$\text{Factor } f \text{ for 3,5-dimethyl-4-nitrophenol} : 5.40$$

∴ Amount of 3,5-dimethyl-2-nitrophenol =

$$= \frac{0.0199}{0.0305} \times 2.55 \times 10^{-5} \times 1.85 \text{ moles}$$

$$= 3.42 \times 10^{-5} \text{ moles}$$

$$\% \text{ of 3,5-dimethyl-2-nitrophenol} = \frac{3.42 \times 10^{-5}}{5.21 \times 10^{-5}} \times 100$$

$$= 65.6 \%$$

Similarly:

$$\% \text{ of 3,5-dimethyl-4-nitrophenol} = 32.1 \%$$

Table 2.16 and Fig. 2.18 give the yields of the products from the nitration of 3,5-dimethylphenol in various concentrations of aqueous sulphuric acid.

2.324 o-METHYLANISOLE

2-Methyl-6-nitrophenol was identified as one of the products from the nitration of o-methylanisole in sulphuric acid by its retention time on h.p.l.c. analysis (see below) and in addition the combined extracts from a series of reactions were concentrated and the 2-methyl-6-nitrophenol was separated by preparative t.l.c. (20% AcOEt/cyclohexane). Its identity was confirmed by its $^1\text{H.n.m.r.}$ spectrum, τ 7.76 (3H, s, ArCH_3), 3.12 (1H, t, H-4, $J_{3,4} = J_{4,5} = 4\text{Hz}$), 2.52 (1H, d, H-3, $J_{3,4} = 4\text{Hz}$), 2.23 (1H, d, H-5, $J_{4,5} = 4\text{Hz}$), which was identical to that of an authentic sample.

2-Methyl-4-nitrophenol was not detected and was not present to a greater extent than 0.1%.

Typical calculation of the yields of 2-methyl-6-nitrophenol by h.p.l.c:-

Fig. 2.17 Chromatogram of the products from the nitration of 3,5-dimethylphenol in 62.2% sulphuric acid

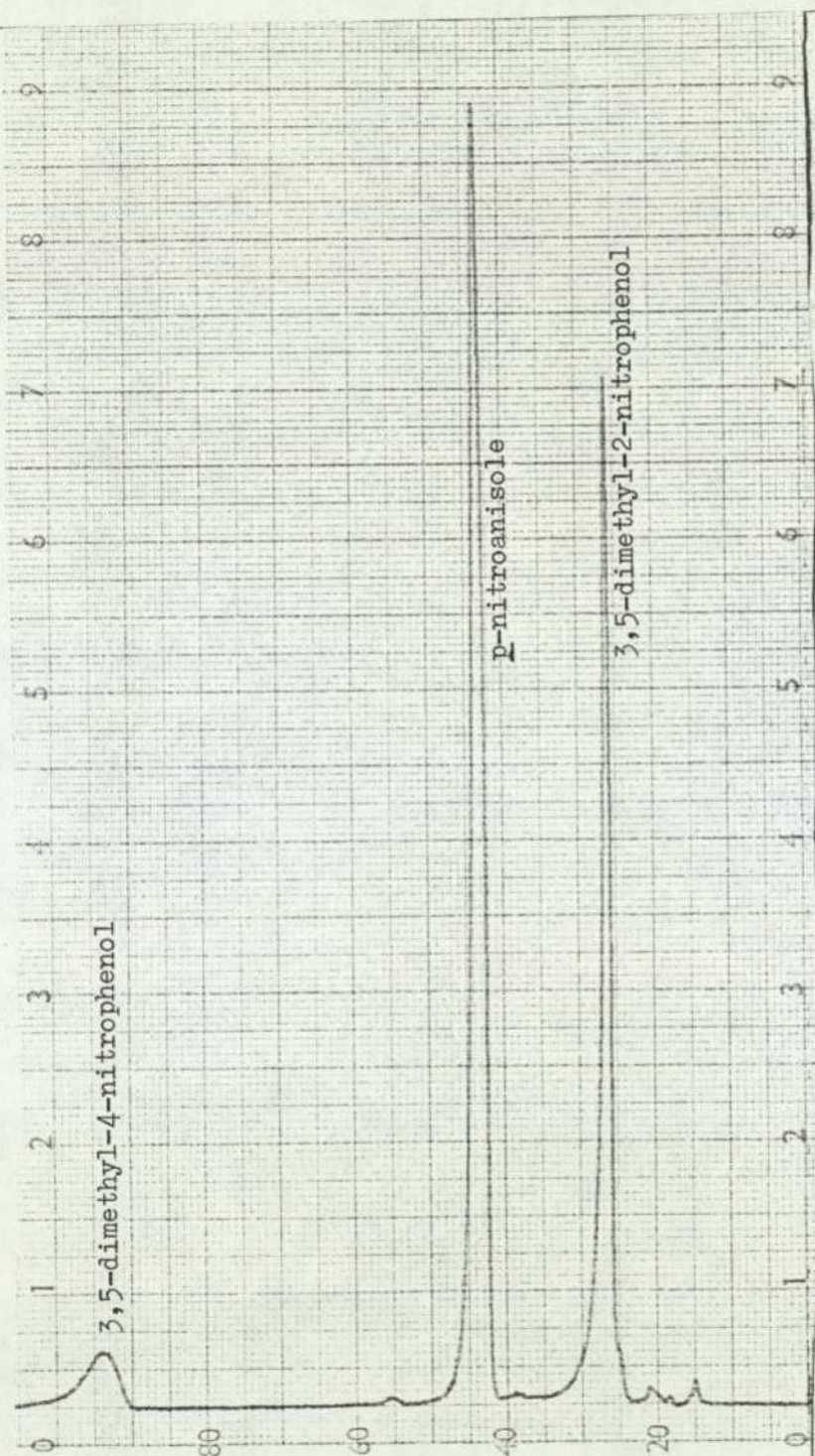


Table 2.16

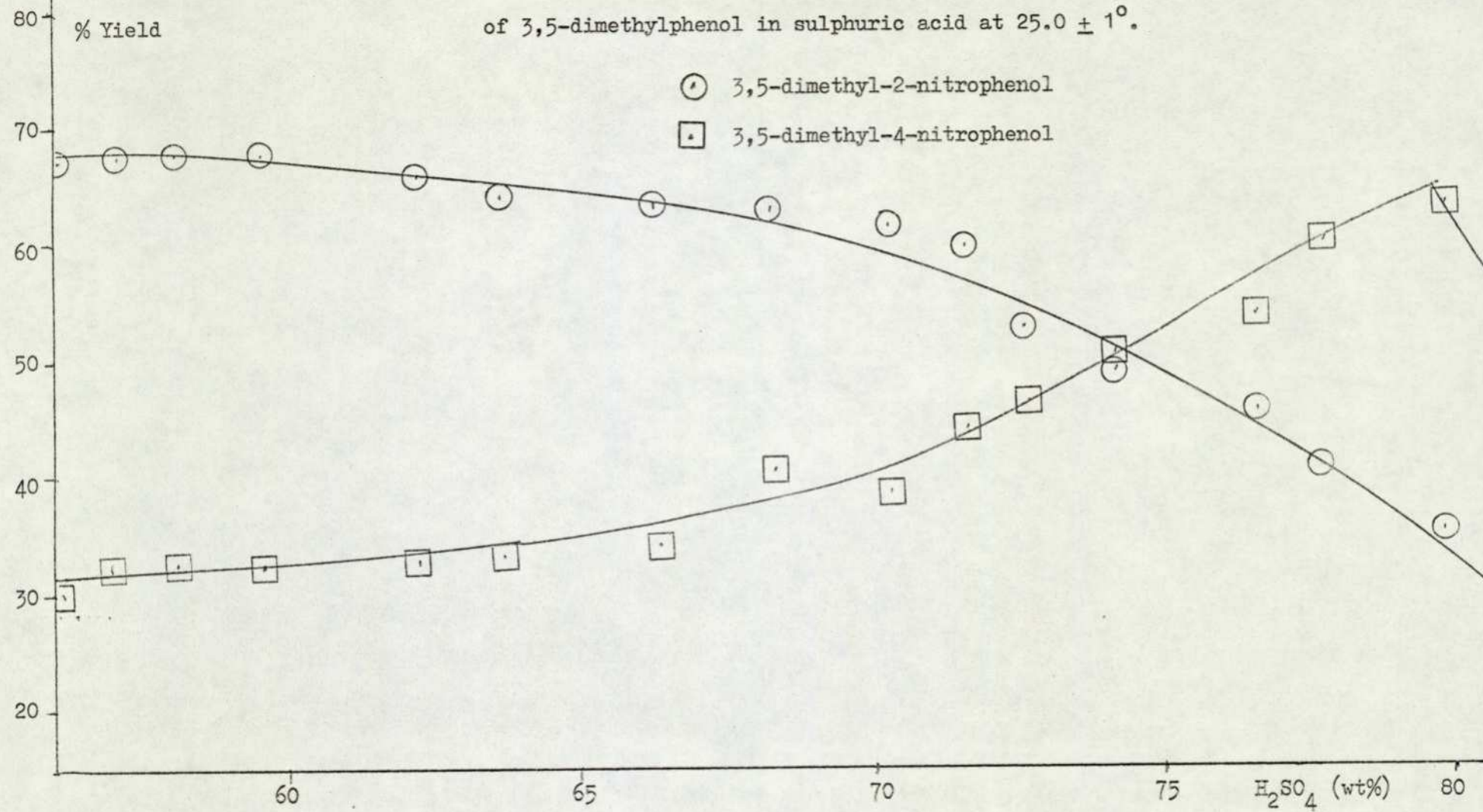
Yields of nitro-compounds from the nitration of
 3,5-dimethylphenol^{b,c} in sulphuric acid at $25.0 \pm 0.2^{\circ}$

H_2SO_4 (%) ^a	3,5-dimethyl- 2-nitrophenol	3,5-dimethyl- 4-nitrophenol	Mass balance (%) ^e
56.1	67.2	30.0	97
58.1	68.5	34.5	103
59.6	68.2	34.5	103
62.2	65.6	32.1	98
63.7	63.7	33.0	97
66.3 ^d	62.7	33.4	96
68.3 ^d	63.3	40.3	104
70.3 ^d	61.4	38.0	99
71.6 ^d	59.3	43.7	103
72.7 ^d	51.8	45.5	97
74.3 ^d	48.6	49.9	98
76.7 ^d	45.1	52.7	98
77.7 ^d	40.1	58.5	99
79.1 ^d	34.7	62.5	97
81.6 ^d	23.4	48.0	71
84.7 ^d	16.7	36.5	53

Table 2.16 Continued)

- a) $\pm 0.1\%$ w/w
- b) $[\text{ArH}] = 2.08 \times 10^{-3} \text{ mole dm}^{-3}$
- c) $[\text{Sulphanilic acid}] \text{ ca } 0.05 \text{ mole dm}^{-3}$
- d) $[\text{HNO}_3] = 2.11 \times 10^{-3} \text{ mole dm}^{-3}$
- e) $\pm 2\%$

Fig, 2.18 Yields of nitro-compounds from the nitration of 3,5-dimethylphenol in sulphuric acid at $25.0 \pm 1^\circ$.



Sulphuric acid	: 62.2% w/w
Amount of <u>o</u> -methylanisole	: 7.22×10^{-5} moles
Amount of nitric acid	: 1.38×10^{-3} moles
Amount of reference standard	
<u>m</u> -nitrophenol	: 6.48×10^{-5} moles

Fig 2.19 shows the chromatogram obtained (h.p.l.c. conditions as in Table 2.4).

Peak weights from chromatogram

Compound	Weight/g.
2-methyl-6-nitrophenol	0.0200
<u>m</u> -nitrophenol (standard)	0.0285

The method of relative response factors was used (Section 7.5).

$$c_x/c_s = A_x/A_s \times f$$

Factor f for 2-methyl-6-nitrophenol : 0.34

∴ Amount of 2-methyl-6-nitrophenol =

$$= \frac{0.0200}{0.0285} \times 6.48 \times 10^{-5} \times 0.341 \text{ moles}$$

$$= 1.54 \times 10^{-5} \text{ moles}$$

$$\% \text{ of 2-methyl-6-nitrophenol} = \frac{1.54 \times 10^{-5}}{7.22 \times 10^{-5}} \times 100$$

$$= 21.3\%$$

The yields of 2-methyl-6-nitrophenol are given in Table 2.17 together with yields of the 2-methylnitroanisoles taken from an earlier study⁵⁰.

2-Methyl-6-nitroanisole (3×10^{-3} mole dm^{-3}) was recovered essentially quantitatively (101%) from a solution in 58.1% sulphuric acid after 48 hours at 25°.

Fig. 2.19 Chromatogram of the products from the nitration of o-methylanisole in 62.2% sulphuric acid

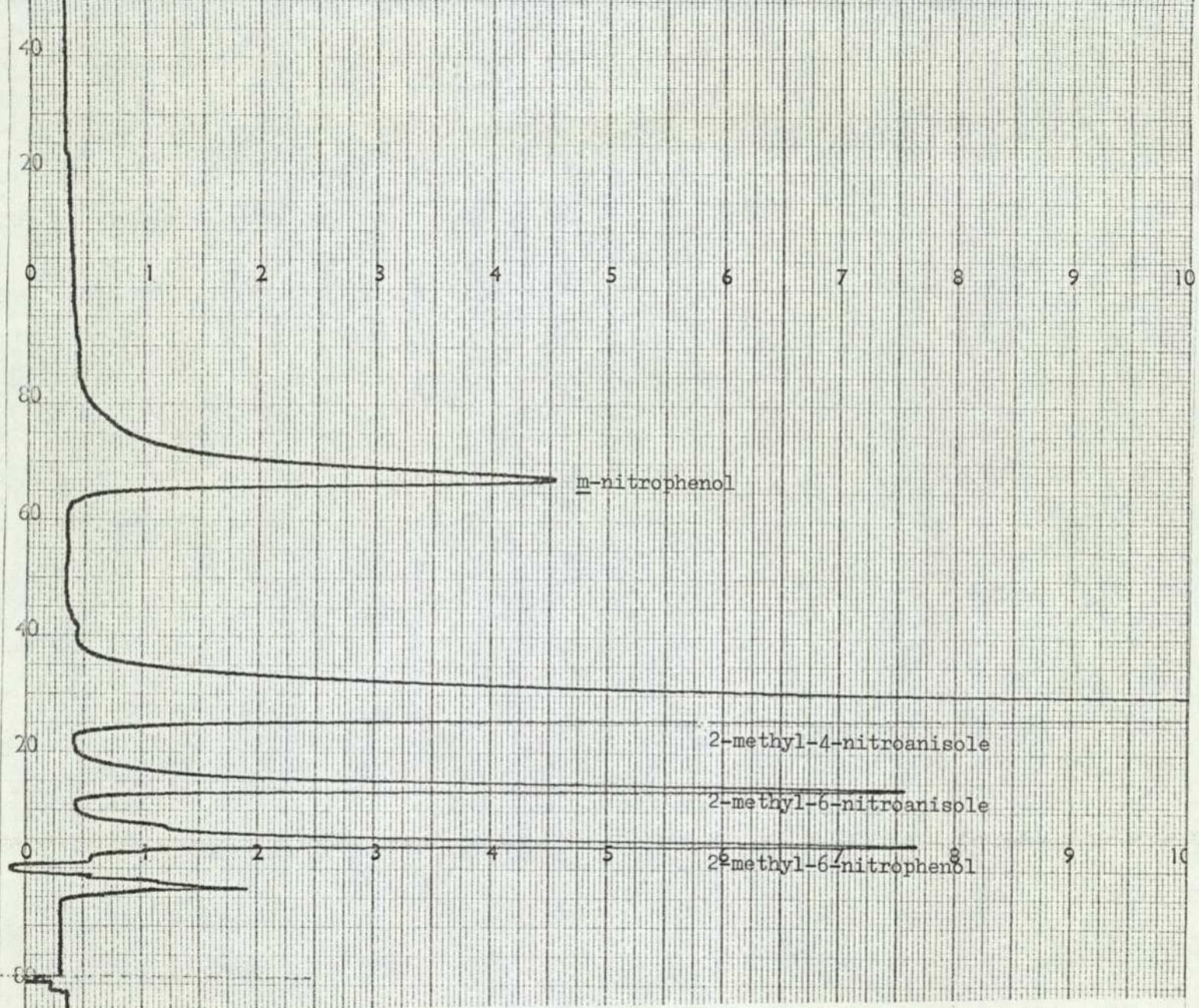


Table 2.17

Yields of nitro-compounds from the nitration of
o-methylanisole^{b,c} in sulphuric acid at $25.0 \pm 0.2^\circ$

H_2SO_4 (%) ^{a,d}	2-methyl- 6-nitro- phenol ^e	2-methyl- 4-nitro- anisole ^f	2-methyl- 6-nitro- anisole ^f	Mass balance (%) ^g
56.1	38.8	44	23	106
58.1	34.6	39	25	99
59.1	32.3	40	23	95
59.6	27.4	40	23	90
62.2	21.3	41	28	90

a) $\pm 0.1\%$ w/w

b) $[\text{ArH}] = 2.88 \times 10^{-3} \text{ mole dm}^{-3}$

c) $[\text{HNO}_3] = 2.3 - 5.5 \times 10^{-2} \text{ mole dm}^{-3}$

d) $[\text{Sulpamic acid}] \text{ ca } 0.05 \text{ mole dm}^{-3}$

e) 2-Methyl-4-nitrophenol was not found ($< 0.1\%$)

f) Values from Ref. 50

g) $\pm 2\%$

2.325 p-ISOPROPYLANISOLE

Typical calculation of the yields by h.p.l.c:-

Sulphuric acid	: 59.6% w/w
Amount of <u>p</u> -isopropylanisole	: 4.89×10^{-5} moles
Amount of nitric acid	: 2.5×10^{-3} moles
Amount of reference standard	
2-methyl-3-nitrophenol	: 3.66×10^{-5} moles

Fig. 2.20 shows the chromatogram obtained (h.p.l.c. conditions as in Table 2.5)

Peak weights from chromatogram

Compound	Weight/g
<u>p</u> -nitrophenol	0.0128
<u>p</u> -nitroanisole	0.0153
4-isopropyl-2-nitrophenol	0.0048
4-isopropyl-2-nitroanisole	0.0365
2-methyl-3-nitrophenol (standard)	0.0283

The method of relative response factors was used (Section 7.5).

$$c_x/c_s = A_x/A_s \times f$$

Factor f for <u>p</u> -nitrophenol	: 0.13
Factor f for <u>p</u> -nitroanisole	: 0.10
Factor f for 4-isopropyl-2-nitrophenol	: 0.96
Factor f for 4-isopropyl-2-nitroanisole	: 0.82

∴ Amount of p-nitroanisole =

$$= \frac{0.0153}{0.0283} \times 3.66 \times 10^{-5} \times 0.10 \text{ moles}$$

$$= 1.98 \times 10^{-6} \text{ moles}$$

Fig. 2.20 Chromatogram of the products from the nitration of *p*-isopropylphenol in 59.6% sulphuric acid

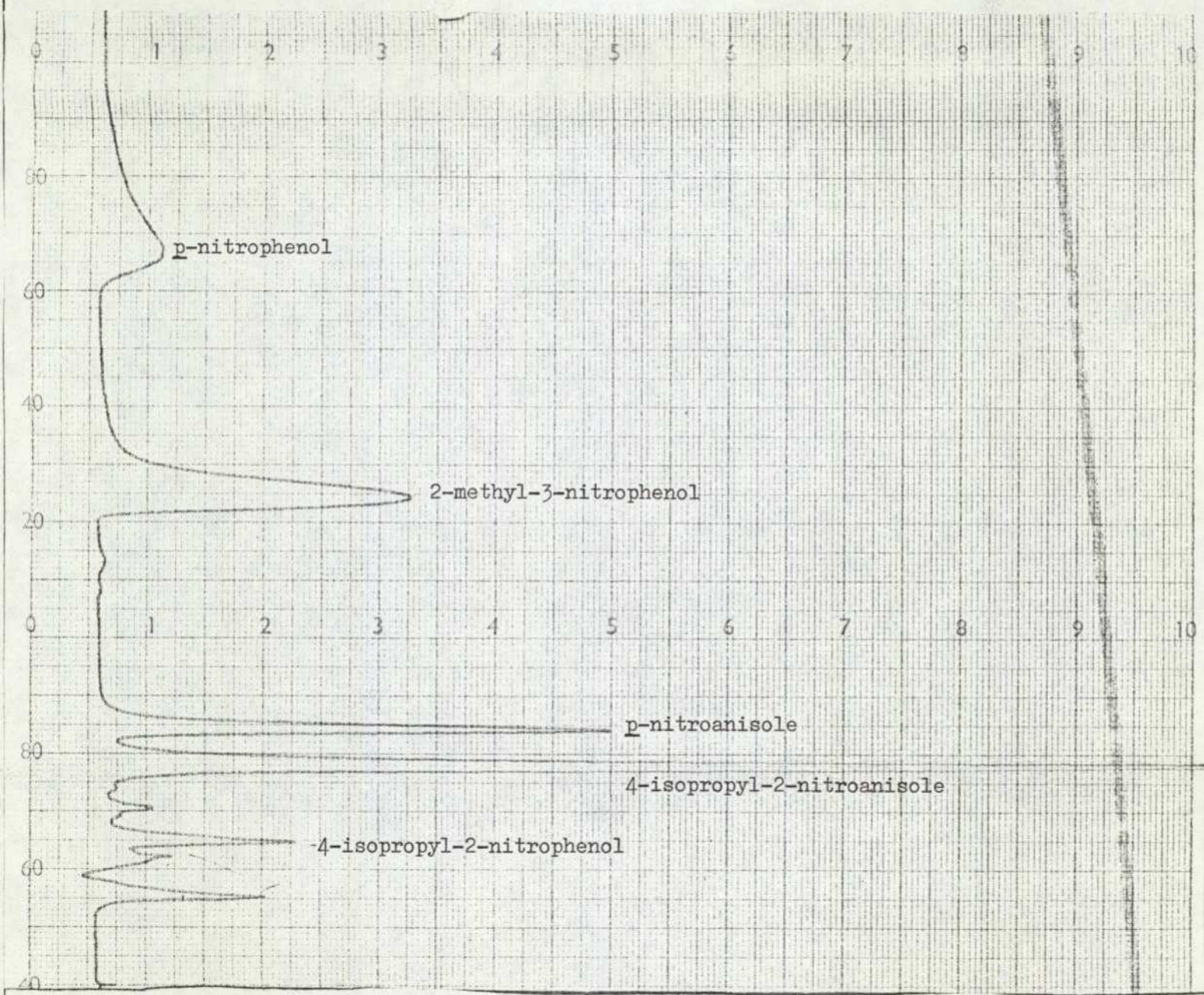


Table 2.18

Yields of nitro-compounds from the nitration of
p-isopropylanisole^{b,c} in sulphuric acid at $25.0 \pm 0.2^\circ$

H_2SO_4 (%) ^{a,d}	p-nitro- phenol	p-nitro- anisole	4-isopropyl- 2-nitro- phenol	4-isopropyl- 2-nitro- anisole ^f	Mass balance (%) ^e
56.1	3.2	1.6	15.9	77.7	98
58.1	3.7	2.6	16.1	76.7	99
59.6	4.2	4.0	12.2	76.7	97
62.2	4.3	8.6	11.6	74.7	99

a) $\pm 0.1\%$ w/w

b) $[ArH] = 1.88 \times 10^{-4} \text{ mole dm}^{-3}$

c) $[HNO_3] = 0.06 \text{ mole dm}^{-3}$

d) $[Sulphanilic \text{ acid}] \text{ ca } 0.05 \text{ mole dm}^{-3}$

e) $\pm 2\%$

f) The response factor for this compound was calculated by
back calculation from the results of a previous study⁶¹

at 62.2% sulphuric acid because the compound provided
was too impure to be used for this determination.

g) The half-lives for reaction were assumed to be similar
to those for p-methylanisole⁵⁰.

$$\begin{aligned}\% \text{ of } p\text{-nitroanisole} &= \frac{1.98 \times 10^{-6}}{4.89 \times 10^{-5}} \times 100 \\ &= 4.0\%\end{aligned}$$

Similarly:

% of <u>p</u> -nitrophenol	: 4.2%
% of 4-isopropyl-2-nitrophenol	: 12.2%
% of 4-isopropyl-2-nitroanisole	: 76.7%

Table 2.18 gives the yields of the nitrocompounds obtained from the nitration of p-isopropylanisole in various concentrations of aqueous sulphuric acid.

2.4 DISCUSSION

2.41 RATE PROFILES

The behaviour of hydroxy substituents in other electrophilic aromatic substitutions reactions suggests that o-cresol, m-cresol and 3,5-dimethylphenol should be reactive enough to be nitrated at the rate of the encounter of the aromatic molecules with nitronium ions. Mesitylene is representative of a number of compounds more reactive than toluene, which give almost exactly the same rate profile^{17,65} which has been identified as the limiting encounter rate. The profiles for o-cresol, m-cresol and 3,5-dimethylphenol are parallel and very close to that for mesitylene. A relatively small spread of observed rates of reaction of compounds sufficiently reactive to react at the encounter rate has been noted previously^{50,65} and the suggestion has been made that hydrogen bonding may be involved in some cases⁵⁰. A point which may be usefully emphasised, however, is that the profiles of many of these reactive compounds have a significantly lower slope than those of less reactive compounds (e.g. benzene and the halogenobenzenes) where diffusion is not the rate-limiting step. This change in slope which has been attributed

to the effect of changing viscosity of the medium on the limiting rate of encounter⁶⁵ may provide a diagnostic test for a substrate in the borderline region. For example, it seems to enable one to distinguish the behaviour of anisole and phenol, the rate profiles of which are parallel to that of mesitylene and for which the reaction is encounter controlled, from that of toluene, for which the rate profile is parallel to that of benzene (in 63 - 68% sulphuric acid) and for which the reaction is not encounter controlled in this region. It is therefore concluded that o-cresol, m-cresol and 3,5-dimethylphenol are reacting with the nitronium ion at or very near the rate of encounter.

2.42 ISOMER PROPORTIONS

In 50 - 83% sulphuric acid o-cresol is quantitatively mononitrated and the 6-nitro : 4-nitro product ratio changes from 1.5 to 0.8 (Table 2.14 and Fig. 2.14) with the percentage of substitution para to the hydroxy group increasing from 38 to 55%. (The two methods of product estimation gave excellent agreement.) This behaviour is closely similar to that previously reported^{50,66} for anisole and phenol, where the proportion of para substitution increased from 36 to 56% and from 30 to 53% respectively although in the case of o-cresol this value is more constant over the range of 50 - 68% sulphuric acid. For m-cresol, (Table 2.15 and Fig. 2.16) where two products of ortho-substitution are observed, the proportion of para-substitution increases from 33 to 52% over the range of 58 - 81% sulphuric acid. In the case of 3,5-dimethylphenol (Table 2.16 and Fig. 2.18) the 2-nitro : 4-nitro ratio varies from 2.2 to 0.56 over 56 - 79% sulphuric acid with the percentage of para-substitution increasing from 30 to 62%.

o-Cresol and m-cresol are substrates that have been activated to electrophilic substitution by the methyl group oriented either meta or ortho, and para respectively to the position where substitution occurs. If the mechanism proposed for anisole⁵⁰ and phenol⁶⁶ in Scheme 1.4 is applicable to these substrates it might be expected that the increased reactivity would lead to Wheland intermediate formation competing more effectively with loss of the hydrogen bonded hydronium ion. It would, therefore, be expected that isomer ratios resulting from reaction of the hydrogen-bonded encounter pair would persist to lower acidities the more activated the substrate, and that the acidity range where changes of isomer ratio occurred would also move to lower values of acidity. The picture that emerges, however, is of a qualitatively similar change in isomer ratios over the same range of acidity for anisole, phenol and o- and m-cresol. These changes are much larger than those usually present for the nitration of alkylbenzenes (e.g. toluene⁴⁸, ethylbenzene⁶⁷ and o-diethylbenzene⁶⁸) and certainly appear to require a special explanation. If the mechanism in Scheme 1.4 is indeed applicable to these systems it follows that the increased reactivity to electrophilic substitution conferred by the additional methyl group has had an effect which is too small to be detected. In the case of 3,5-dimethylphenol, however, where two methyl groups are activating the substrate towards electrophilic substitution, the region of isomer ratio change has indeed shifted to lower acidities (by about 4 - 6% sulphuric acid). This shift is similar in magnitude to that observed in the case of comparison between 3,5-dimethylanisole and anisole in perchloric acid⁵³. It must be concluded that the effect of activating methyl substitution is undetectable unless two such groups are present. The

effect of the substituents on the rate of loss of the hydrogen bond may be relevant to this conclusion and it is also conceivable that an equilibrium is set up between the two encounter pairs of Scheme 1.4.

This observation of a general medium effect on the isomer ratios from the nitration of hydroxy- and methoxy-substituted compounds of this type is, however, apparently at variance with the earlier results on the nitration of p-methylanisole⁵⁰. In this case the ratio of substitution para to the methoxy group to that ortho was approximately constant over the range 46 - 80% sulphuric acid (Fig. 2.19)⁵⁰. However para-substitution (ipso to C-Me) was measured by the amount of a demethylated product formed (Scheme 2.1)⁵⁰ and in the region 80 - 82% sulphuric acid this fell rapidly, to be replaced by the ortho-substituted product, presumably as the rate of demethoxylation failed to compete effectively with the return of the ipso-substituted Wheland intermediate to the encounter pair. This effect, however, may occur over a wider range of acidity and over the range ca 70 - 80% sulphuric acid the amount of demethylated product may be progressively lowered to be replaced by the ortho-substituted product. This trend would be the opposite of that expected by the general medium effect described above and it is possible that the combination of the two phenomena gives fortuitously an approximately constant ratio of the two products.

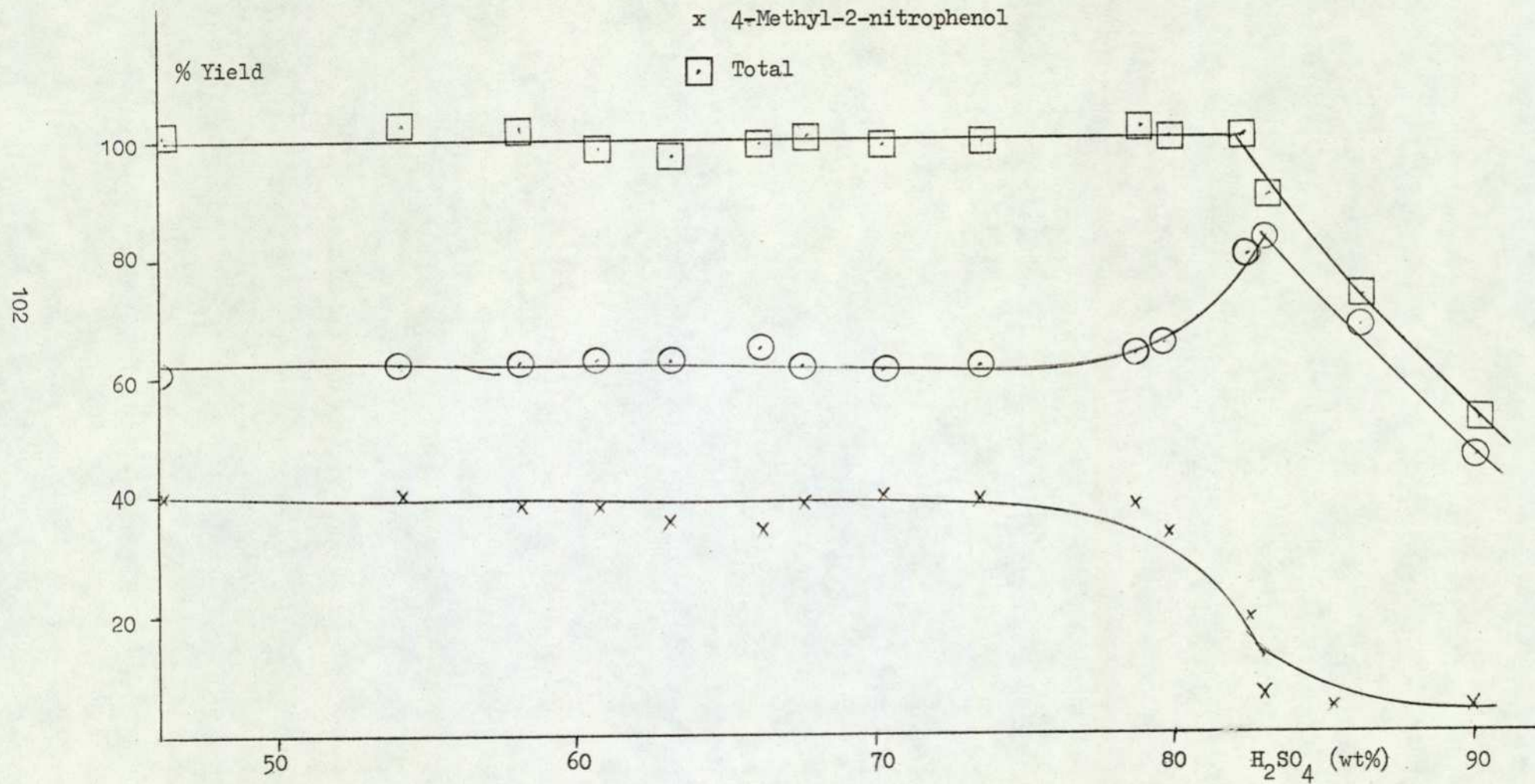
The pattern of products from o-cresol contrasts with the published data from o-methylanisole (Fig. 2.20)⁵⁰ where the total yield of nitro compounds was not quantitative in media below 68% sulphuric acid. In both cases ipso-substitution at C-Me is to be expected. The reinvestigation of the nitration of o-methylanisole establishes that 2-methyl-6-nitrophenol, but not the 4-nitro isomer, is an additional product of the reaction. With the recognition of this product the

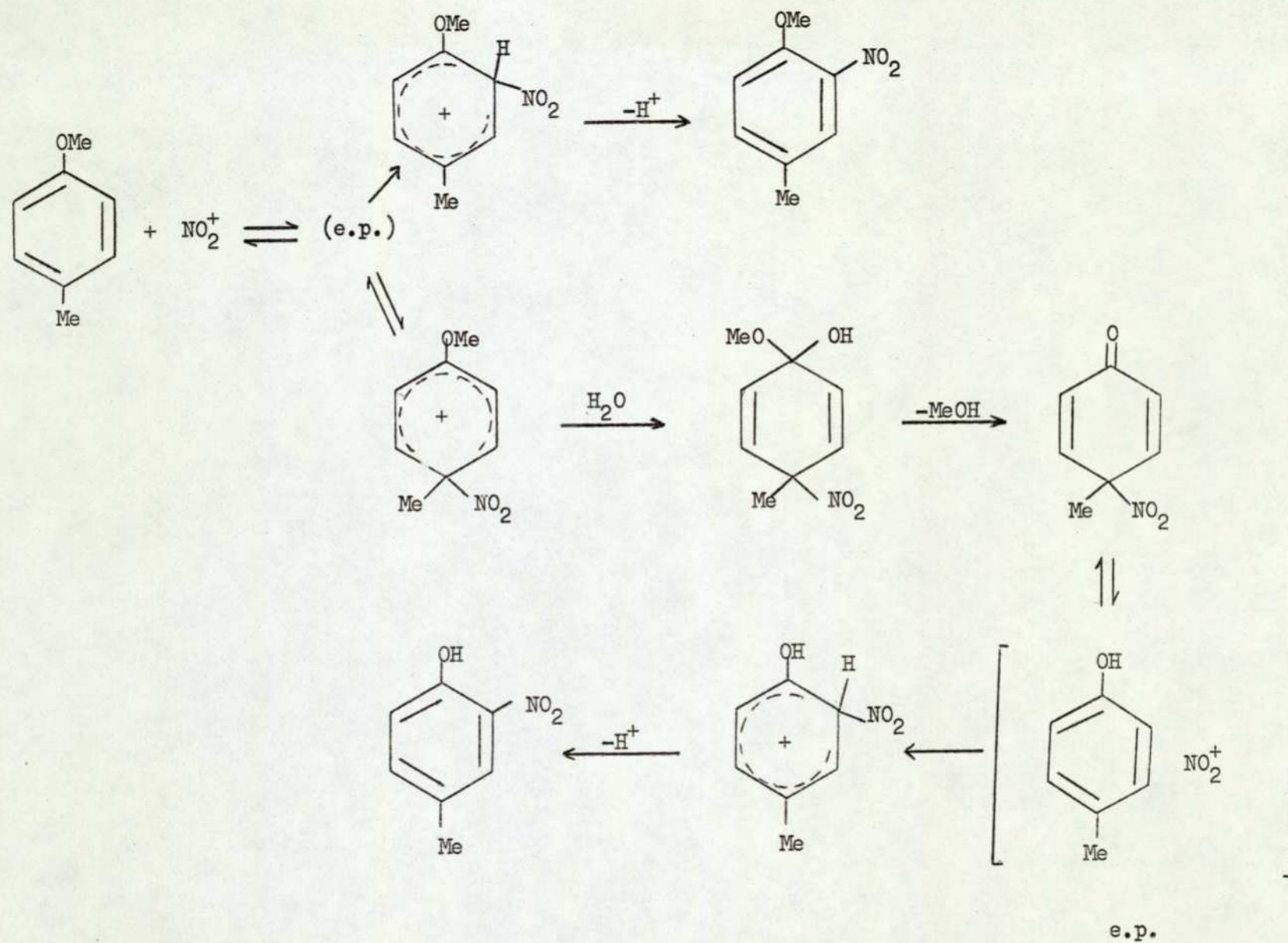
Fig. 2.19 Yields of nitro compounds from the nitration of p-methylanisole

○ 4-Methyl-2-nitroanisole

x 4-Methyl-2-nitrophenol

□ Total





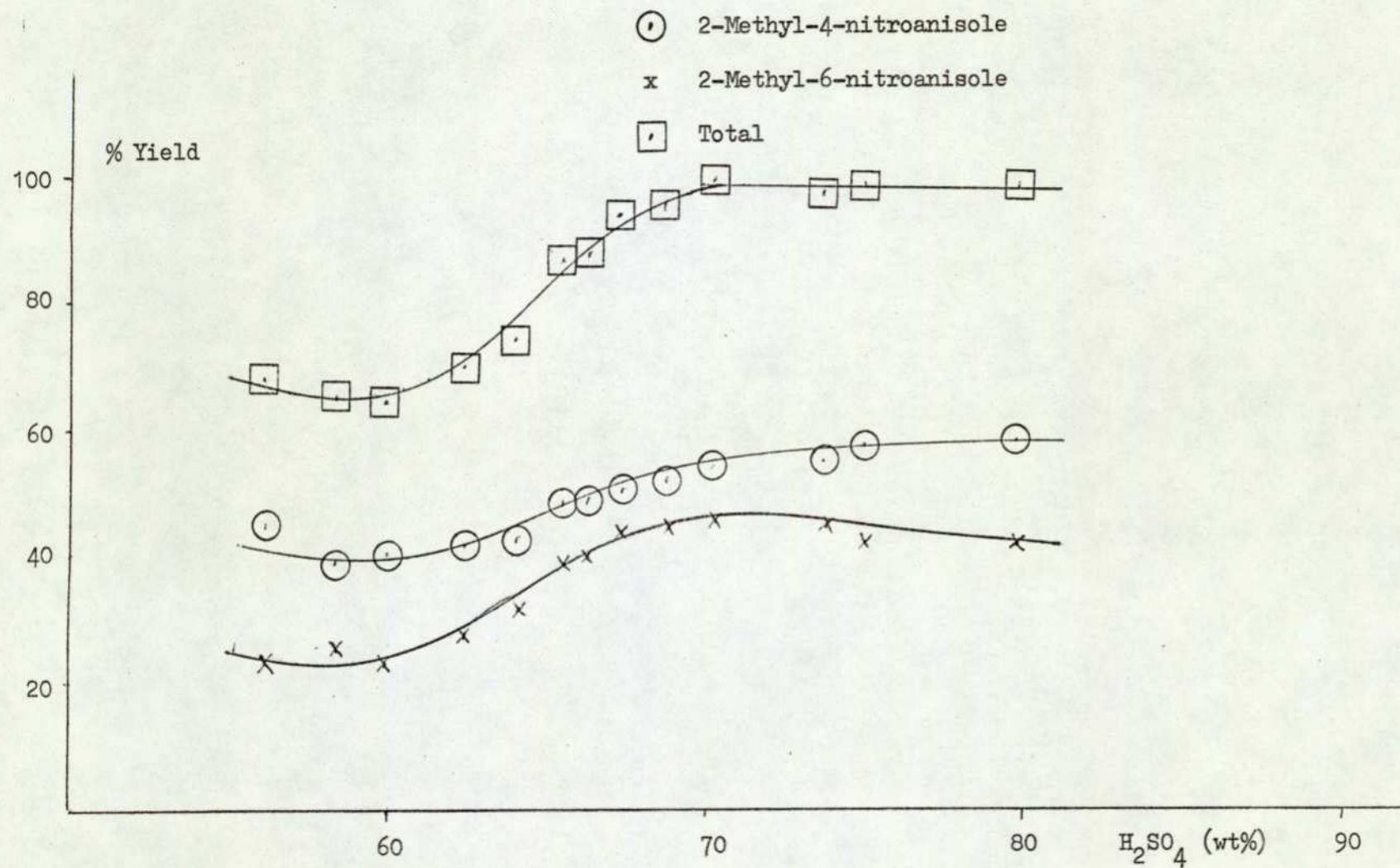
Scheme 2.1

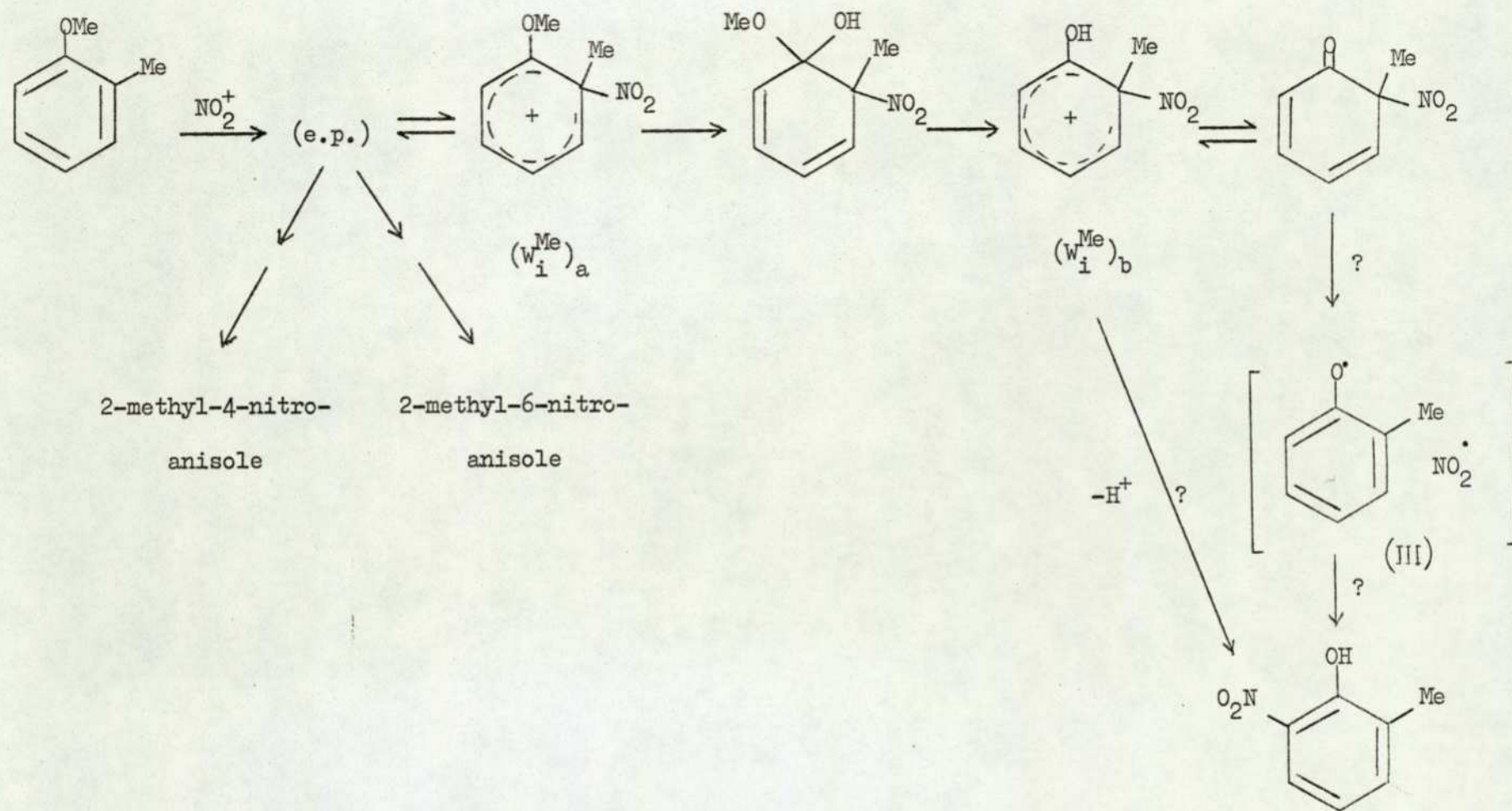
yields become reasonably quantitative (Table 2.17). Demethylation prior to nitration seems unlikely and is ruled out by the absence of 4-nitro isomer, which would have been formed from o-cresol. The previous observation that 2-methyl-6-nitroanisole is stable for the duration of a nitration experiment was also confirmed. It is then suggested, that this demethoxylation is the consequence of ipso-substitution at C-Me (Scheme 2.2). This forms $(W_i^{Me})_a$ which is captured by water at low acidities to form $(W_i^{Me})_b$, protonated 2-methyl-2-nitrocyclohexadienone, by demethoxylation. The pathway by which the 2-methyl-6-nitrophenol is then formed is speculative. Heterolytic fission of the C-N bond in $(W_i^{Me})_b$ to form an o-cresol nitronium ion encounter pair can be ruled out as some 2-methyl-4-nitrophenol would then be formed. Any postulated heterolytic route must involve a specific 1,3-rearrangement. Homolytic fission in the unprotonated 2-methyl-2-nitrocyclohexa-3,5-dien-1-one to give (III) (see Scheme 2.2) is another possibility to be considered, and it may be that the specific 1,3-rearrangement of the nitro group to the 6-position is associated with the presence of the oxygen substituent facilitating the process, perhaps by involving phenyl nitrate as an intermediate.

It has also been pointed out¹³² that the required rearrangement of the σ -complex (X) can be drawn as a 1,3-sigmatropic shift (Scheme 2.3, path a). The alternative analogous rearrangement of (X) to the 4-nitro compound (path b) could be disfavoured by the electron distribution in (X).

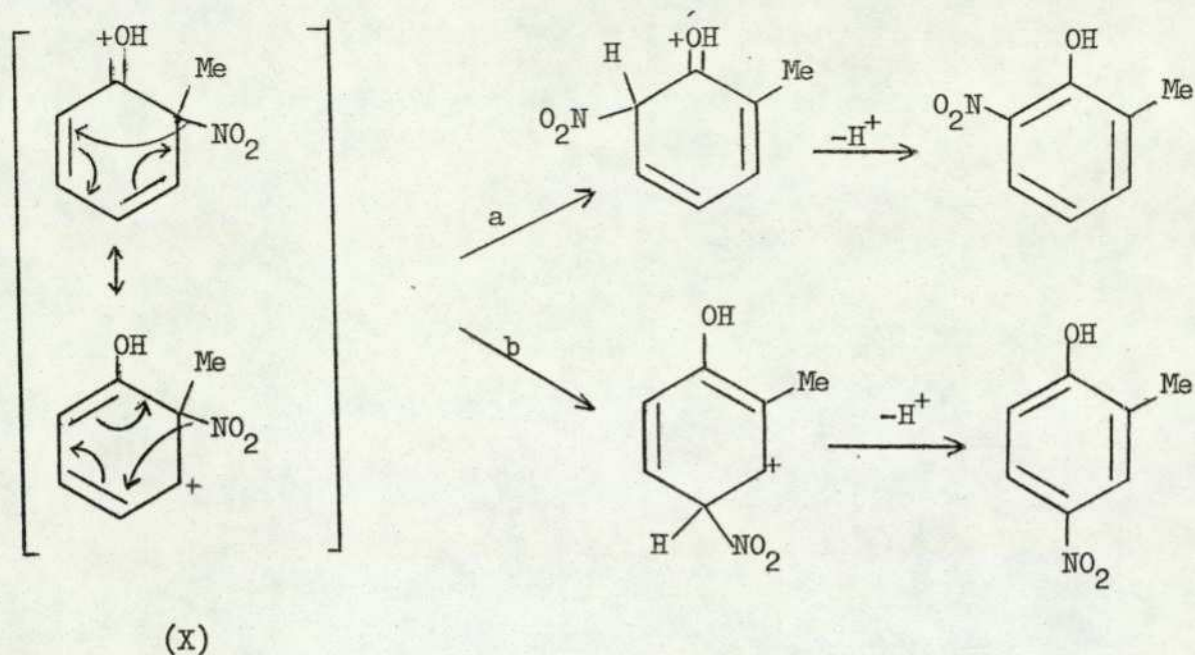
Any of these mechanisms imply that a significant but unquantified amount of the 2-methyl-6-nitrophenol formed during the nitration of o-cresol itself, in at least up to 70% sulphuric acid, involves ipso-substitution at C-Me, proton loss and rearrangement.

Fig. 2.20 Yields of nitro compounds from the nitration of o-methylanisole⁵⁰





Scheme 2.2



Scheme 2.3

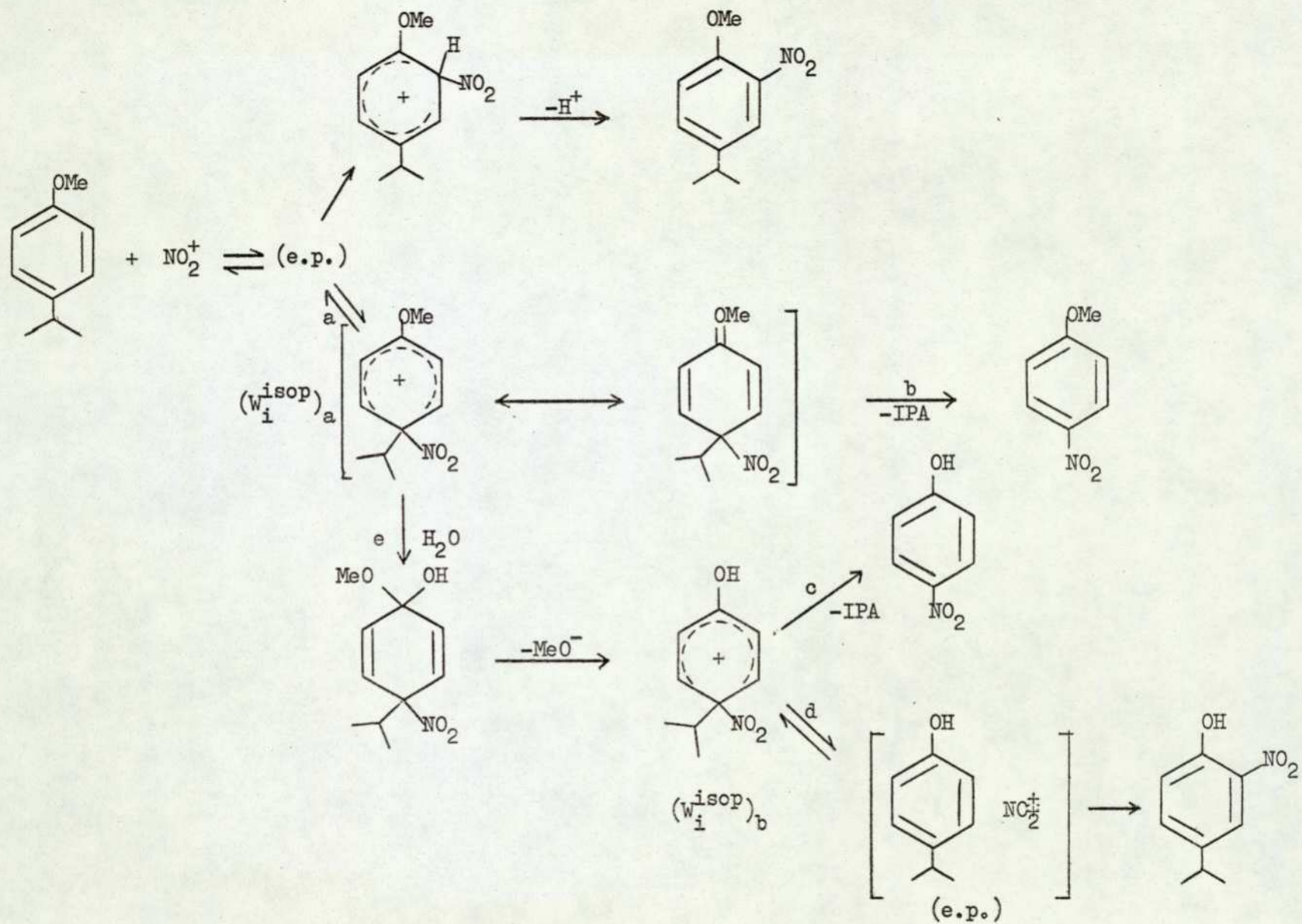
If the fate of $(W_i^{\text{Me}})_a$ when demethoxylation does not occur is to return to the encounter pair, then the ratio of 2-methyl-6-nitroanisole to the 4-nitro isomer does not vary in the way expected from the general medium effect on these compounds. However, if it is assumed that ipso-substitution can only result in demethoxylation or the formation of 2-methyl-6-nitroanisole, then the behaviour of the substrate is quite similar to that of anisole, phenol, o-cresol and m-cresol; the proportion of para-substitution, for example, increases from 39 to 57% in from 58 to 80% sulphuric acid, although the changes seem displaced a little to lower acidity. The similarity suggests that the consequence of ipso-substitution, in the absence of demethoxylation may be the formation of 2-methyl-6-nitroanisole, by another specific and unusual rearrangement. In contrast to the rearrangement of the demethoxylated compound, reaction of a cyclohexadienone species is not possible here and these considerations may strengthen the possibility that the formation of 2-methyl-6-

nitrophenol involves a specific heterolytic process or a synchronous 1,3-sigmatropic shift.

It is noteworthy that nucleophilic trapping of ipso-Wheland intermediates in any of these compounds leading to other than demethoxylated products has not been observed. This contrasts with the situation for alkylated benzenes.

Ipso-substitution at C-isopr. is expected in the nitration of p-isopropylanisole which is expected to react in a similar manner as p-methylanisole⁵⁰. The method of h.p.l.c. established the full product analysis for the nitration of this compound (Table 2.18) and in addition to 4-isopropyl-2-nitroanisole and 4-isopropyl-2-nitrophenol, p-nitroanisole and p-nitrophenol were also found. It is then suggested, that ipso-substitution at C-isopr. forms $(W_i^{\text{isopr}})_a$ (Scheme 2.4) which can be captured by water at low acidities to form $(W_i^{\text{isop}})_b$ (step e) and at higher acidities either form isopropanol (IPA) and p-nitroanisole (step b), or, by return to the encounter pair give 4-isopropyl-2-nitroanisole (step a). The Wheland intermediate $(W_i^{\text{isop}})_b$ can either form isopropanol and p-nitrophenol (step c) or form the p-isopropylphenol/nitronium ion encounter pair giving 4-isopropyl-2-nitrophenol (step d) (c.f. p-cresol, Section 1.53), the former of these processes competing more effectively with increasing acidity.

As before (see Section 1.54) a drop in total yield in above ca 82% sulphuric acid occurs for all substrates studied in this region. In the case of anisole⁵⁰, dinitration has been shown to be only partly responsible for this and in the case of o- and m-cresol where mononitration products are less reactive than those of anisole, this is presumably also the case. In the case of 3,5-dimethylphenol



Scheme 2.4

where the mononitro compounds are more reactive than those of anisole, dinitration is presumably the main reason for the drop in yield in above 80% sulphuric acid. As before nitration is much faster than sulphonation under the reaction conditions. Most of the lowered yields at high acidities therefore remain unaccounted for.

CHAPTER 3

THE NITRATION OF p-BROMOPHENOL, p-CHLOROPHENOL,
o-BROMOPHENOL AND 2,4-DIBROMOPHENOL

3.1 INTRODUCTION

Few mechanistically authenticated examples of nitrodehalogenation are to be found in the literature. Many examples of the displacement of halogen in nitration solutions from polysubstituted phenols and phenol ethers have been noted⁷⁰, but most are mechanistically ambiguous and may involve at least some nitrosodehalogenation⁶⁹.

A number of instances are known where I^+ is displaced from aromatics. Iodo-aromatics for which such ipso-displacements have been reported include 4-iodoanisole^{49,69b}, 2-iodomesitylene^{69d}, 2-iodo-1,3,5-tri-neopentylbenzene⁷¹ and 4-iodo-o-xylene⁷². Nitrobenzene could not be detected, however, from nitration of iodobenzene with nitric acid in nitromethane^{69d} and while the iodo group appears to be one of the better ipso leaving groups⁷¹, nitrodeiodination can also be complicated by the liberated I^+ (or equivalent species) iodinating either the iodo- or nitro-substituted aromatics^{54,69,72}.

As regards nitrodebromination most observations relate to activated substrates^{69,54}. Thus p-bromoanisole, nitrated in acetic anhydride containing urea, gave 31% of p-nitroanisole, together with 2-bromo-4-nitroanisole, 4-bromo-2-nitroanisole and 2,4-dibromoanisole⁵⁴. Curious rearrangements have been recorded in reactions of this kind, but the polybromocompounds isolated are probably formed by brominations following expulsion of a brominating agent in the nitrodebromination step. Examples of such rearrangements are the formation of 2,6-dibromo-4-nitroanisole when 2,4-dibromoanisole is treated with colourless nitric acid⁷³ and of 2-bromo-3-methyl-4,6-dinitrophenol from 4-bromo-3-methylphenol⁷⁴. Nitrodebromination was the sole outcome of treating some 4-bromo-2,6-dialkylphenols with nitric acid in acetic acid⁷⁵.

True nitrodebromination is much more likely to be occurring, when

deactivated substrates are involved. One of the products from nitrating 1,2,4,5-tetrabromobenzene in sulphuric acid was hexabromobenzene⁷⁶ formed by nitrodebromination to give a brominating reagent which reacted with the starting material.

The formation of p-bromonitrobenzene was noted⁷⁷ when p-dibromobenzene was nitrated in 70% nitric acid and nitration of p-dibromobenzene in sulphuric acid¹² yielded 2,5-dibromonitrobenzene and p-bromonitrobenzene in ratios from 3.8 to 200 in the acidity range 68-90% sulphuric acid, lower acidities favouring nitrodebromination. Nitrodebromination was also observed in an earlier study⁷⁸ from the nitration of p-bromotoluene, p-chlorobromobenzene and p-bromofluorobenzene in sulphuric acid, but no nitrodebromination was observed in the nitration of o-dibromobenzene and 2-bromo-m-xylene.

Nitration of p-chloroanisole⁵¹ in sulphuric acid yields 4-chloro-2-nitrophenol and 4-chloro-2-nitroanisole which suggests that ipso-substitution at C-Cl occurs but no nitrodechlorination product was detected. Also in the nitration of o-dichlorobenzene, p-dichlorobenzene, p-chlorotoluene and p-bromochlorobenzene no products of nitrodechlorination were detected⁷⁸.

Generally the evidence supports the view that the ease of halogen displacement increases from chlorine to bromine to iodine. This Chapter describes work on some substituted halogenophenols namely p-bromophenol, p-chlorophenol, o-bromophenol and 2,4-dibromophenol, aimed at clarifying the effect of structure and solvent composition on the process of nitrodehalogenation and investigating further the general medium effect on methoxy and hydroxy substituted compounds discussed in Chapter 2 and Section 1.344.

3.2 EXPERIMENTAL

3.21 MATERIALS

These were as described in Section 7.2 with the addition of the following. p-Bromophenol, p-chlorophenol, o-bromophenol, 2,4-dibromophenol, 2,6-dibromo-4-nitrophenol, p-nitrophenol, m-nitroanisole, 2-methyl-3-nitrophenol, o-nitrophenol and p-nitroanisole were commercial reagents redistilled or recrystallized as necessary. These compounds had physical properties corresponding to these in the literature. 2-Bromo-4-nitrophenol, 2-chloro-4-nitrophenol and 4-chloro-2-nitrophenol were the gift of Professor K. Schofield.

3.211 4-BROMO-2-NITROPHENOL

A solution of o-nitrophenol (10g) in glacial acetic acid (20 ml) was cooled and stirred for 20 minutes. A solution of bromine (4 ml) in acetic acid (35 ml) was then added dropwise during 2 hours and the resulting mixture was left for further 20 hours. Addition of ice-water to the clear deep-red solution gave a yellow precipitate which was filtered, drained by suction and washed with a water-acetic acid (1:1) mixture. The yellow precipitate obtained was added to an aqueous potassium carbonate solution (5g in 40 ml) and was then warmed on a water-bath for 20 minutes. After cooling a deep-red precipitate appeared which was filtered by suction and washed twice with a little water. This precipitate was potassium 2,4-dibromo-6-nitrophenoxide. An excess of dil. HCl was added to the mother liquor and a clear yellow precipitate separated which was filtered by suction, washed three times with water and recrystallized from ethanol. The final product was still impure and was purified by preparative t.l.c. (10% EtOAc/cyclohexane); m.p. 88° (lit.⁷⁹ 89°).

$^1\text{H.n.m.r. (CDCl}_3\text{): } \tau -0.43 \text{ (1H, s, OH), } 1.76 \text{ (1H, s H-3), } 2.35 \text{ (1H, d, H-5, } J_{5,6}=4\text{Hz), } 2.93 \text{ (1H, d, H-6, } J_{6,5}=4\text{Hz).}$

3.212 2,4-DIBROMO-6-NITROPHENOL

The potassium 2,4-dibromo-6-nitrophenoxide obtained above was hydrolysed with dil. HCl and the yellow product was steam distilled and finally recrystallized from acetic acid giving yellow needles; m.p. 116° (lit.⁷⁹ 118°)

$^1\text{H.n.m.r. (CDCl}_3\text{): } \tau -0.98 \text{ (1H, s, OH), } 1.76 \text{ (1H, s, H-3), } 2.04 \text{ (1H, s, H-5).}$

3.213 2-BROMO-6-NITROPHENOL

o-Bromophenol (10g) was dissolved in glacial acetic acid (15 ml) and nitric acid (3 ml, d 1.42) was added dropwise, the reaction mixture being cooled (20°). The mixture was allowed to stand for another hour and addition of ice-water gave a yellow precipitate. Steam distillation of the product mixture yielded 2-bromo-6-nitrophenol, which was recrystallized from methanol giving yellow needles; m.p. 67° (lit.⁸⁰ 68°).

$^1\text{H.n.m.r. (CDCl}_3\text{): } \tau -1.00 \text{ (1H, s, OH), } 2.00 \text{ (1H, d, H-5, } J_{4,5}=4\text{Hz), } 2.25 \text{ (1H, d, H-3, } J_{3,4}=4\text{Hz), } 3.22 \text{ (1H, t, H-4, } J_{3,4}=J_{4,5}=4\text{Hz).}$

3.22 KINETIC MEASUREMENTS

For all the substrates, these were as described in Section 7.3.

3.23 PRODUCT ANALYSIS

The conventional h.p.l.c. method as described in Sections 7.4(i) and 7.4(ii) was used to ascertain the isomer distributions from the nitration of p-bromophenol, p-chlorophenol, o-bromophenol and 2,4-dibromophenol. Details of the h.p.l.c. procedures are given in Tables 3.1, 3.2, 3.3 and 3.4 for p-bromophenol, p-chlorophenol, o-bromophenol and 2,4-dibromophenol respectively.

3.3 RESULTS

3.31 KINETICS

3.311 p-BROMOPHENOL

A typical determination of a rate coefficient:-

Concentration of sulphuric acid	: 67.1% w/w
Concentration of nitric acid	: $1.73 \times 10^{-3} \text{ mole dm}^{-3}$
Concentration of <u>p</u> -bromophenol	: $1.56 \times 10^{-4} \text{ mole dm}^{-3}$
Concentration of sulphamic acid	<u>ca</u> $0.05 \text{ mole dm}^{-3}$
Temperature	: $25.0 \pm 0.2^{\circ}$
Wavelength of measurement	: 285 nm

Fig. 3.1 shows the extinction curve obtained, Table 3.5 the data obtained therefrom and Fig. 3.2 the plot of $\log_{10}(A_{\infty} - A_t)$ vs time.

$$k_2(\text{obs}) = -2.303 \times \text{slope} / [\text{HNO}_3] \text{ dm}^3 \text{ mole}^{-1} \text{ s}^{-1}$$

$$k_2(\text{obs}) = 0.173 \text{ dm}^3 \text{ mole}^{-1} \text{ s}^{-1}$$

Second-order rate coefficients for the nitration of p-bromophenol determined over a range of percentages of sulphuric acid are given in Table 3.6 and a plot of $\log_{10} k_2(\text{obs})$ vs % H_2SO_4 is shown in Fig. 3.3 together with the values for mesitylene and benzene for comparison.

Table 3.1

H.p.l.c. conditions for the separation of
4-bromo-2-nitrophenol, 2-bromo-4-nitrophenol
p-nitrophenol, 2,4-dibromophenol and 2,4-dibromo-6-nitrophenol.

Column : 25cm x 1/4" Merkosorb S160
Solvent : 10% EtOAc/cyclohexane
Flow rate : 2 ml/min
Wavelength : 300 nm
Detector : Cecil 272
Pump : Waters Associates model 6000A
Temperature : Ambient

Compound	Retention times/s
4-bromo-2-nitrophenol	155
2-bromo-4-nitrophenol	510
2,4-dibromo-6-nitrophenol	138
2,4-dibromophenol	327
<u>p</u> -nitrophenol	950
<u>m</u> -nitroanisole (reference standard)	248

Table 3.2

H.p.l.c. conditions for the separation of
4-chloro-2-nitrophenol, 2-chloro-4-nitrophenol
and p-nitrophenol.

Column : 25cm x 1/4" Merkosorb SI60
Solvent : 10% EtOAc/cyclohexane
Flow rate : 2 ml/min
Wavelength : 290 nm
Detector : Cecil 272
Pump : Waters Associates model 6000A
Temperature : Ambient

Compound	Retention Times /s
4-chloro-2-nitrophenol	174
2-chloro-4-nitrophenol	720
p-nitrophenol	950
2-methyl-3-nitrophenol (standard)	546

Table 3.3

H.p.l.c. conditions for the separation of
2-bromo-4-nitrophenol, 2-bromo-6-nitrophenol
and o-nitrophenol.

Column : 25cm x 1/4" Merkosorb SI60
Solvent : 8% EtOAc/cyclohexane
Flow rate : 2 ml/min
Wavelength : 300 nm
Detector : Cecil 272
Pump : Water Associates, model 6000A
Temperature : Ambient

Compound	Retention times /s
2-bromo-4-nitrophenol	920
2-bromo-6-nitrophenol	120
<u>o</u> -nitrophenol	150
<u>p</u> -nitroanisole (reference standard)	180

Table 3.4

H.p.l.c. conditions for the separation of
2-bromo-4-nitrophenol, 2,6-dibromo-4-nitrophenol
and 2,4-dibromo-6-nitrophenol.

Column : 25cm x 1/4" Merkosorb SI60
Solvent : 8% EtOAc/cyclohexane
Flow rate : 2 ml/min
Wavelength : 310 nm
Detector : Cecil 272
Pump : Waters Associates, model 6000A
Temperature : Ambient

Compound	Retention times /s
2-bromo-4-nitrophenol	900
2,6-dibromo-4-nitrophenol	650
2,4-dibromo-6-nitrophenol	140
p-nitroanisole (reference standard)	180

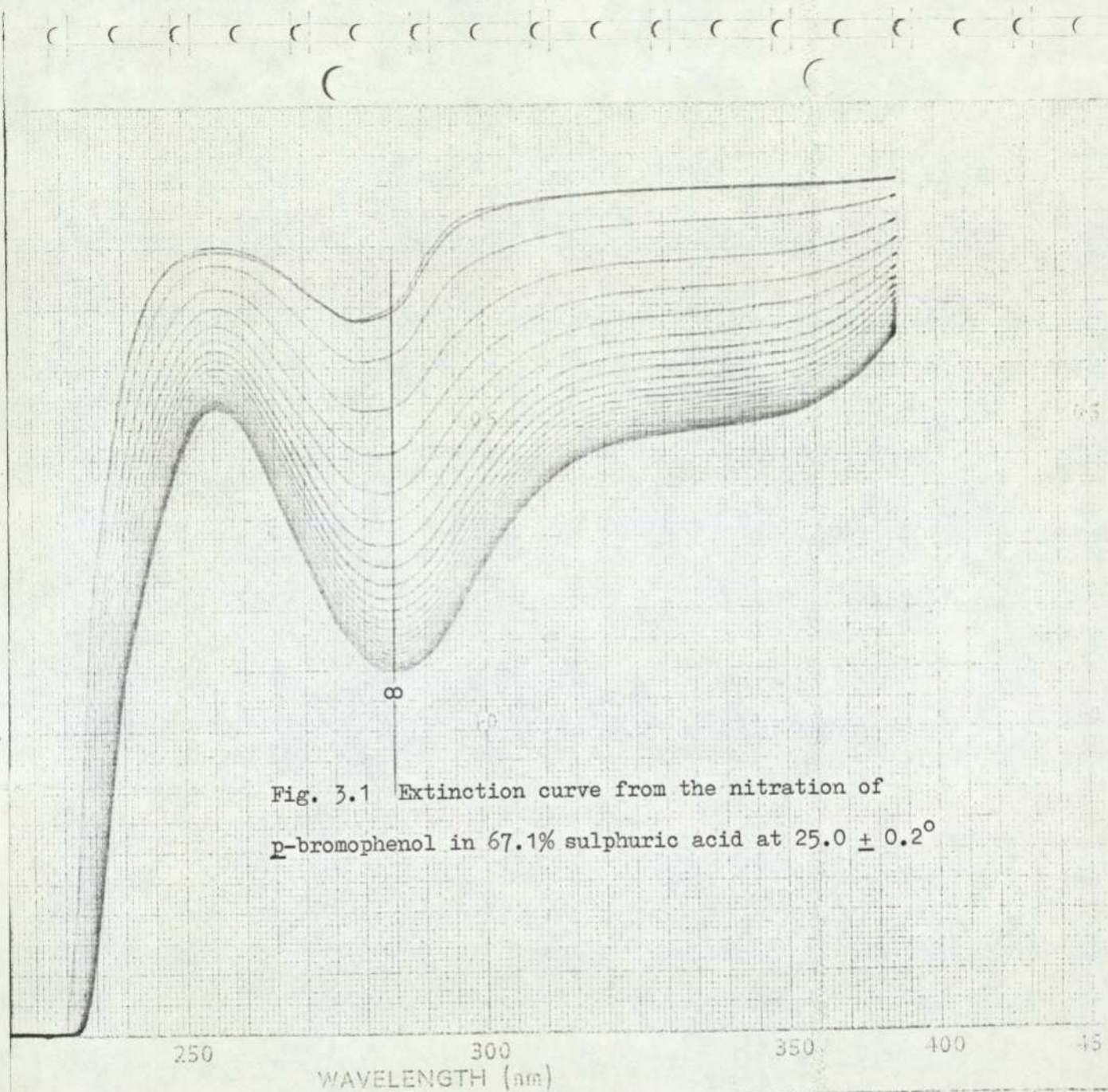


Fig. 3.1 Extinction curve from the nitration of p-bromophenol in 67.1% sulphuric acid at $25.0 \pm 0.2^\circ$

Table 3.5

Data from a typical determination of the rate
coefficient of p-bromophenol in 67.1%
sulphuric acid at $25.0 \pm 0.2^\circ$

Time (t) /min	Absorbance (A_t)	$\log_{10}(A_\infty - A_t)$
1	0.30	-0.21
10	0.38	-0.27
20	0.47	-0.35
30	0.54	-0.43
40	0.61	-0.51
50	0.65	-0.59
60	0.69	-0.66
70	0.73	-0.74
80	0.76	-0.82
90	0.78	-0.89
100	0.80	-0.95
110	0.82	-1.04
t_∞	0.91	

Fig. 3.2 Plot of $\log_{10}(A_{\infty} - A_t)$ vs time from the nitration of p-bromophenol in 67.1% sulphuric acid at $25.0^{\circ} \pm 0.2^{\circ}$

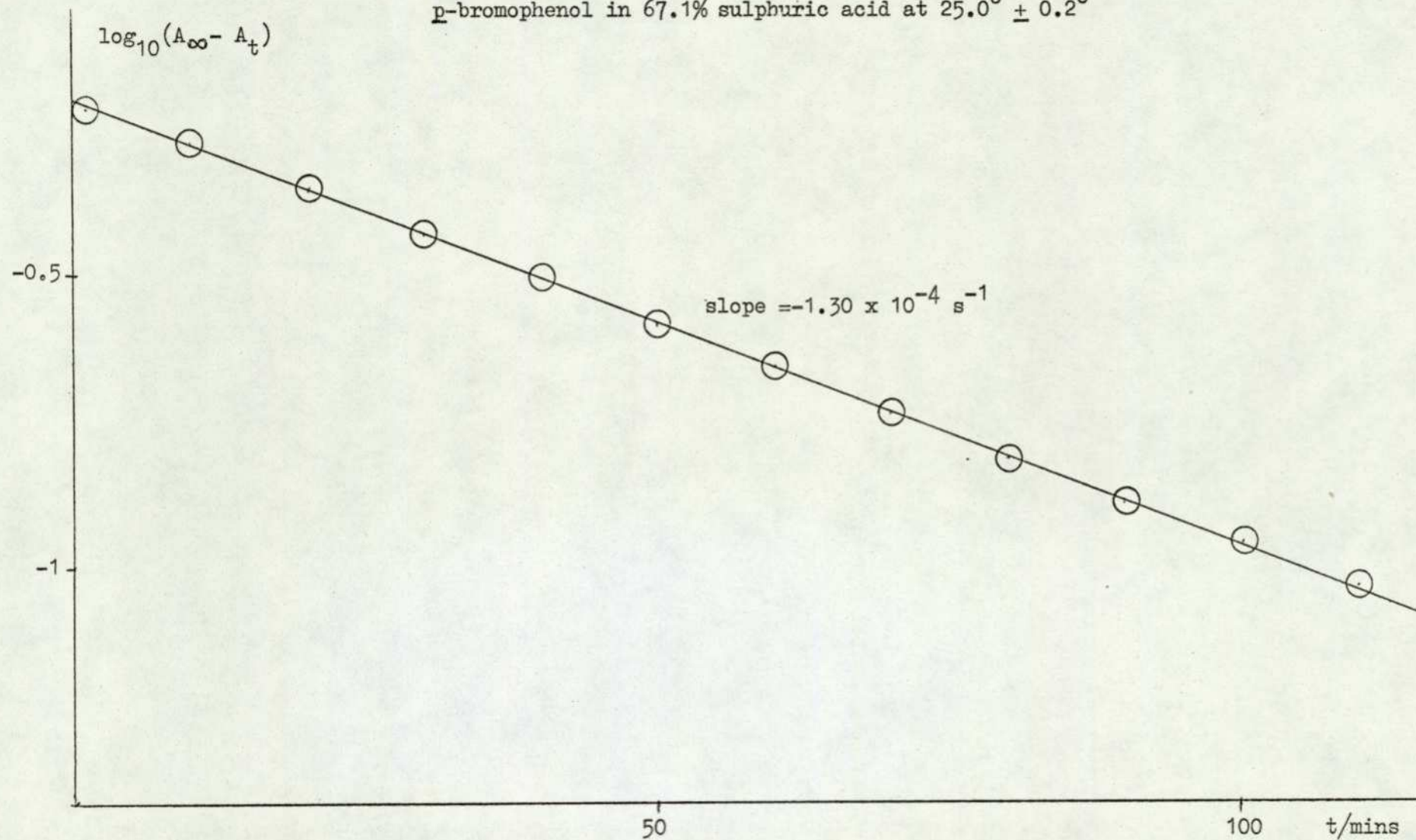


Table 3.6

Second-order rate coefficients for the nitration
of p-bromophenol^{b,c,d} in sulphuric acid at $25.0 \pm 0.2^\circ$

H_2SO_4 (%) ^a	$10^2 [\text{HNO}_3]$ /mole dm ⁻³	$k_2(\text{obs})$ /dm ³ mole ⁻¹ s ⁻¹
59.6	5.5	2.33×10^{-3}
62.3	2.3	9.78×10^{-3}
63.6	2.3	2.02×10^{-2}
66.3	2.3	9.72×10^{-2}
67.1	0.17	0.173
69.1	0.09	0.918
70.8	0.09	3.66
71.1	0.09	4.12
72.5	0.09	16.64

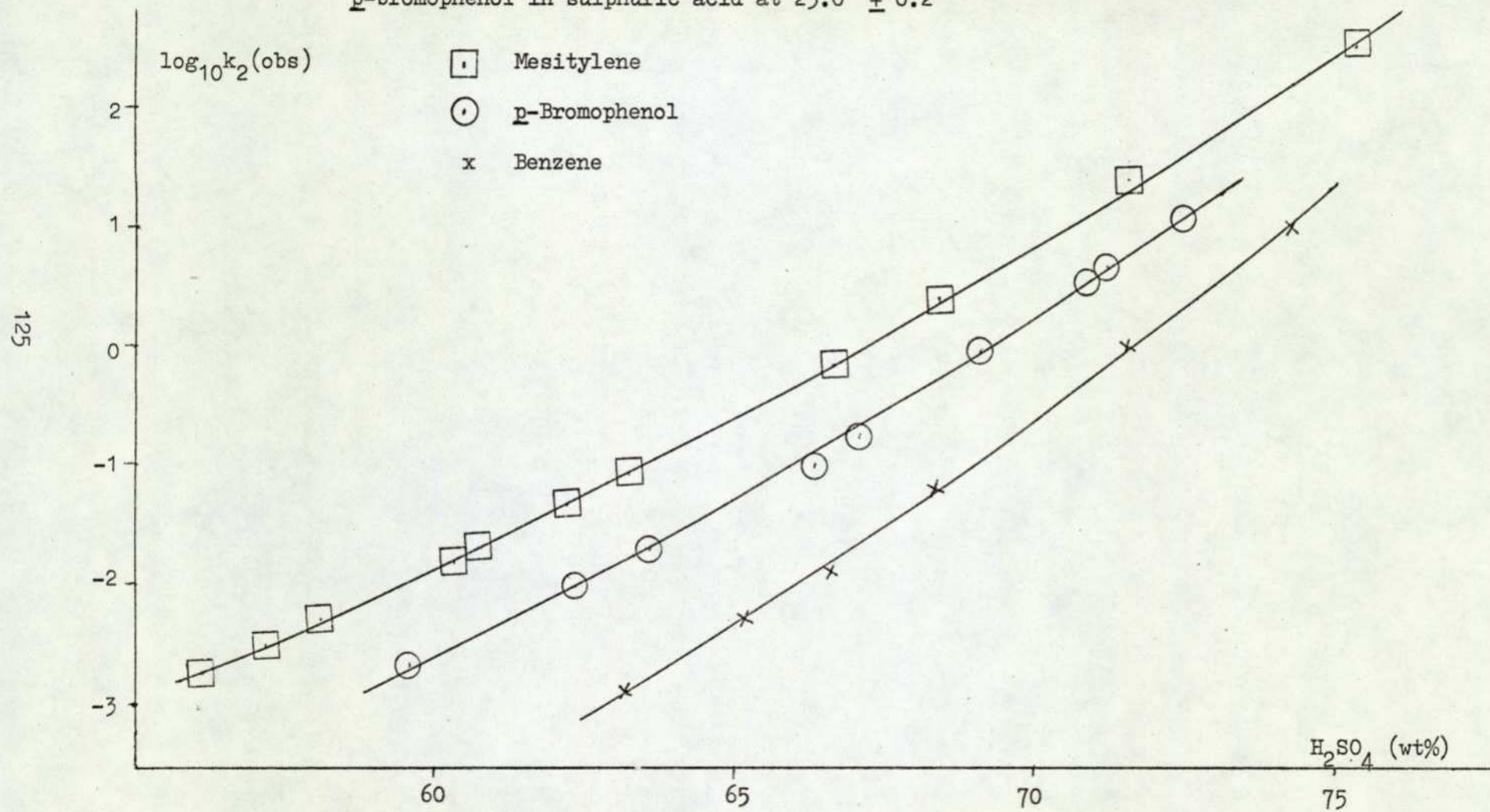
a) $\pm 0.1\%$ w/w

b) $[\text{ArH}] = 1.56 \times 10^{-4}$ mole dm⁻³

c) Measurement at 280 or 285 nm

d) $[\text{Sulphamic acid}] \text{ ca } 0.05$ mole dm⁻³

Fig. 3.3 Rate profile for the nitration of
p-bromophenol in sulphuric acid at $25.0^{\circ} \pm 0.2^{\circ}$



3.312 p-CHLOROPHENOL

A typical determination of a rate coefficient:-

Concentration of sulphuric acid	: 66.3% w/w
Concentration of nitric acid	: 2.33×10^{-2} mole dm ⁻³
Concentration of <u>p</u> -chlorophenol	: 1.57×10^{-4} mole dm ⁻³
Concentration of sulphamic acid	<u>ca</u> 0.05 mole dm ⁻³
Temperature	: 25.0° ($\pm$ 0.2°)
Wavelength of measurement	: 280 nm

Fig. 3.4 shows the extinction curve obtained, Table 3.7 the data obtained therefrom and Fig. 3.5 the plot of $\log_{10}(A_{\infty} - A_t)$ vs time.

$$k_2(\text{obs}) = -2.303 \times \text{slope} / [\text{HNO}_3] \text{ dm}^3 \text{ mole}^{-1} \text{ s}^{-1}$$

$$k_2(\text{obs}) = 0.129 \text{ dm}^3 \text{ mole}^{-1} \text{ s}^{-1}$$

Second-order rate coefficients for the nitration of p-chlorophenol over a range of percentages of sulphuric acid are given in Table 3.8 and a plot of $\log_{10} k_2(\text{obs})$ vs % H₂SO₄ is shown in Fig 3.6 together with the values for mesitylene and benzene for comparison.

3.313 o-BROMOPHENOL

A typical determination of a rate coefficient:-

Concentration of sulphuric acid	: 70.8% w/w
Concentration of nitric acid	: 8.98×10^{-4} mole dm ⁻³
Concentration of <u>o</u> -bromophenol	: 1.44×10^{-4} mole dm ⁻³
Concentration of sulphamic acid	<u>ca</u> 0.05 mole dm ⁻³
Temperature	: 25.0° ($\pm$ 0.1°)
Wavelength of measurement	: 300 nm

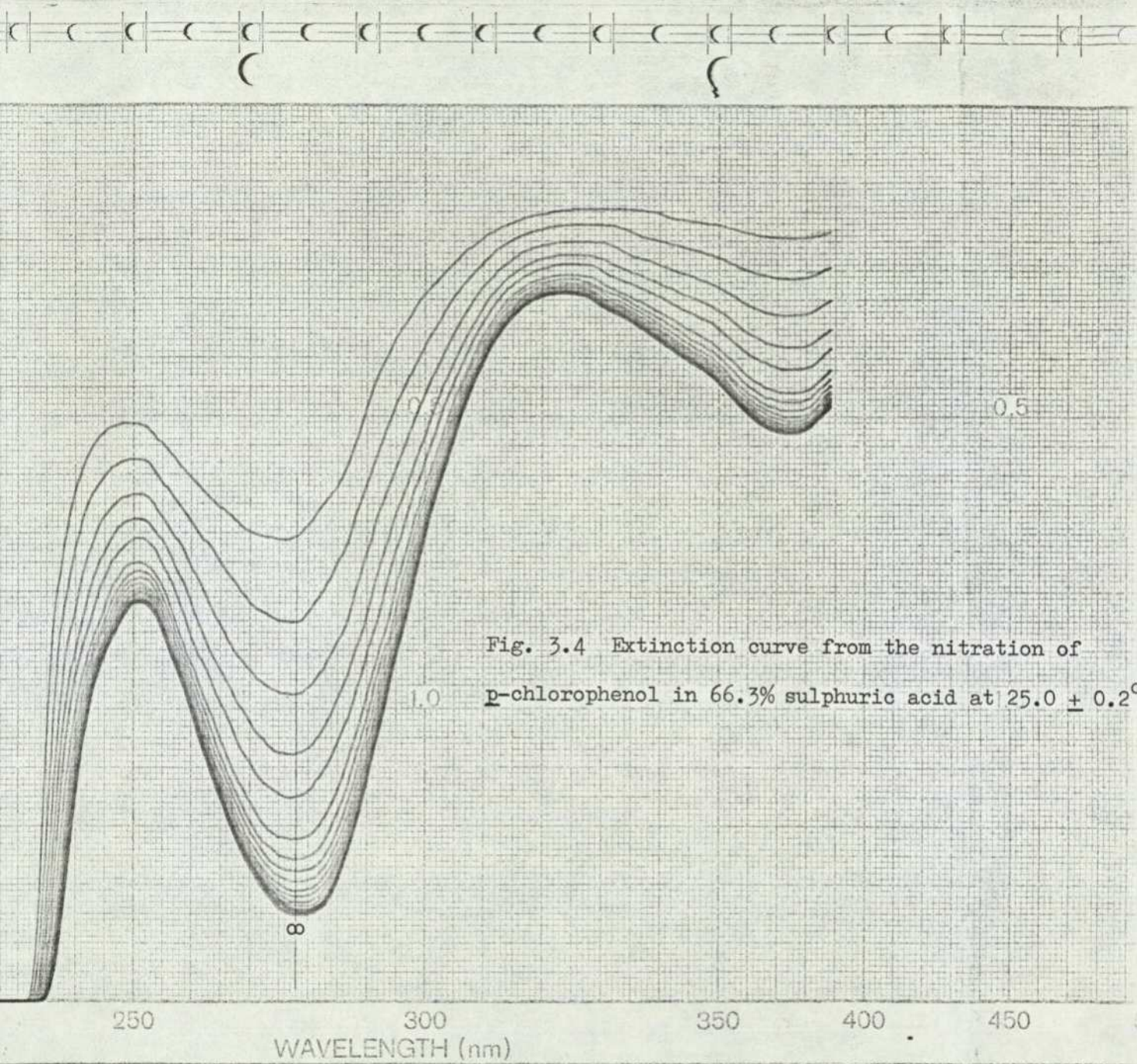


Fig. 3.4 Extinction curve from the nitration of p-chlorophenol in 66.3% sulphuric acid at $25.0 \pm 0.2^\circ$

Table 3.7

Data from a typical determination of the rate
coefficient of *p*-chlorophenol in 66.3%
sulphuric acid at $25.0 \pm 0.2^\circ$

Time (t) /s	Absorbance (A_t)	$\log_{10}(A_\infty - A_t)$
60	0.75	-0.19
150	0.85	-0.30
250	0.97	-0.42
350	1.08	-0.56
450	1.15	-0.70
600	1.22	-0.90
700	1.26	-1.04
800	1.28	-1.14
900	1.30	-1.26
1000	1.31	-1.41
t_∞	1.35	

Fig. 3.5 Plot of $\log_{10}(A_{\infty} - A_t)$ vs time from the nitration of p-chlorophenol in 66.3% sulphuric acid at $25.0 \pm 0.2^{\circ}$.

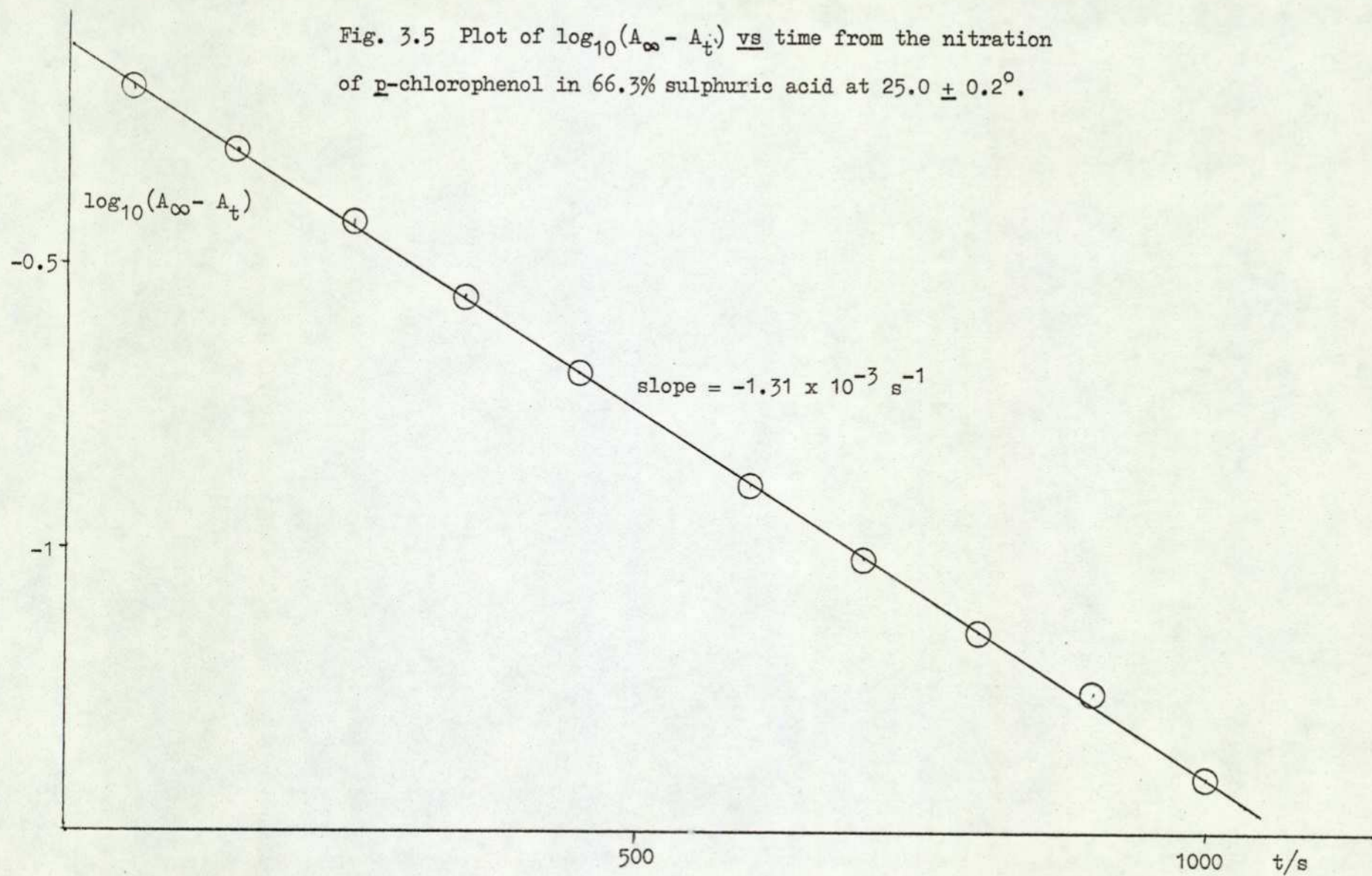


Table 3.8

Second-order rate coefficients for the nitration of
p-chlorophenol^{b,c,d} in sulphuric acid at $25.0 \pm 0.2^\circ$

H_2SO_4 (%) ^a	$10^2[\text{HNO}_3]$ /mole dm^{-3}	$k_2(\text{obs})$ / $\text{dm}^3 \text{ mole}^{-1} \text{ s}^{-1}$
59.6	5.5	1.82×10^{-3}
62.2	5.5	9.12×10^{-3}
63.8	2.3	2.99×10^{-2}
66.3	2.3	0.13
68.5	0.09	0.66
70.8	0.09	3.3

a) $\pm 0.1\%$ w/w

b) $[\text{ArH}] = 1.57 \times 10^{-4} \text{ mole dm}^{-3}$

c) Measurement at 280 or 370 nm

d) $[\text{Sulphamic acid}] \text{ ca } 0.05 \text{ mole dm}^{-3}$

Fig. 3.6 Rate profile for the nitration of
p-chlorophenol in sulphuric acid at $25.0 \pm 0.2^\circ$

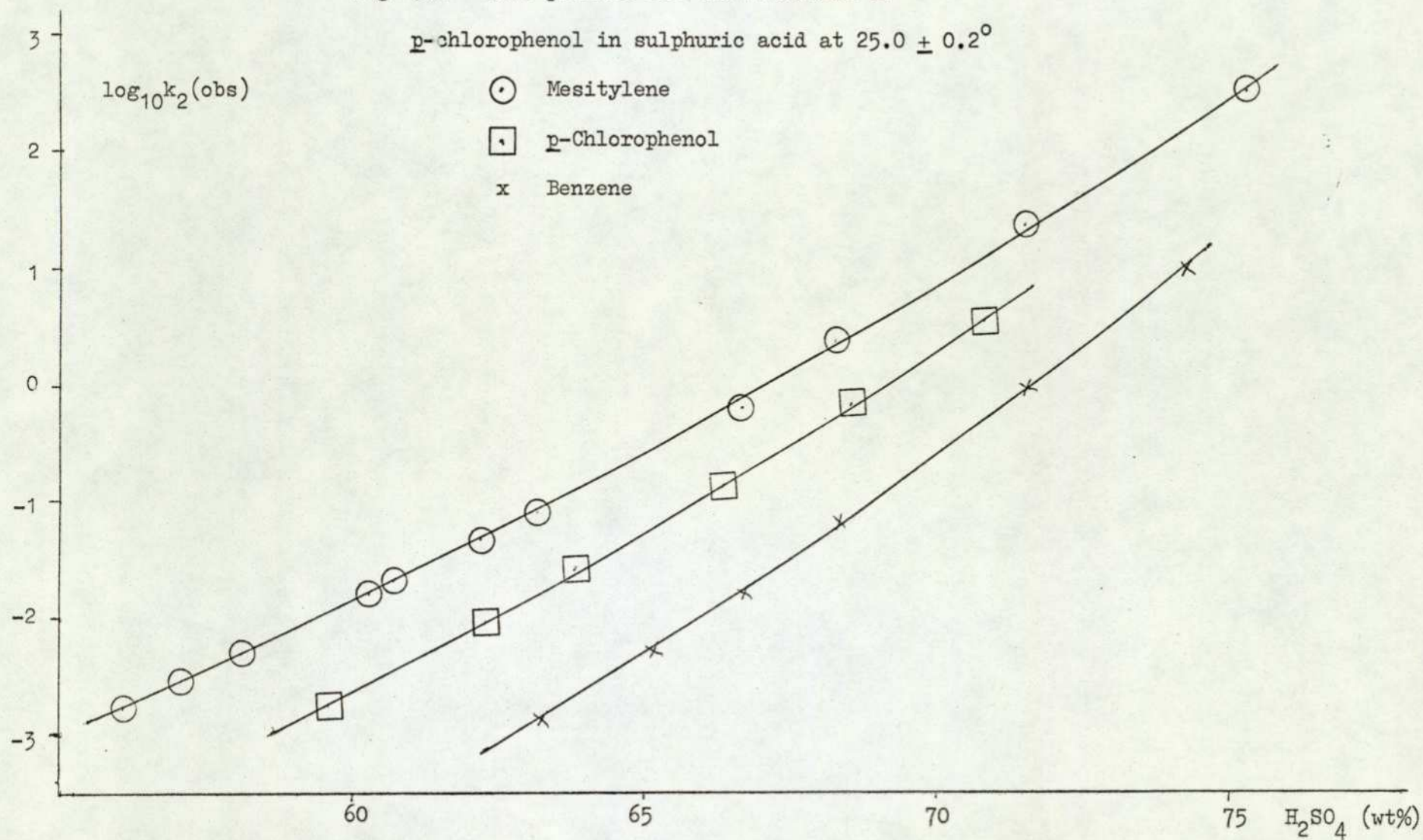


Fig. 3.7 shows the extinction curve obtained, Table 3.9 the data obtained therefrom and Fig. 3.8 the plot of $\log_{10}(A_{\infty} - A_t)$ vs time.

$$k_2(\text{obs}) = -2.303 \times \text{slope} / [\text{HNO}_3] \text{ dm mole}^{-1} \text{ s}^{-1}$$

$$k_2(\text{obs}) = 3.12 \text{ dm mole}^{-1} \text{ s}^{-1}$$

Second-order rate coefficients for the nitration of *o*-bromophenol over a range of percentages of sulphuric acid are given in Table 3.10 and a plot of $\log_{10} k_2(\text{obs})$ vs % H_2SO_4 is shown in Fig. 3.9 together with the values for mesitylene and benzene for comparison.

3.314 2,4-DIBROMOPHENOL

A typical determination of a rate coefficient:-

Concentration of sulphuric acid : 68.5% w/w

Concentration of nitric acid : $2.3 \times 10^{-2} \text{ mole dm}^{-3}$

Concentration of 2,4-dibromophenol: $1.87 \times 10^{-4} \text{ mole dm}^{-3}$

Concentration of sulphamic acid ca $0.05 \text{ mole dm}^{-3}$

Temperature : $25.0 \pm 0.2^\circ$

Wavelength of measurement : 290 nm

Fig. 3.10 shows the extinction curve obtained, Table 3.11 the data obtained therefrom and Fig. 3.11 the plot of $\log_{10}(A_{\infty} - A_t)$ vs time.

$$k_2(\text{obs}) = -2.303 \times \text{slope} / [\text{HNO}_3] \text{ dm}^3 \text{ mole}^{-1} \text{ s}^{-1}$$

$$k_2(\text{obs}) = 0.059 \text{ dm}^3 \text{ mole}^{-1} \text{ s}^{-1}$$

Second-order rate coefficients for the nitration of 2,4-dibromophenol over a range of percentages of sulphuric acid are given in Table 3.12 and a plot of $\log_{10}(\text{obs})$ vs % H_2SO_4 is shown in Fig. 3.12 together with the values for mesitylene, *p*-bromophenol, *o*-bromophenol and benzene for comparison.

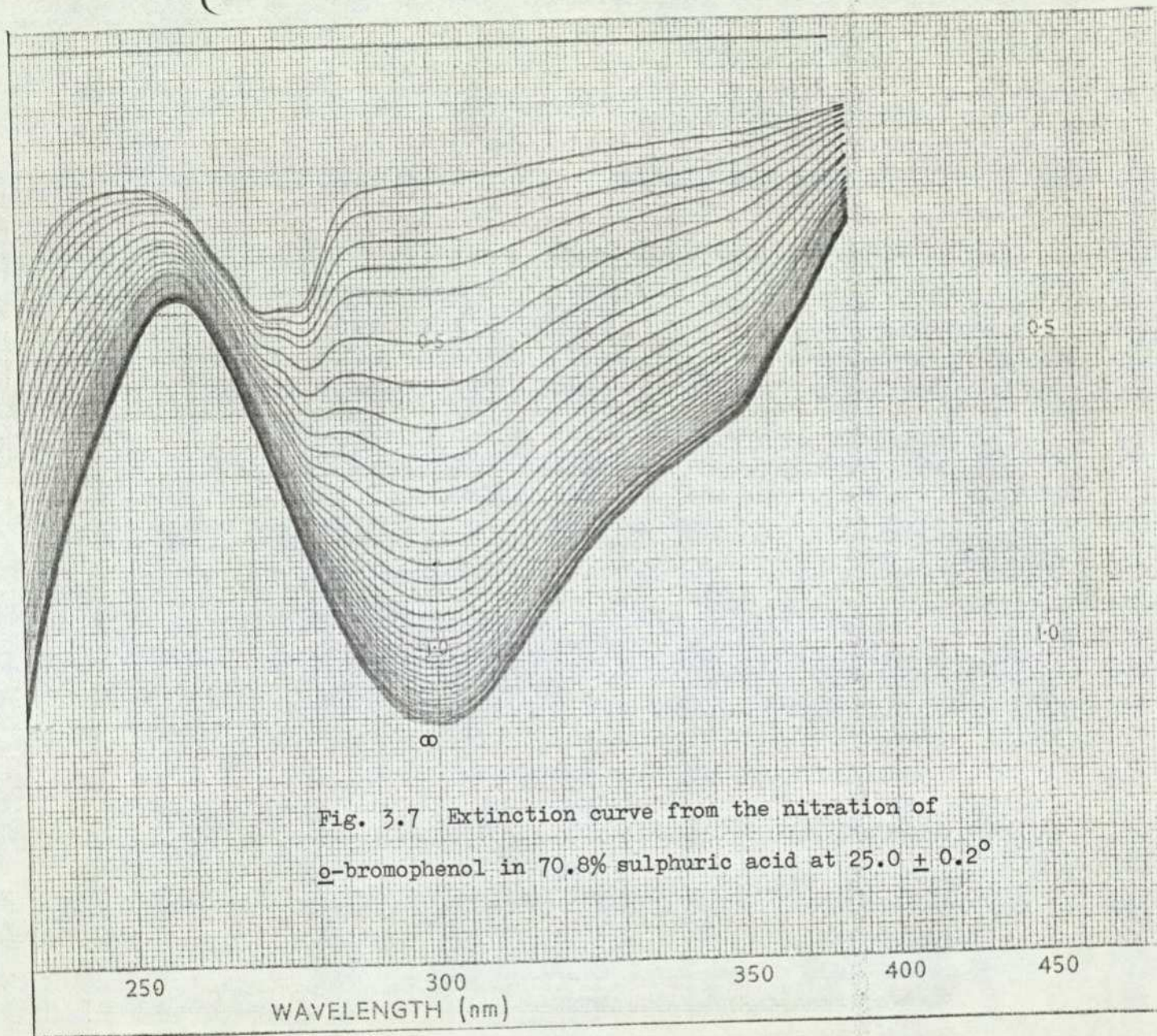


Fig. 3.7 Extinction curve from the nitration of
o-bromophenol in 70.8% sulphuric acid at $25.0 \pm 0.2^\circ$

Table 3.9

Data from a typical determination of the rate
coefficient of o-bromophenol in 70.8%
sulphuric acid at $25.0 \pm 0.2^\circ$

Time (t) /min	Absorbance (A_t)	$\log_{10}(A_\infty - A_t)$
1	0.23	-0.05
3	0.32	-0.09
5	0.41	-0.15
9	0.56	-0.25
13	0.68	-0.36
17	0.78	-0.47
21	0.85	-0.57
25	0.91	-0.68
33	0.99	-0.89
37	1.02	-1
41	1.04	-1.10
t_∞	1.12	

Fig. 3.8 Plot of $\log_{10}(A_{\infty} - A_t)$ vs time from the nitration of c-bromophenol in 70.8% sulphuric acid at $25.0 \pm 0.2^{\circ}$.

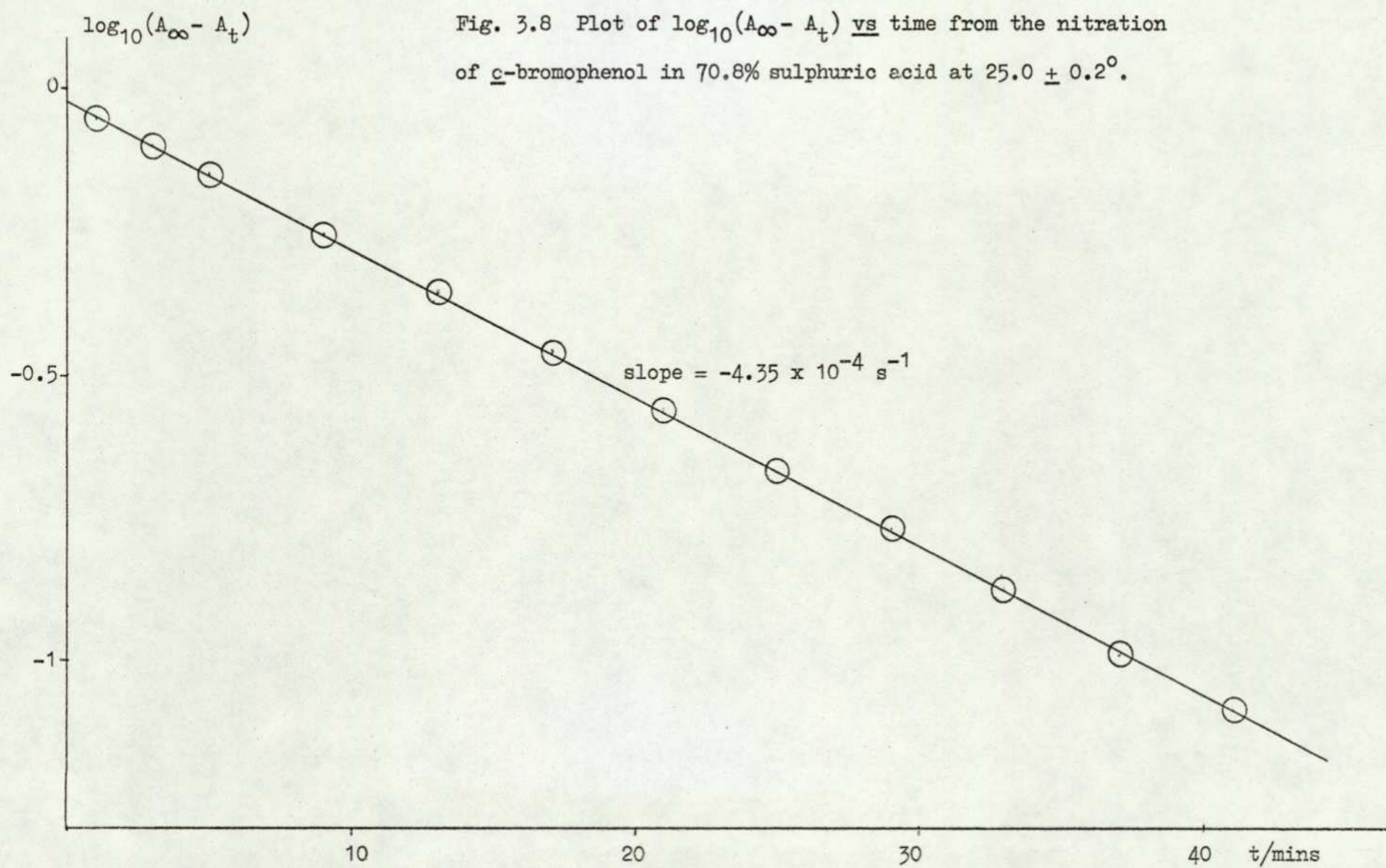


Table 3.10

Second-order rate coefficients for the nitration
of o-bromophenol^{b,c,d} in sulphuric acid at $25.0 \pm 0.2^\circ$

H_2SO_4 (%) ^a	$10^2[\text{HNO}_3]$ /mole dm ⁻³	$k_2(\text{obs})$ /dm ³ mole ⁻¹ s ⁻¹
62.2	5.5	4.07×10^{-3}
63.8	5.5	9.63×10^{-3}
66.3	2.3	5.9×10^{-2}
68.5	0.09	0.25
70.8	0.09	3.1
72.5	0.09	9.3

a) $\pm 0.1\%$ w/w

b) $[\text{ArH}] = 1.44 \times 10^{-4}$ mole dm⁻³

c) Measurement at 290 or 300 nm

d) [Sulphamic acid] ca 0.05 mole dm⁻³

Fig. 3.9 Rate profile for the nitration of
o-bromophenol in sulphuric acid at $25.0 \pm 0.2^\circ$.

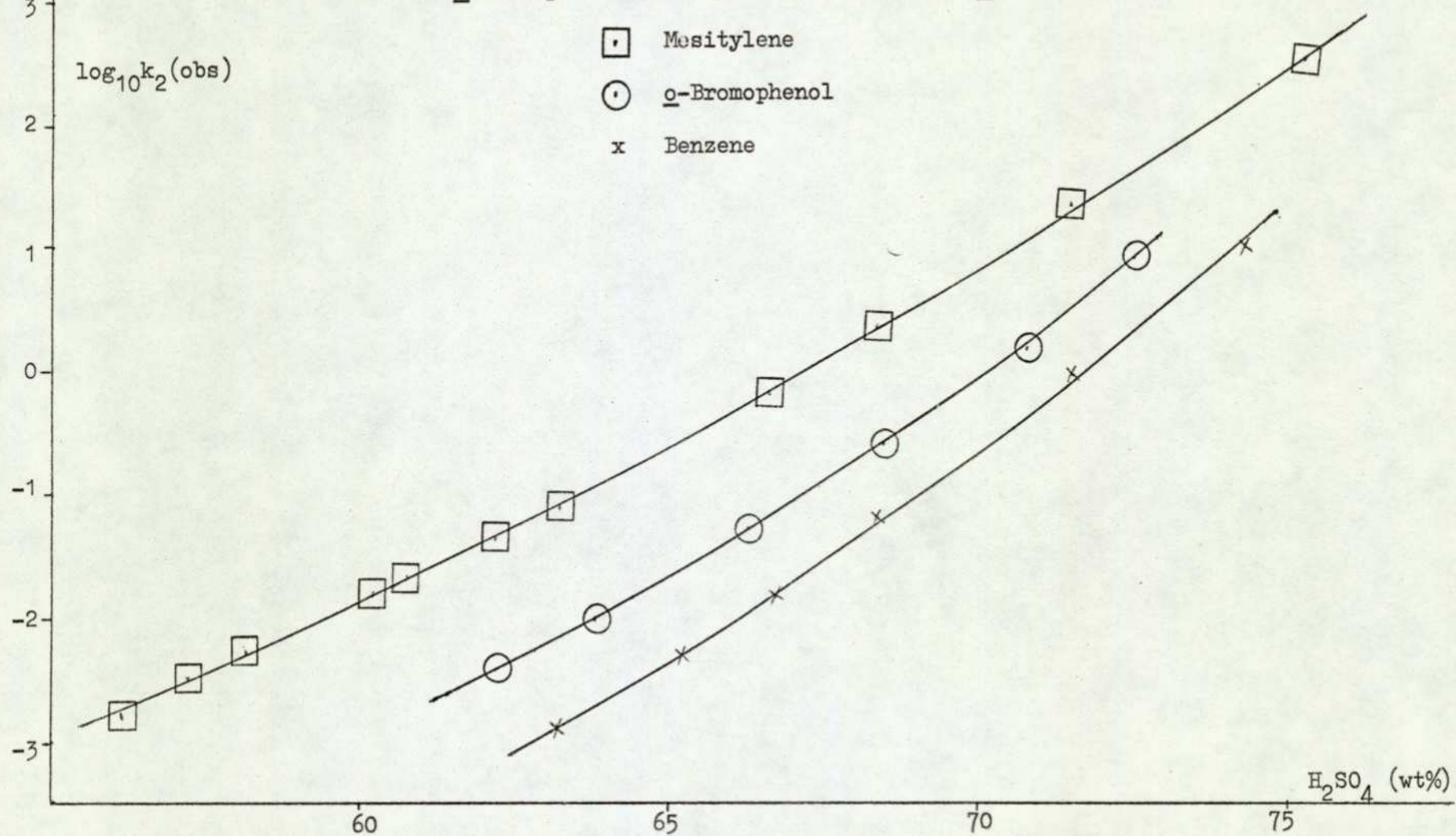


Fig. 3.10 Extinction curve from the nitration of
2,4-dibromophenol in 68.5% sulphuric acid at $25.0 \pm 0.2^\circ$

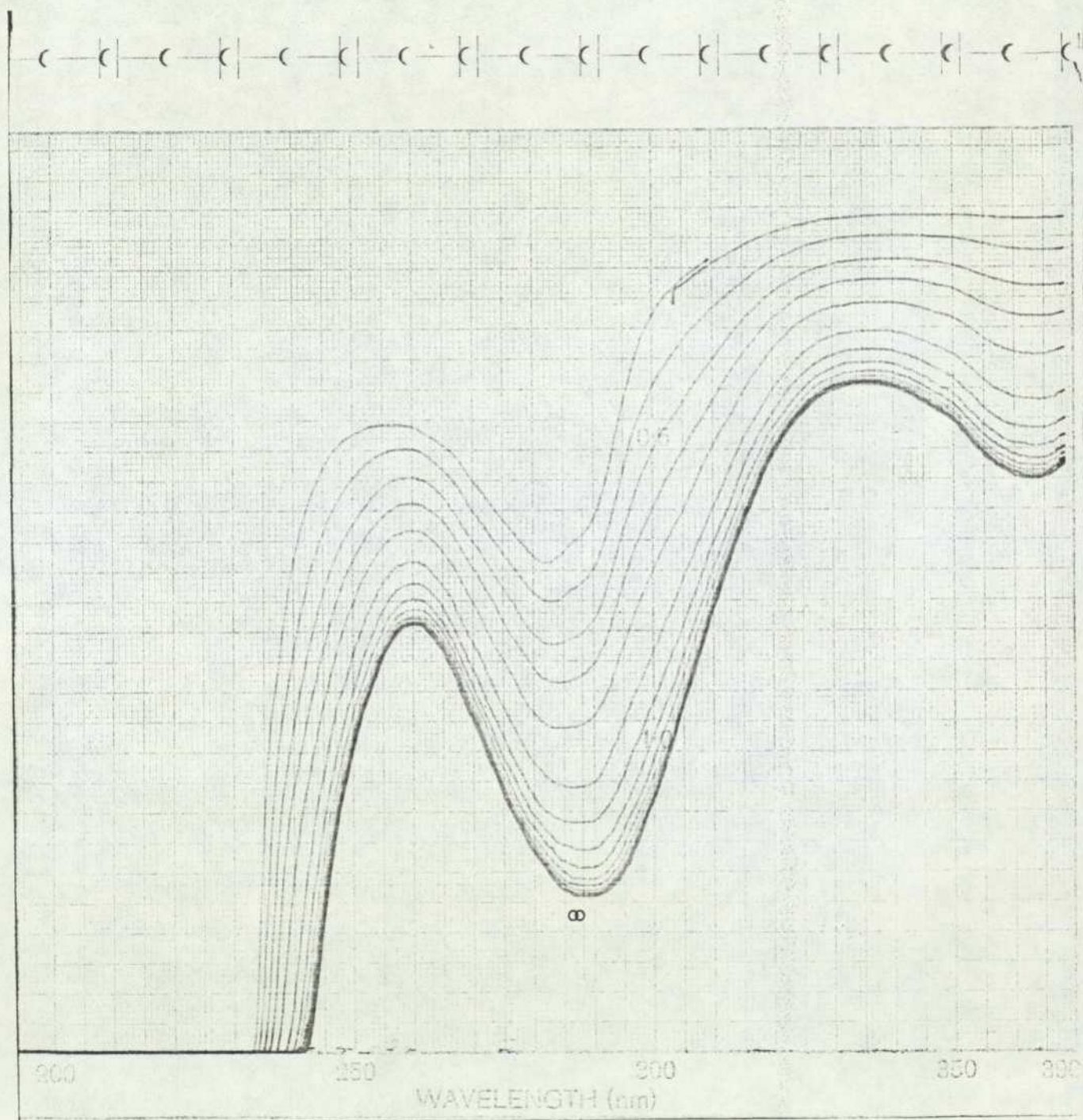


Table 3.11

Data from a typical determination of the rate
coefficient of 2,4-dibromophenol in 68.5%
sulphuric acid at $25.0 \pm 0.2^{\circ}$

Time (t) /min	Absorbance (A_t)	$\log_{10}(A_{\infty} - A_t)$
1	0.62	-0.20
3	0.72	-0.27
5	0.81	-0.35
7	0.87	-0.42
10	0.96	-0.53
15	1.06	-0.72
20	1.12	-0.88
25	1.16	-1.06
30	1.19	-1.23
35	1.21	-1.41
t_{∞}	1.25	

Fig. 3.11 Plot of $\log_{10}(A_{\infty} - A_t)$ vs time from the nitration of 2,4-dibromophenol in 68.5% sulphuric acid at $25.0 \pm 0.2^{\circ}$.

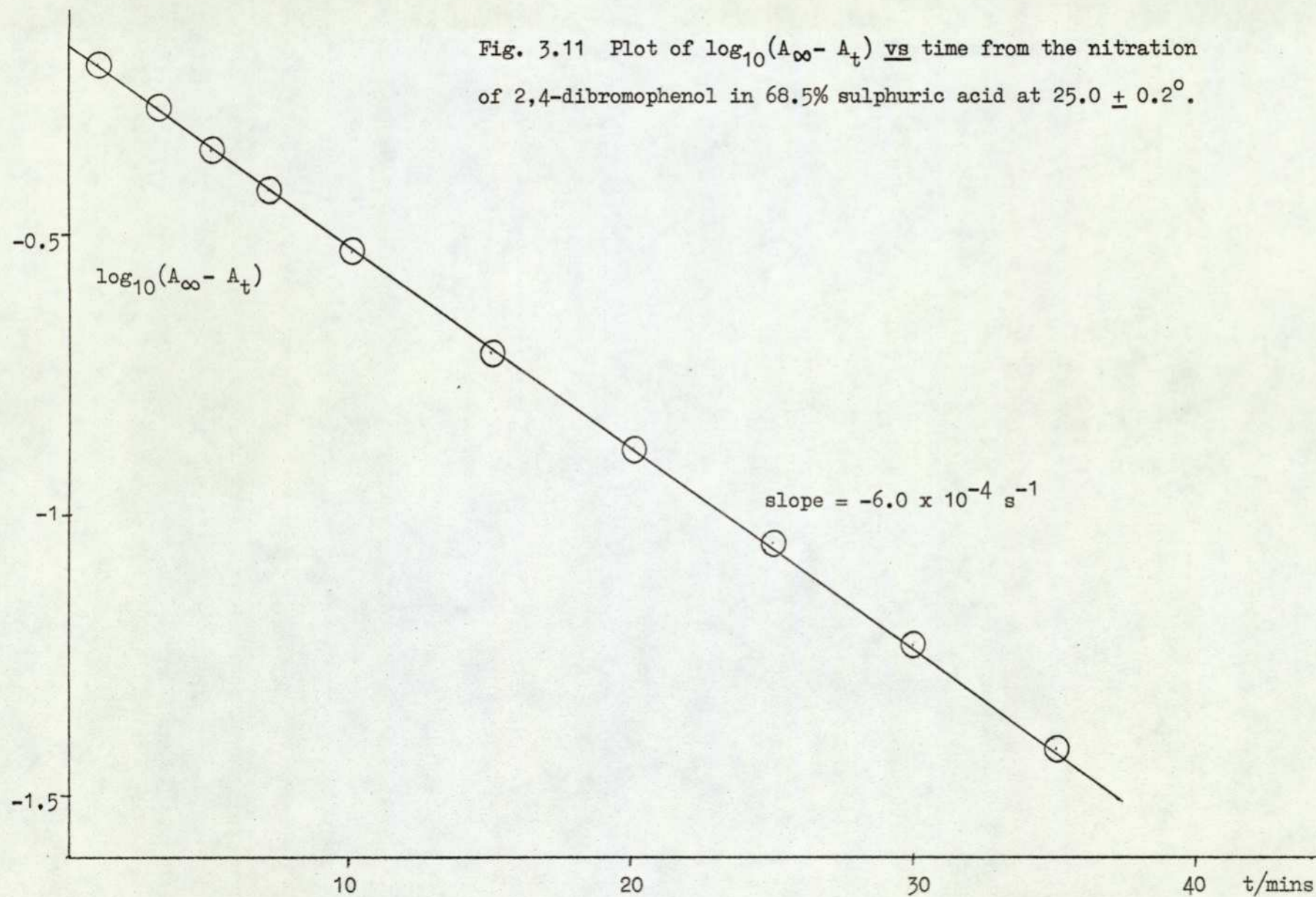


Table 3.12

Second-order rate coefficients for the nitration of
2,4-dibromophenol^{b,c,d} in sulphuric acid at $25.0 \pm 0.2^\circ$

H_2SO_4 (%) ^a	$10^2 [\text{HNO}_3]$ /mole dm^{-3}	$k_2(\text{obs})$ / $\text{dm}^3 \text{ mole}^{-1} \text{ s}^{-1}$
63.7	5.5	2.6×10^{-3}
66.3	2.3	1.2×10^{-2}
68.5	2.3	5.9×10^{-2}
70.5	2.3	0.35
70.8	2.3	0.38
72.7	0.09	1.8

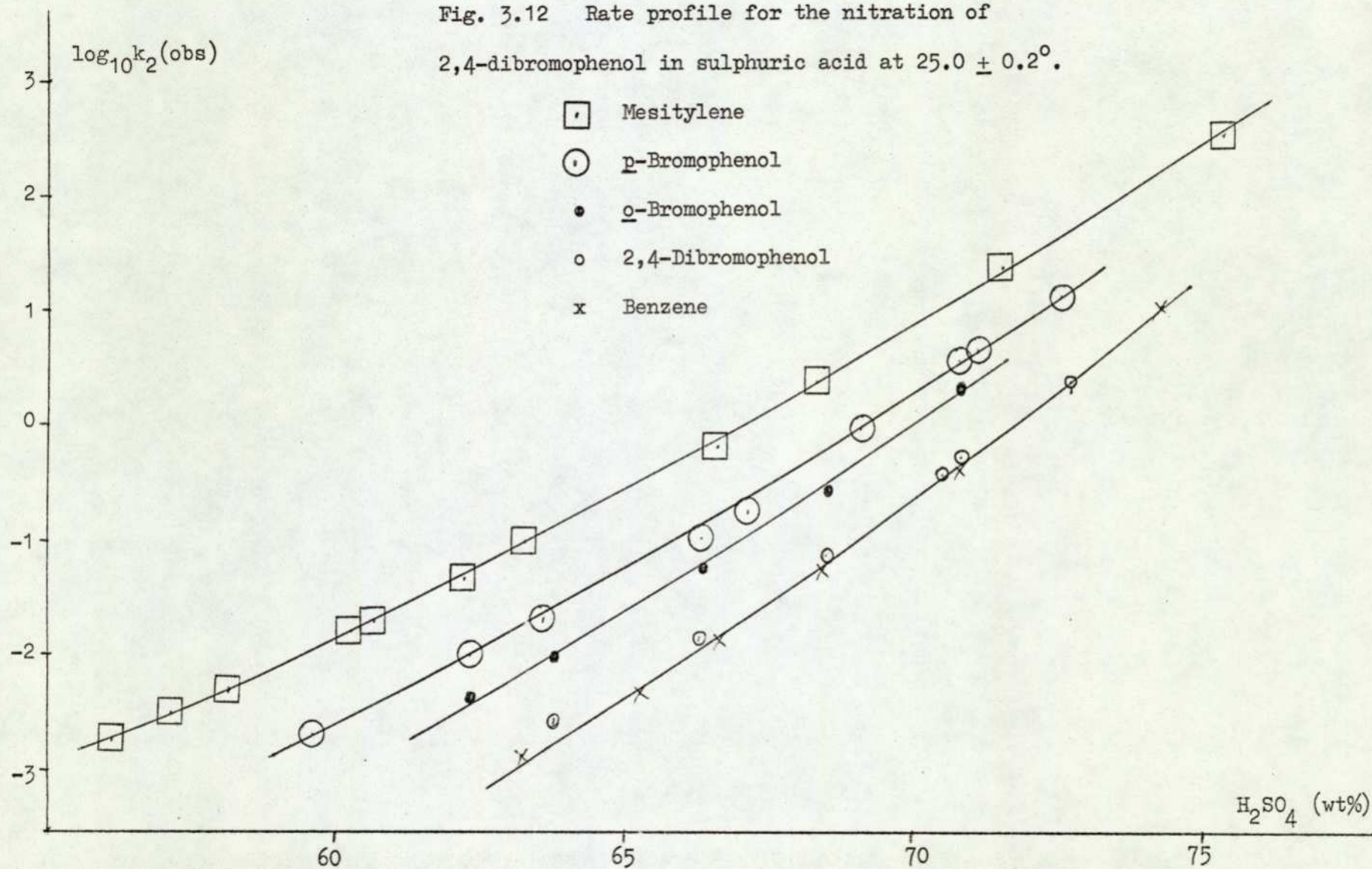
a) $\pm 0.1\%$ w/w

b) $[\text{ArH}] = 4.87 \times 10^{-4} \text{ mole dm}^{-3}$

c) Measurement at 280 or 290 nm

d) $[\text{Sulphamic acid}] \text{ ca } 0.05 \text{ mole dm}^{-3}$

Fig. 3.12 Rate profile for the nitration of
2,4-dibromophenol in sulphuric acid at $25.0 \pm 0.2^\circ$.



3.32 YIELDS OF NITRO-COMPOUNDS

3.321 p-BROMOPHENOL

Typical calculation of the yields:-

Sulphuric acid	: 70.8% w/w
Amount of nitric acid	: 9.97×10^{-5} moles
Amount of <u>p</u> -bromophenol	: 9.97×10^{-5} moles
Amount of reference standard	
<u>m</u> -nitroanisole	: 6.0×10^{-5} moles

Fig. 3.13 shows the chromatogram obtained (h.p.l.c. conditions as in Table 3.1).

Peak weights from chromatogram

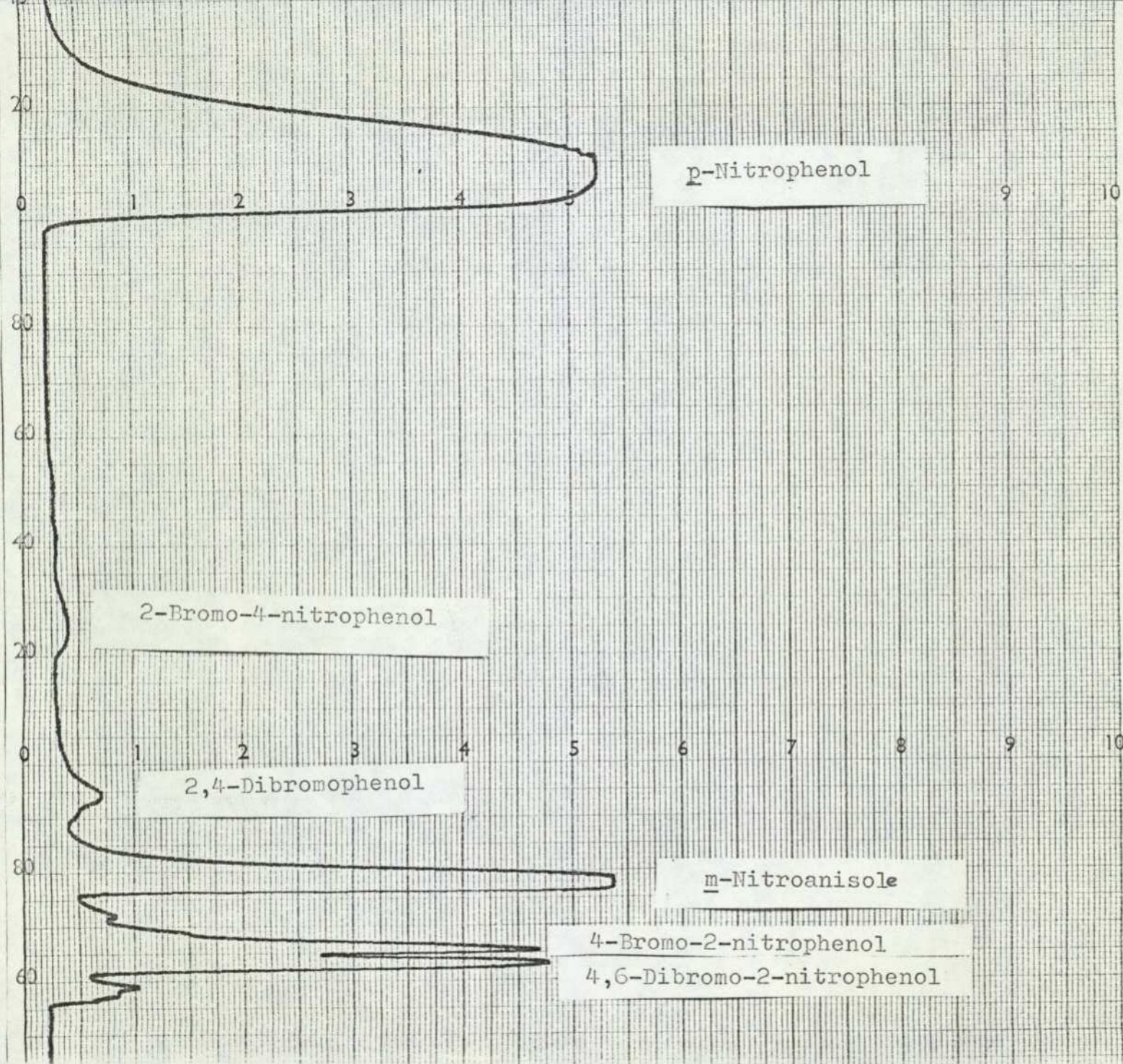
Compound	Weight/g
4-bromo-2-nitrophenol	0.0232
2-bromo-4-nitrophenol	0.0029
2,4-dibromo-6-nitrophenol	0.0228
2,4-dibromophenol	0.0053
<u>p</u> -nitrophenol	0.1653
<u>m</u> -nitroanisole	0.0471

The method of relative response factors as described in Section 7.5 was used:-

$$c_x/c_s = A_x/A_s \times f$$

Factor <i>f</i> for 4-bromo-2-nitrophenol	: 1.48
Factor <i>f</i> for 2-bromo-4-nitrophenol	: 0.10
Factor <i>f</i> for 2,4-dibromo-6-nitrophenol	: 0.61
Factor <i>f</i> for 2,4-dibromophenol	: 0.63
Factor <i>f</i> for <u>p</u> -nitrophenol	: 0.22

Fig. 3.13 Chromatogram of the products from the nitration of p-bromophenol in 70.8% sulphuric acid



Amount of 4-bromo-2-nitrophenol =

$$= \frac{0.0232}{0.0471} \times 6 \times 10^{-5} \times 1.48 \text{ moles}$$

$$= 3.57 \times 10^{-5} \text{ moles}$$

$$\begin{aligned} \% \text{ of 4-bromo-2-nitrophenol} &= \frac{3.57 \times 10^{-5}}{9.94 \times 10^{-5}} \times 100 \\ &= 35.9 \% \end{aligned}$$

Similarly:

2-bromo-4-nitrophenol	: 0.7 %
2,4-dibromo-6-nitrophenol	: 14.0 %
2,4-dibromophenol	: 4.3 %
<u>p</u> -nitrophenol	: 46.6 %

Table 3.13 and Fig. 3.14 give the yields of the products from the nitration of p-bromophenol in various concentrations of sulphuric acid at $25.0 \pm 1.0^{\circ}$.

3.322 p-CHLOROPHENOL

A typical determination of the yields:-

Sulphuric acid	: 70.8% w/w
Amount of nitric acid	: 6.00×10^{-5} moles
Amount of <u>p</u> -chlorophenol	: 5.95×10^{-5} moles
Amount of reference standard	
2-methyl-3-nitrophenol	: 6.43×10^{-5} moles

Fig. 3.15 shows the chromatogram obtained (h.p.l.c. conditions as in Table 3.2).

Peak weights from chromatogram

Compound	Weight/g
4-chloro-2-nitrophenol	0.0172
2-methyl-3-nitrophenol (standard)	0.0156

Table 3.13

Yields of nitro-compounds from the nitration of
p-bromophenol in sulphuric acid at $25.0 \pm 0.2^\circ$

H_2SO_4 (%) ^{a,b,c}	p-nitro- phenol	4-bromo- 2-nitro- phenol	2-bromo- 4-nitro- phenol	2,4-dibromo- phenol	2,4-dibromo 6-nitro- phenol	Mass balance (%) ^e
62.2	40.4	28.1	0.2	5.0	28.0	102
63.8	38.5	29.1	0.1	6.4	25.6	100
66.3	39.2	32.1	0.1	6.2	20.6	98
68.8	38.6	34.1	0.1	7.9	17.5	100
70.8 ^d	46.6	35.9	0.7	4.3	14.0	100
73.5 ^d	33.8	44.8	0.5	4.9	13.0	94
75.2 ^d	25.3	51.2	0.3	7.2	9.2	93
76.6 ^d	15.0	75.9	—	4.2	3.1	98
78.2 ^d	12.6	87.3	— ^f	— ^f	— ^f	100
80.8 ^d	8.3	91.7	—	—	—	100
82.8 ^d	4.8	94.5	—	—	—	99
84.6 ^d	2.2	65.0	—	—	—	67
87.8 ^d	1.9	47.4	—	—	—	49

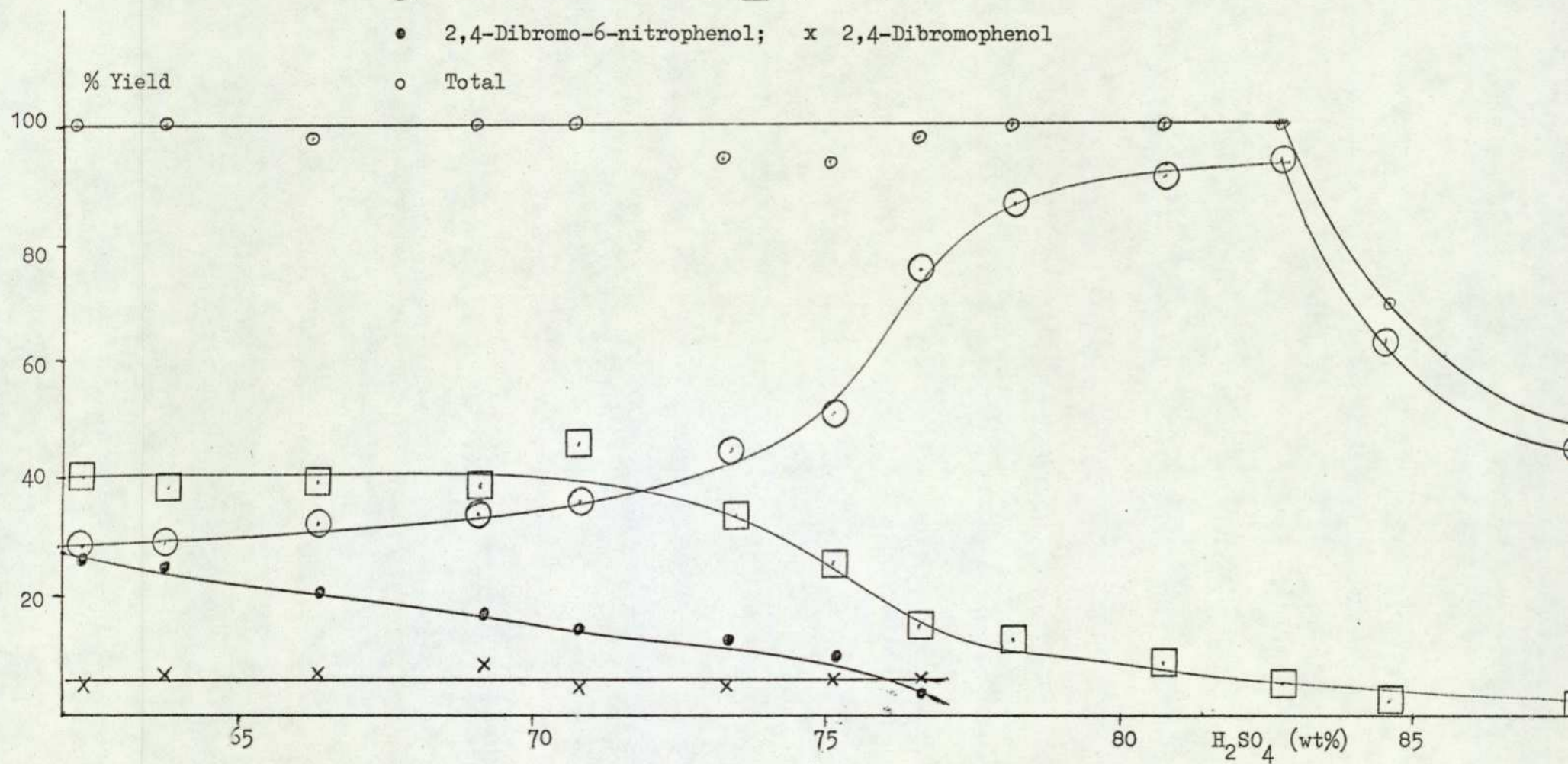
a) $\pm 0.1\%$ w/w; b) $[ArH] = 3.97 \times 10^{-3}$ mole dm^{-3} ;

c) [Sulphamic acid] ≈ 0.05 mole dm^{-3} ; d) $[HNO_3] = 3.99 \times 10^{-3}$ mole dm^{-3} ;

e) $\pm 2\%$; f) — (<0.05%).

Fig. 3.14 Yields of nitro-compounds from the nitration of
p-bromophenol in sulphuric acid at $25.0 \pm 1^\circ$

⊙ 4-Bromo-2-nitrophenol; □ p-Nitrophenol;
 • 2,4-Dibromo-6-nitrophenol; x 2,4-Dibromophenol
 ○ Total



The method of relative response factors as described in Section 7.5 was used:-

$$c_x/c_s = A_x/A_s \times f$$

Factor f for 4-chloro-2-nitrophenol : 0.83

Amount of 4-chloro-2-nitrophenol =

$$= \frac{0.0172}{0.0156} \times 6.43 \times 10^{-5} \times 0.83 \text{ moles}$$

$$= 5.91 \times 10^{-5} \text{ moles}$$

$$\begin{aligned} \text{\% of 4-chloro-2-nitrophenol} &= \frac{5.91 \times 10^{-5}}{5.95 \times 10^{-5}} \times 100 \\ &= 99.2\% \end{aligned}$$

Table 3.14 gives the yield of 4-chloro-2-nitrophenol from the nitration of p-chlorophenol in various concentrations of sulphuric acid at $25.0 \pm 1.0^\circ$. No p-nitrophenol or 2-chloro-4-nitrophenol was detected (<0.2%).

3.323 o-BROMOPHENOL

A typical determination of the yields:-

Sulphuric acid	: 62.2% w/w
Amount of nitric acid	: 1.38×10^{-3} moles
Amount of <u>o</u> -bromophenol	: 1.44×10^{-4} moles
Amount of reference standard	
<u>p</u> -nitroanisole	: 2.67×10^{-5} moles

Fig. 3.16 shows the chromatogram obtained (h.p.l.c. conditions as in Table 3.3).

Peak weights from chromatogram

Compound	Weight/g
2-bromo-4-nitrophenol	0.0322
2-bromo-6-nitrophenol	0.0235
<u>p</u> -nitroanisole (standard)	0.0230

Fig. 3.15 Chromatogram of the products from the nitration of *p*-chlorophenol in 70.8% sulphuric acid

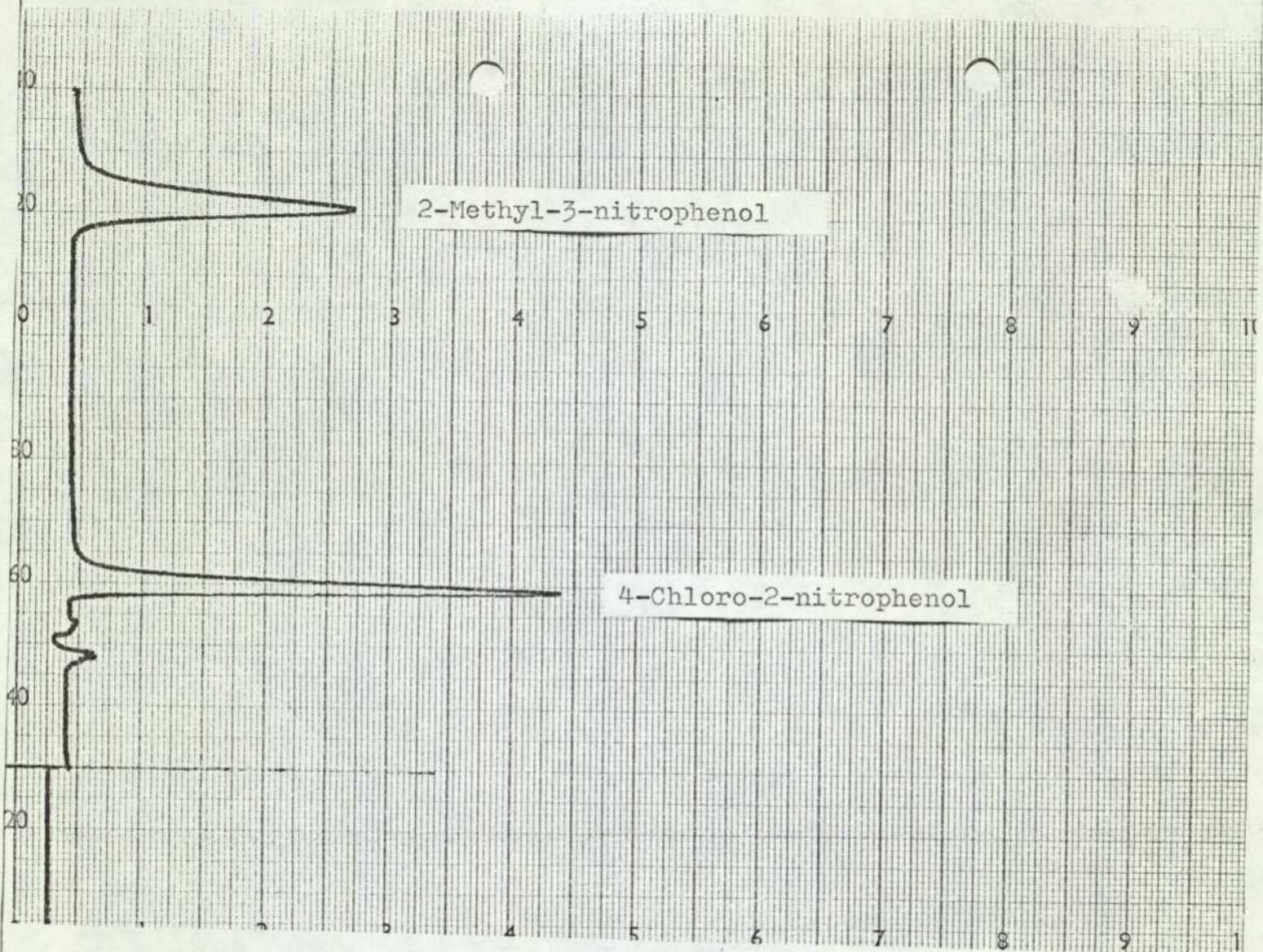


Table 3.14

Yields of nitro-compounds from the nitration of
p-chlorophenol in sulphuric acid at $25.0 \pm 0.2^\circ$

H_2SO_4 (%) ^{a,b,c}	4-chloro-2-nitro phenol (%) ^e
63.8	101.1
66.3	102.2
68.5	98.1
70.8 ^d	99.2
73.5 ^d	101.1
75.2 ^d	97.3
78.2 ^d	97.1

a) $\pm 0.1\%$ w/w

b) $[\text{ArH}] = 2.38 \times 10^{-3} \text{ mole dm}^{-3}$

c) $[\text{Sulphamic acid}] \text{ ca } 0.05 \text{ mole dm}^{-3}$

d) $[\text{HNO}_3] = 2.40 \times 10^{-3} \text{ mole dm}^{-3}$

e) $\pm 2\%$

The method of relative response factors as described in Section 7.5 was used:-

$$c_x/c_s = A_x/A_s \times f$$

Factor f for 2-bromo-6-nitrophenol : 2.65

Factor f for 2-bromo-4-nitrophenol : 1.97

Amount of 2-bromo-6-nitrophenol =

$$= \frac{0.0235}{0.0230} \times 2.67 \times 10^{-5} \times 2.65 \text{ moles}$$

$$= 6.95 \times 10^{-5} \text{ moles}$$

$$\begin{aligned} \text{\% of 2-bromo-6-nitrophenol} &= \frac{6.95 \times 10^{-5}}{1.44 \times 10^{-4}} \times 100 \\ &= 47.5\% \end{aligned}$$

Similarly:

$$\text{\% of 2-bromo-4-nitrophenol} = 52.1\%$$

Table 3.15 and Fig. 3.17 give the yields of the nitro compounds from the nitration of o-bromophenol in various percentages of aqueous sulphuric acid at $25.0 \pm 0.2^\circ$.

3.324 2,4-DIBROMOPHENOL

A typical determination of the yields:-

Sulphuric acid : 63.8% w/w

Amount of nitric acid : 1.38×10^{-3} moles

Amount of 2,4-dibromophenol : 1.24×10^{-4} moles

Amount of reference standard

p-nitroanisole : 6.3×10^{-5} moles

Fig. 3.18 shows the chromatogram obtained (h.p.l.c. conditions as in Table 3.4).

Fig. 3.16 Chromatogram of the products from the nitration of *o*-bromophenol in 62.2% sulphuric acid

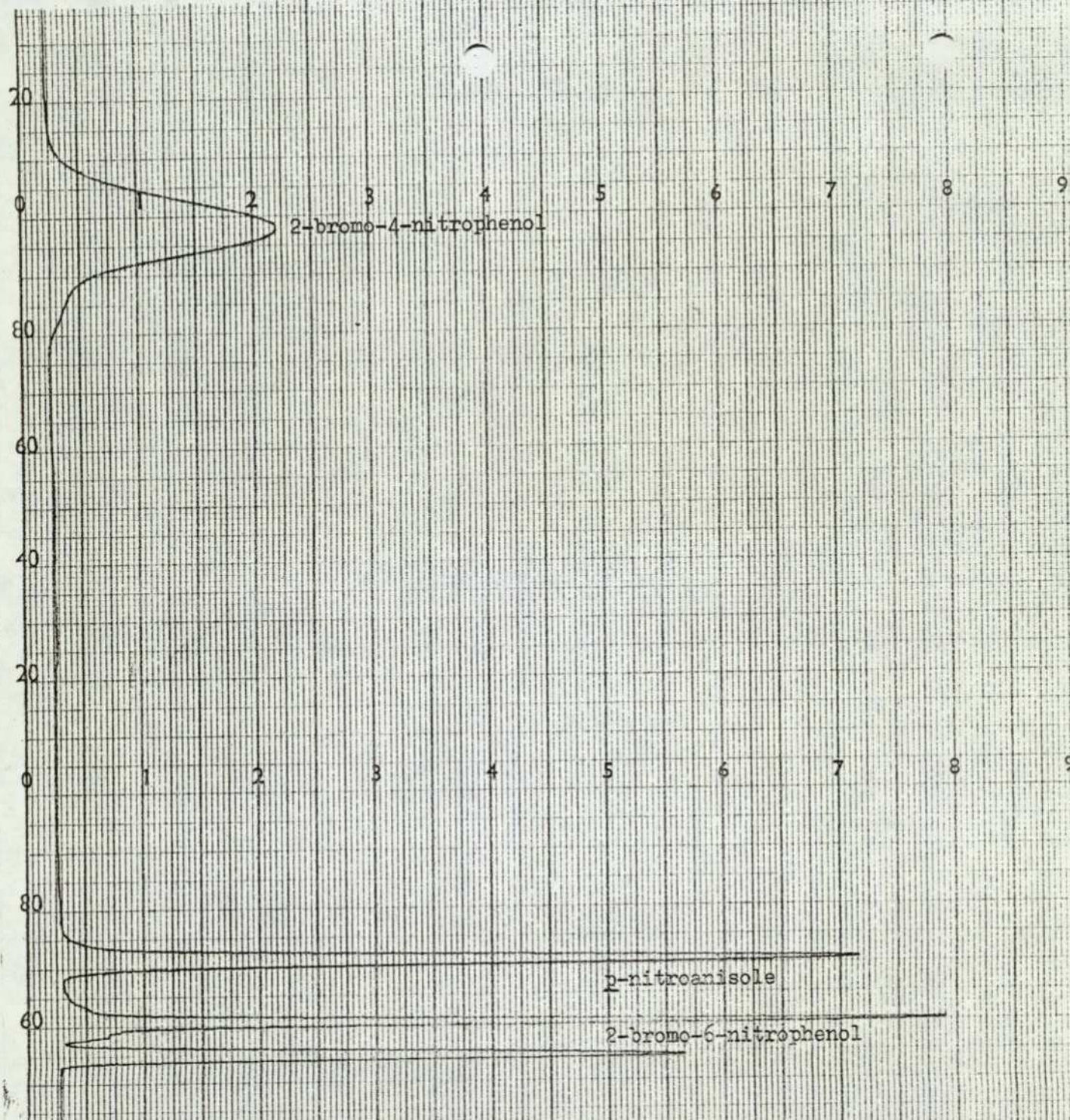


Table 3.15

Yields of nitro-compounds from the nitration of
o-bromophenol in sulphuric acid at $25.0 \pm 0.2^\circ$

H_2SO_4 (%) ^{a, b, c}	2-bromo-4-nitro- phenol	2-bromo-6-nitro- phenol	Mass balance (%) ^e
62.2	52.1	47.5	100
63.8	52.5	47.7	100
66.3	51.3	48.1	99
68.5	51.7	47.6	99
70.8 ^d	50.1	48.8	100
72.7 ^d	50.3	49.9	100
75.1 ^d	50.0	50.3	100
77.8 ^d	50.7	50.0	101
80.7 ^d	50.1	49.6	99
82.7 ^d	48.1	47.1	99
84.6 ^d	40.1	42.2	82

a) $\pm 0.1\%$ w/w

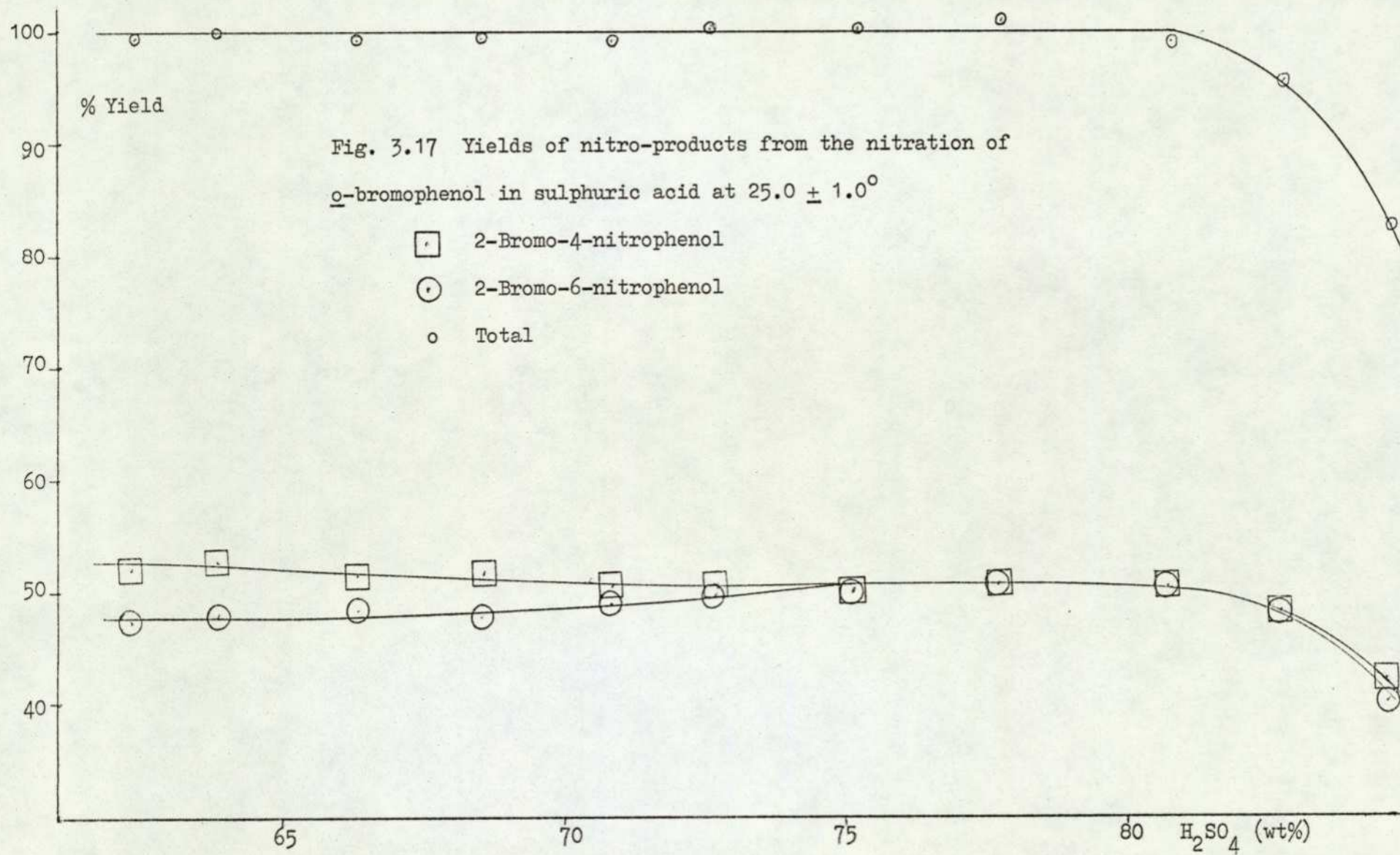
b) $[\text{ArH}] = 3.6 \times 10^{-3} \text{ mole dm}^{-3}$

c) $[\text{Sulphamic acid}] \text{ ca } 0.05 \text{ mole dm}^{-3}$

d) $[\text{HNO}_3] = 3.8 \times 10^{-3} \text{ mole dm}^{-3}$

e) $\pm 2\%$

f) No o-nitrophenol was detected ($< 0.5\%$)



Peak weights from chromatogram

Compound	Weight/g
2-bromo-4-nitrophenol	0.0103
2,4-dibromo-6-nitrophenol	0.0312
<u>p</u> -nitroanisoie (standard)	0.0231

The method of relative response factors as described in Section 7.5 was used:-

$$c_x/c_s = A_x/A_s \times f$$

Factor f for 2-bromo-4-nitrophenol : 1.97

Factor f for 2,4-dibromo-6-nitrophenol : 0.98

Amount of 2,4-dibromo-6-nitrophenol =

$$= \frac{0.0312}{0.0231} \times 6.3 \times 10^{-5} \times 0.98 \text{ moles}$$

$$= 9.15 \times 10^{-5} \text{ moles}$$

$$\% \text{ of 2,4-dibromo-6-nitrophenol} = \frac{9.15 \times 10^{-5}}{1.24 \times 10^{-4}} \times 100$$

$$= 74.1 \%$$

Similarly:

$$\% \text{ of 2-bromo-4-nitrophenol} = 23.6 \%$$

Table 3.16 and Fig. 3.19 give the yields of the nitro-products from the nitration of 2,4-dibromophenol in various concentrations of aqueous sulphuric acid at $25.0 \pm 0.2^\circ$.

Fig. 3.18 Chromatogram of the products from the nitration of 2,4-dibromophenol in 63.8% sulphuric acid

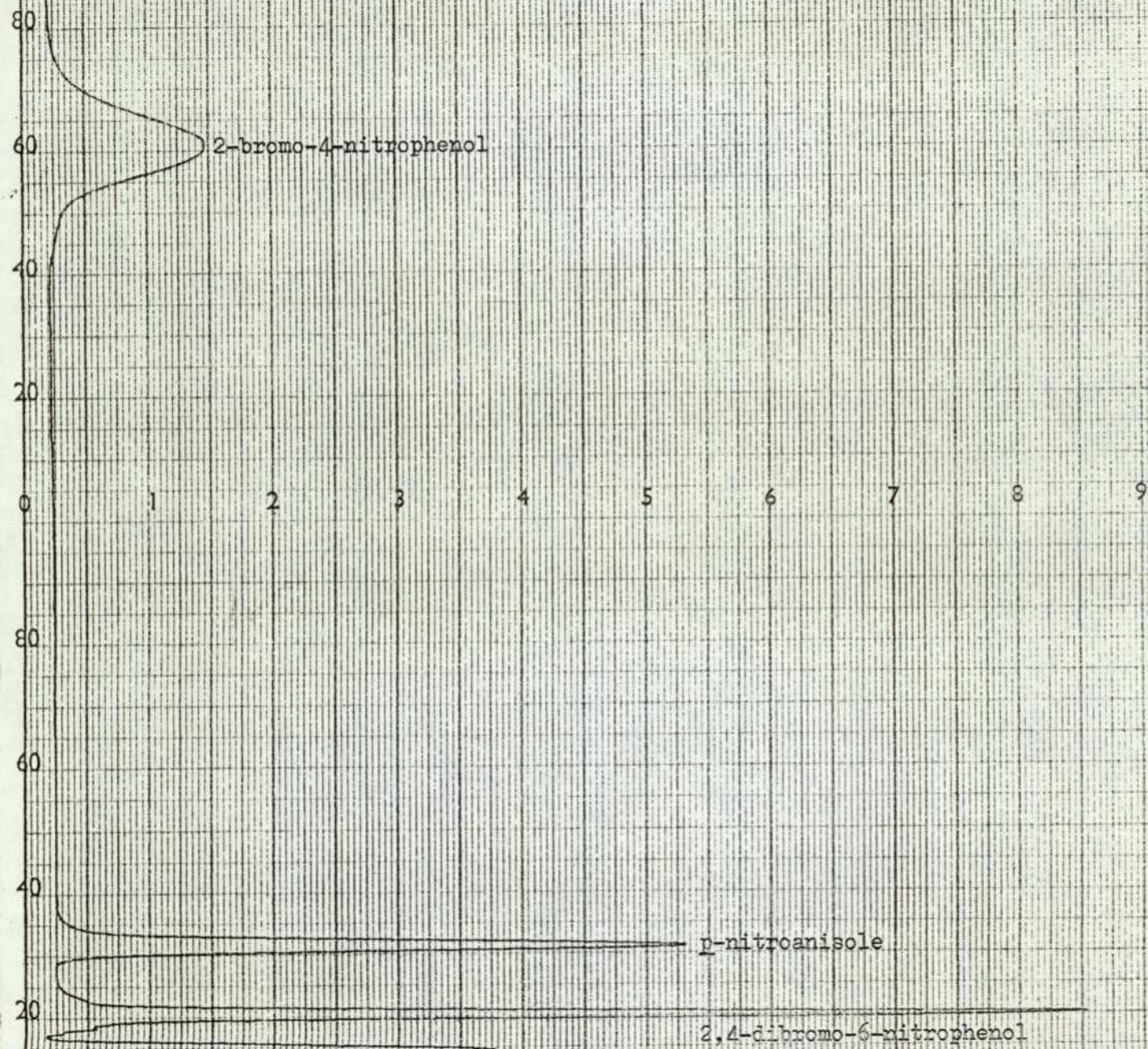


Table 3.16

Yields of nitro-compounds^f from the nitration of
2,4-dibromophenol in sulphuric acid at $25.0 \pm 0.2^\circ$

H_2SO_4 (%) ^{a,b,c}	2-bromo-4-nitro- phenol	2,4-dibromo- 6-nitrophenol	Mass balance (%) ^e
62.2	23.4	71.9	95
63.8	23.6	72.1	96
66.3	23.1	73.0	96
68.5	21.4	75.2	97
70.5	18.3	79.5	98
72.7 ^d	12.0	83.4	96
74.3 ^d	5.8	87.8	94

a) $\pm 0.1\%$ w/w

b) $[\text{ArH}] = 4.96 \times 10^{-3} \text{ mole dm}^{-3}$

c) $[\text{Sulphamic acid}] \text{ ca } 0.05 \text{ mole dm}^{-3}$

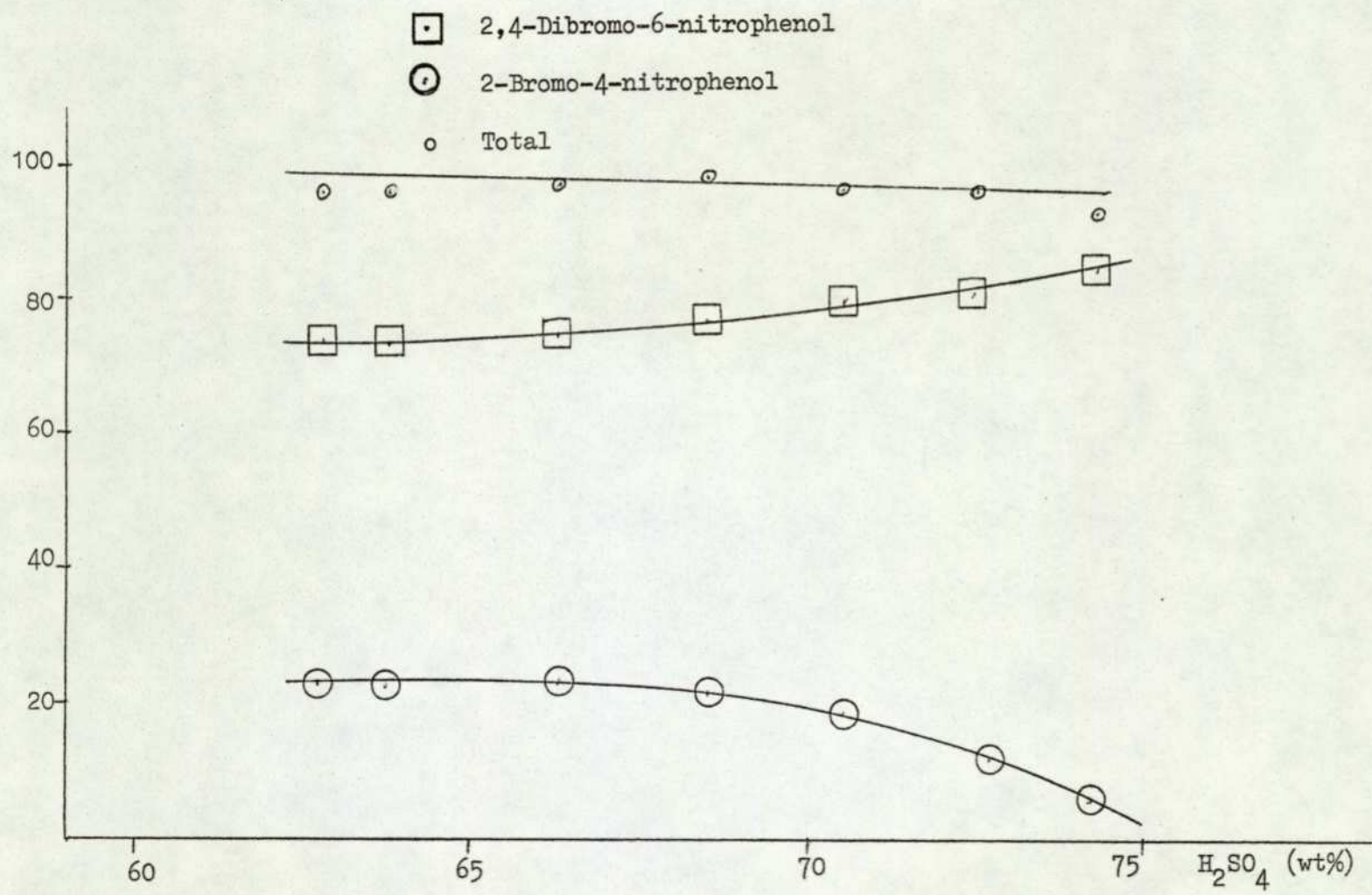
d) $[\text{HNO}_3] = 5.06 \times 10^{-3} \text{ mole dm}^{-3}$

e) $\pm 2\%$

f) No 2,6-dibromo-4-nitrophenol was detected ($< 1\%$).

This compound was, however, insoluble in the
extraction solvents used.

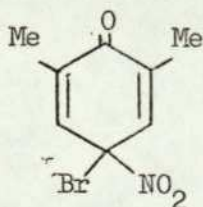
Fig. 3.19 Yields of nitro-compounds from the nitration of 2,4-dibromophenol in sulphuric acid at $25.0 \pm 1.0^\circ$



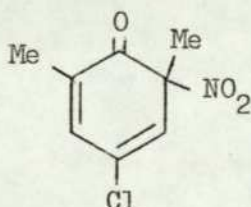
3.4 DISCUSSION

3.41 RATE PROFILES

The kinetic results call only for the comment that p-bromophenol, p-chlorophenol and o-bromophenol are more reactive than benzene but significantly less reactive than mesitylene and phenol, the slopes of the rate profiles being of intermediate value between those for mesitylene and benzene (Fig. 3.3, 3.6 and 3.9). Their rates of nitration (which are very close to each other) are therefore depressed only to a small extent by diffusion control. The rate profile for 2,4-dibromophenol (Fig. 3.12) is very close and slightly above to that of benzene which suggests that the rate of nitration of 2,4-dibromophenol is not diffusion controlled. There is no evidence from the UV spectra recorded during the reaction for the presence of cyclohexadienone intermediates, a possible consequence of ipso-substitution. Such an intermediate has been reported previously in the cases of p-cresol^{66,81} and is also present in the nitration of p-methylanisole. Some 2,6-disubstituted-4-bromophenols are known to give stable cyclohexadienones⁸² on reaction with nitric acid (e.g. 2,6-dimethyl-4-bromo-4-nitrocyclohexa-2,5-dien-1-one I) but clearly the cyclohexadienone intermediates for p-bromophenol and 2,4-dibromophenol, if present, are not long lived enough to be observed in these experiments. No analogous cyclohexadienone derivative of a p-chlorophenol has been reported. Even in the case of 2,6-disubstituted-4-chlorophenols the products isolated have the nitro group ipso at 2- or 6-positions^{82,83} but not ipso at C-Cl (e.g. 4-chloro-2,6-dimethyl-2-nitrocyclohexa-3,5-dien-1-one II).



I

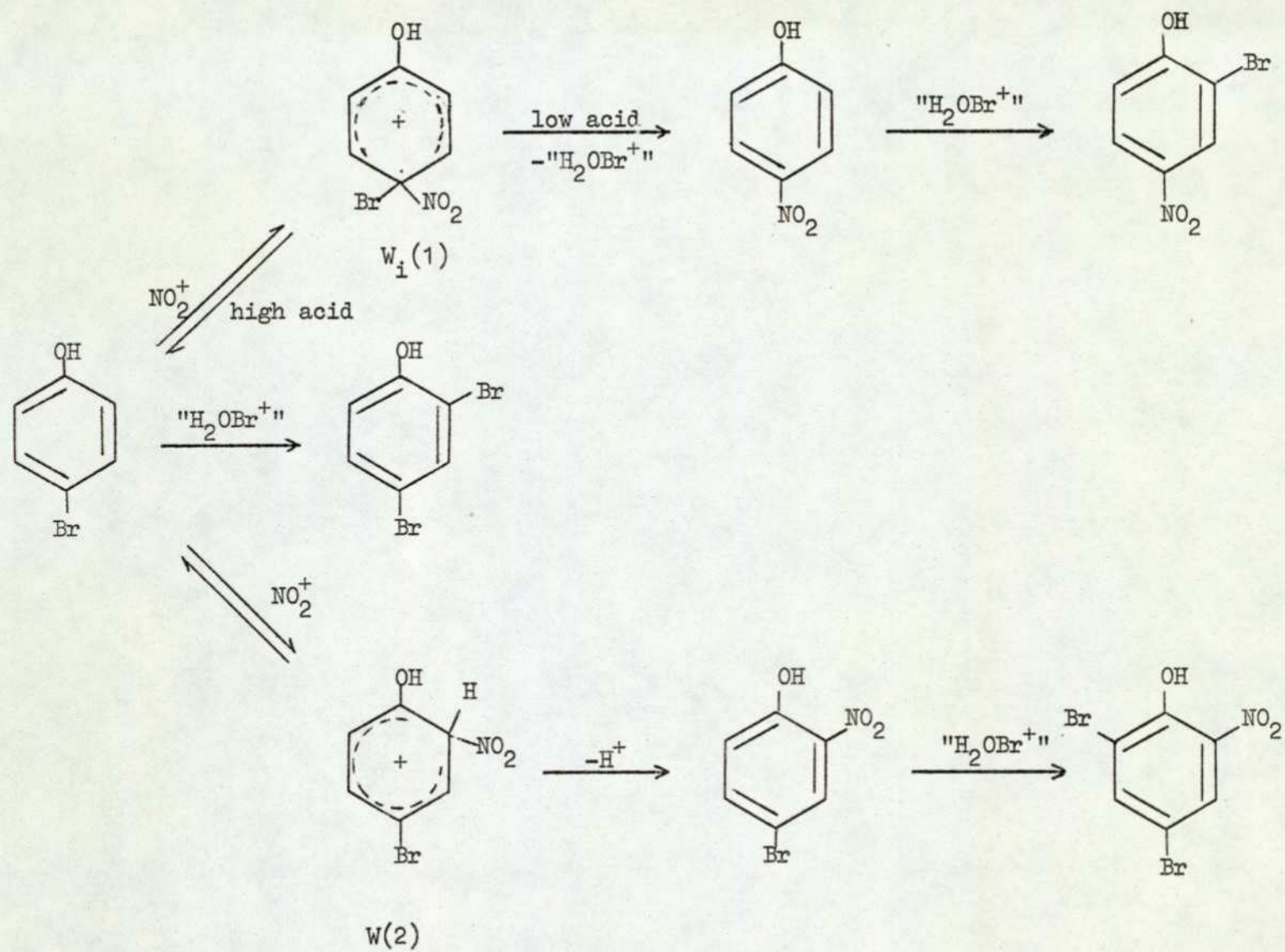


II

3.42 ISOMER PROPORTIONS

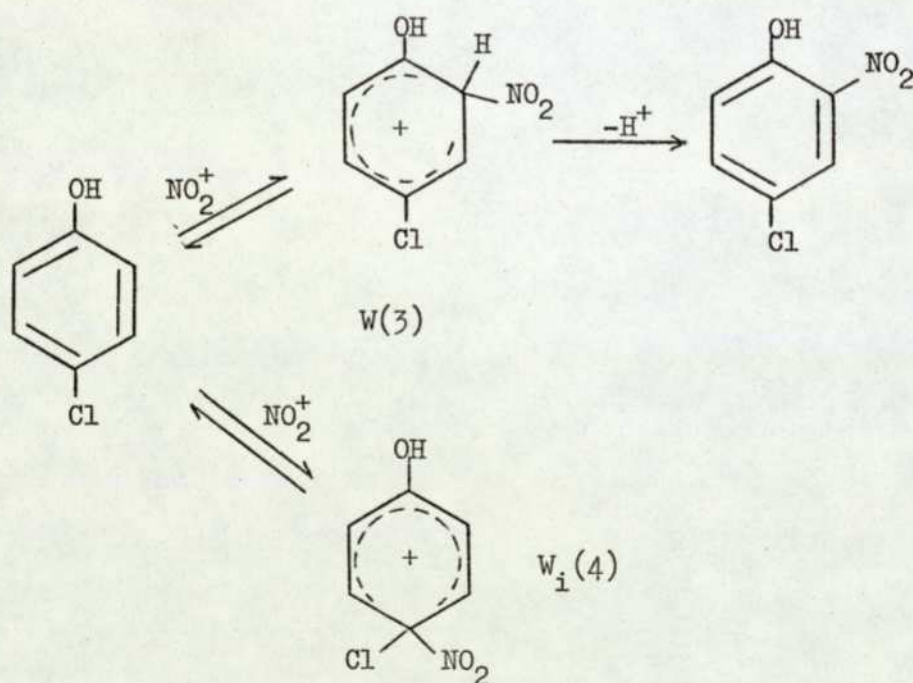
In the nitration of p-bromophenol the yields of the products are quantitative in the region of 62 - 83% sulphuric acid (Table 3.13 and Fig. 3.14) and the amount of nitrodebromination decreases with increasing acidity in the region of 73 - 83% sulphuric acid. The variation is such as to suggest that the debromination step is correctly described as the reverse of "positive bromination". In 83% sulphuric acid the 4-bromo-2-nitrophenol is 95% of the product and in 62% sulphuric acid 40% of the nitrodebromination product, p-nitrophenol, is formed. Scheme 3.1 accounts for the observed features of the reaction and " H_2OBr^+ "⁷⁸ represents the species formed in nitrodebromination (the Br^+ is removed by the base H_2O). 80 - 90% of the " H_2OBr^+ " formed seems to react with aromatic species.

The Wheland intermediate $\text{W}_i(1)$ (Scheme 3.1) can lose "positive bromine" to give p-nitrophenol which in turn can react with " H_2OBr^+ " to give 2-bromo-4-nitrophenol which in this case has been detected in very small amounts ($<1\%$). The $\text{W}_i(1)$ at high acidities and therefore low water concentrations can return to the starting materials. The Wheland intermediate $\text{W}(2)$ loses a proton to give the major product, 4-bromo-2-nitrophenol, which could also react with " H_2OBr^+ " present at low acidities to give the 2,4-dibromo-6-nitrophenol. "Positive bromine" can also react with the starting material to give 2,4-dibromophenol which was observed. Nitration of this product would give another route to the observed 2,4-dibromo-6-nitrophenol and also to 2-bromo-4-nitrophenol by ipso-attack at C-4. Ipso-attack at C-2 would give another route to 4-bromo-2-nitrophenol but is unlikely to occur as no nitrodebromination product was detected in the nitration of o-bromophenol (see below). The possible importance of routes involving 2,4-dibromophenol is discussed again below.



Scheme 3.1

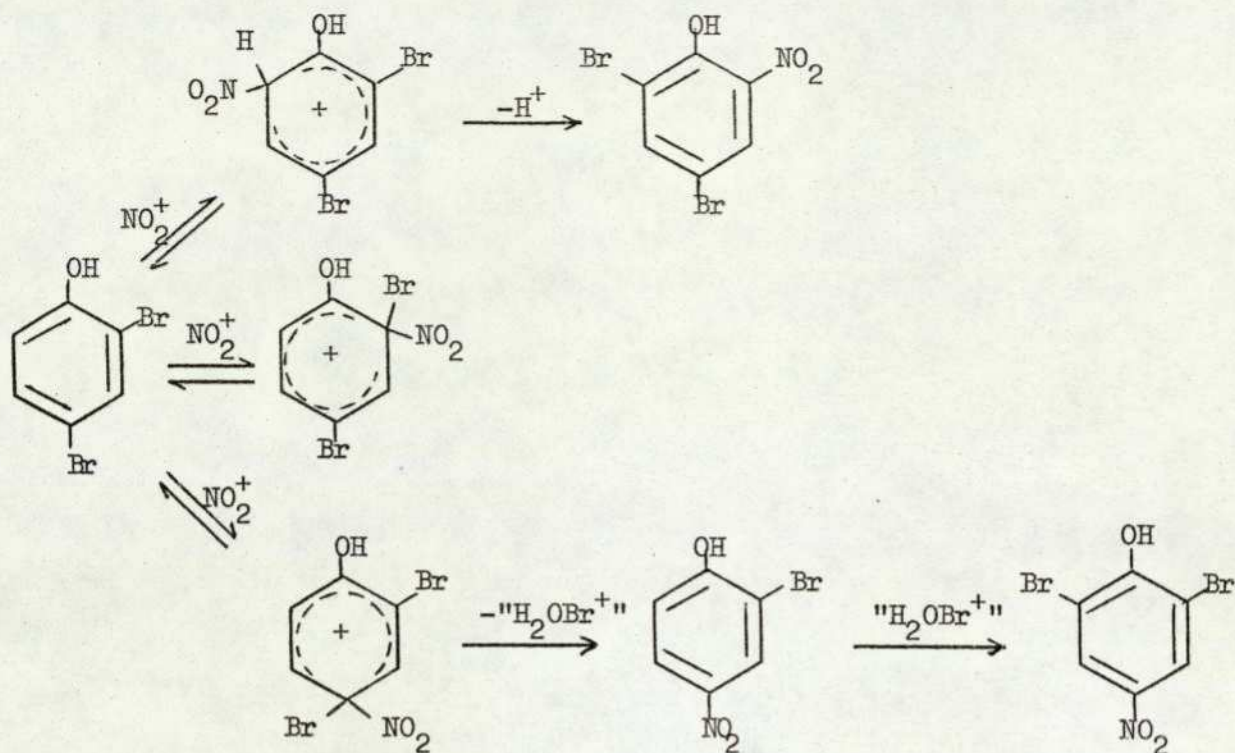
In the nitration of p-chlorophenol, 4-chloro-2-nitrophenol is formed quantitatively (Table 3.14). Scheme 3.2 illustrates the proposed mechanism in which the product arises either from direct nitration or through the initial formation of the Wheland intermediate $W_i(4)$. Evidence for the latter process comes from the nitration of p-chloroanisole⁵¹ (Scheme 1.10) where 4-chloro-2-nitrophenol is one of the products ($\sim 40\%$) and which can most reasonably be accounted for by ipso-substitution at C-Cl and subsequent demethoxylation. Well established instances of ipso-substitution at C-Cl⁸⁴ also support the existence of Wheland intermediates such as $W_i(4)$. It is noteworthy that experiments on the acetic acid decomposition of 1-halogeno-1-nitro-2-oxo-1,2-dihydronaphthalene⁸⁵ indicate the sequence of leaving ability $\text{Br}^+ > \text{NO}_2^+ > \text{Cl}^+$ so that in nitration $W_i(4)$ may well regress to the starting materials in preference to losing "positive chlorine".



Scheme 3.2

In the nitration of o-bromophenol the yields of the products are quantitative over the range of 62 - 82% sulphuric acid (Table 3.15 and Fig. 3.17) and no nitrodebromination product (~~of~~ o-nitrophenol) was detected. The ratio of 6-nitro to 4-nitro-2-bromophenol is approximately 1 and it does not vary with acidity as do the corresponding quantities in the cases of o-cresol and o-methylanisole. There is thus no sign of the general medium effect on product isomer ratios noted for more reactive compounds (Chapter 2 and Section 1.344). This may be to the relative unreactivity of the substrate leading to loss of the hydrogen bond from the hydrogen bonded encounter pair, the rate of formation of which is not rate limiting, competing successfully with Wheland intermediate formation at all acidities studied. A similar result was obtained⁸⁶ in the nitration of o-bromoanisole in aqueous sulphuric acid where the ratio of the 4- to 6-nitro products does not vary with acidity and no demethoxylation was observed. In the present case as with o-dibromobenzene⁷⁸, o-bromophenol and 2-bromo-m-xylene⁷⁸ there is thus no evidence to reveal the role of ipso-attack at C-Br.

2,4-Dibromophenol is nitrated quantitatively in the region of 64 - 74% sulphuric acid (Table 3.16 and Fig. 3.19) and the amount of nitrodebromination product, 2-bromo-4-nitrophenol, decreases from 23% in 64% sulphuric acid to 6% in 74% sulphuric acid. Bromination of the nitrodebrominated product, 2-bromo-4-nitrophenol, would yield 2,6-dibromo-4-nitrophenol but this product was not detected on the h.p.l.c. chromatogram (<1%). The reason for this is probably the observed very low solubility of this compound in the extraction solvents used (chloroform or dichloromethane). 2,6-Dibromo-4-nitroanisole, however, was one of the products in the nitration of 2,4-dibromoanisole⁷³ which suggests that 2,6-dibromo-4-nitrophenol is most probably formed



Scheme 3.3

(ca 3 - 5%) in the nitration of 2,4-dibromophenol. The proposed mechanism for the nitration of 2,4-dibromophenol is shown in Scheme 3.3.

The studies of 2,4-dibromophenol have relevance to the discussion of the results from the nitration of *p*-bromophenol. The significant amount of 2-bromo-4-nitrophenol formed contrasts with the product situation from *p*-bromophenol and indicates that in the latter case 2,4-dibromophenol is not an intermediate in the major route for the formation of 2,4-dibromo-6-nitrophenol, which is presumably therefore mainly formed by bromination of 4-bromo-2-nitrophenol.

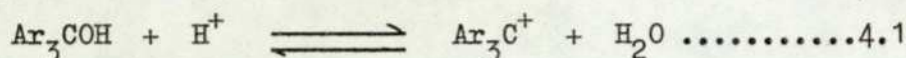
CHAPTER 4

THE NITRATION OF 1,3,5-TRIMETHOXYBENZENE
AND OF PHLOROGLUCINOL; THE 'ZEROth ORDER'

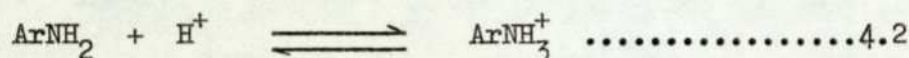
NITRATION OF PHENOL

4.1 INTRODUCTION

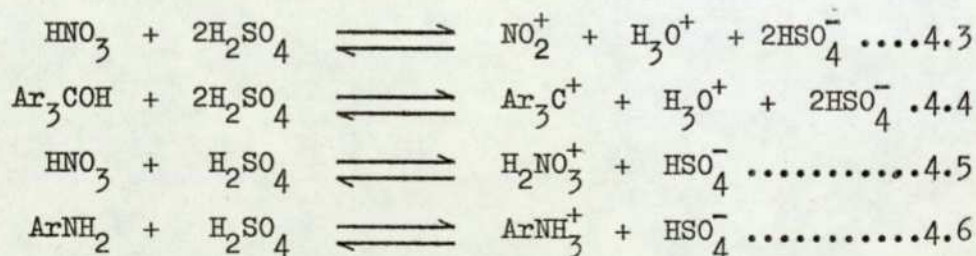
The continued effectiveness of the nitronium ion for nitration in relatively dilute solutions has been indicated by comparing the dependence of the rates on the concentration of sulphuric acid with the acidity-dependence of the ionization of model compounds. The H_R acidity scale^{87,88,89} was determined from the ionization of a series of triarylcarbinols, which undergo ionization as follows:-



The acidity function Ho ⁹⁰, however, is based on the behaviour of indicators ionizing according to the equation below:-



If the assumption is made that the ionization characteristics of nitric acid are similar to those of the organic bases used to define the acidity functions, then a correspondence between the acidity dependence of rates of nitration and H_R would suggest the involvement of the nitronium ion. A correspondence with Ho would support the idea that nitric acidium ion ($H_2NO_3^+$) was the effective electrophile. The formal similarities are clear from the following equations:-



Specific structural differences of organic indicators are now thought to lead to a diminishing of the generality of the derived acidity scales⁹¹ and the assumption that nitric acid behaves in a quantitatively

similar manner to an organic indicator must be in doubt. However, in view of the large differences between the H_R and H_o scales and the correspondence of the acidity dependence of nitration so much more closely with H_R than with H_o , the effectiveness of the nitronium ion is firmly established¹³. Although the difference between H_o and H_R is great enough to allow gross mechanistic distinction to be made, the acidity dependence of nitration deviates from an exact correspondence with H_R ⁹².

A better correlation has been found by comparing $\log_{10} k_2(\text{obs})$ with $-(H_R + \log_{10} a_{H_2O})$ ^{15,93,94}. In these comparisons a straight line of slope approximately 1 for a number of compounds has been found, where the bulk species present is being nitrated. A possible explanation for this behaviour is that in these acidities¹⁵, the nitric acid molecule is present predominantly as a monohydrate but it may be that the H_R function is not appropriate for nitric acid.

The aim of the study described in this Chapter was to try and obtain evidence for any other electrophile operating at low acidities with sufficiently activated compounds. For very reactive substrates reaction with the nitronium ion is limited by encounter and thus, low acidities where other electrophiles exist in greater relative concentrations, provide the most likely conditions for these other species to become effective. The compounds chosen for this study were 1,3,5-trimethoxybenzene and phloroglucinol. These compounds would be expected to have intrinsic reactivities of about 10^{12} times that of benzene, although this reactivity might be modified by steric effects. If another electrophile was operating such as $H_2NO_3^+$ the slope of a plot of $\log_{10} k_2(\text{obs})$ vs acidity would change. The expected situation is shown in Fig. 4.1.

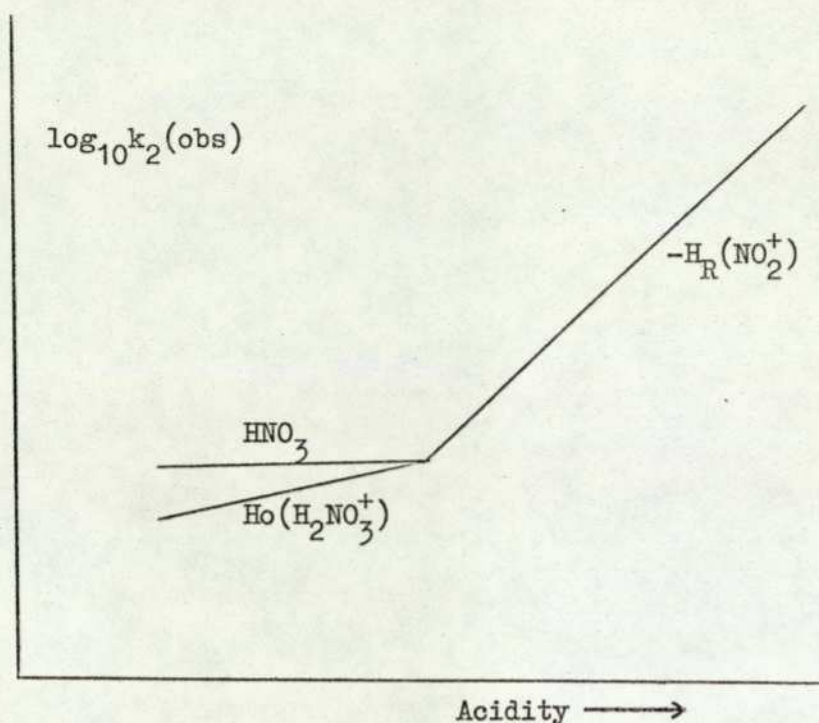


Fig. 4.1

Kinetic studies for the nitration of these compounds were carried out at various temperatures (as high as possible) in order to determine second-order rate coefficients at as low acidities as possible. The nitration of 1,3,5-trimethoxybenzene has been previously studied by J.G. Golding⁶⁶ at 25 and 40°, and above these temperatures complications arose, which were thought to be due to fortuitous nitrosation which might be alleviated by the use of sulphanilic acid as the nitrous acid trap.

A further aim of the study described in this Chapter was to determine values of rate coefficients for nitronium ion formation over a wider range of acidities and calculate the half-life of the nitronium ion at low acidities by extrapolation, so that it might be possible to comment on the occurrence of pre-association mechanisms of nitration at these acidities. The substrate chosen for this study

was phenol which was relatively soluble in aqueous sulphuric acid.

The rate equation 4.10 can be derived from equations 1.12 and 1.13 (page 15) using a steady state approximation with respect to the concentration of the nitronium ion. With sufficiently low

$$\frac{-d[\text{HNO}_3]}{dt} = \frac{-d[\text{ArH}]}{dt} = \frac{k_1 k_r [\text{HNO}_3] [\text{ArH}]}{k_{-1} + k_r [\text{ArH}]} \dots\dots\dots 4.10$$

concentrations of aromatic substrate the reaction is first-order in both nitric acid and aromatic substrate (Eq. 4.10). This is the situation which normally one obtains in these media, even with aromatic compounds sufficiently reactive to react upon encounter with the nitronium ion ¹⁷, because with most substrates low solubilities make low concentrations unavoidable. Under such circumstances only k_2 (Eq. 4.11) can be determined.

$$k_2 = k_1 k_r / k_{-1} \dots\dots\dots 4.11$$

Provided that the concentration of the aromatic substrate can be made high enough for $k_r [\text{ArH}] \gg k_{-1}$ then k_1 , the rate of formation of the nitronium ion can be directly determined.

4.2 EXPERIMENTAL

4.21 MATERIALS

These were as described in Section 7.2 with the addition of the following: Phenol and phloroglucinol dihydrate were of AnalaR grade and 1,3,5-trimethoxybenzene was a commercial reagent purified by recrystallization. 1,3,5-Trimethoxy-2-nitrobenzene was as previously described⁶⁶.

4.211 NITROPHLOROGLUCINOL

Anhydrous phloroglucinol (20g) was stirred in 50% sulphuric acid (200 ml) for 5 minutes and then a mixture of concentrated nitric acid (20 ml) and 50% sulphuric acid (100 ml) was added slowly at 20°. The reaction mixture was stirred for one hour and then 400g of ice was added. After filtration the precipitate was left standing for 15 minutes with a further 150g of ice. Filtration gave 3.8g of phloroglucinol as a brown crystalline solid; m.p. 183 - 184° (lit.⁹⁵ 184°).
¹H.n.m.r. (Acetone-d₆): τ 2.97 (2H, s, ArH), 5.56 (3H, s, OH).

4.22 KINETIC MEASUREMENTS

For 1,3,5-trimethoxybenzene and phloroglucinol these were as described in Section 7.3. In the case of phenol the same procedure was followed but the concentrations of the aromatic substrate were high enough for the reaction to be less than first-order in aromatic, thus, rate constants (k_1) for the formation of the nitronium ion from solute nitric acid can be determined (Eqs. 4.11 and 4.12).

4.3 RESULTS

4.31 KINETICS

4.311 1,3,5-TRIMETHOXYBENZENE

A typical determination of a rate coefficient:-

Concentration of sulphuric acid	: 53.9% w/w
Concentration of nitric acid	: 5.51×10^{-2} mole dm ⁻³
Concentration of 1,3,5-trimethoxybenzene	: 1.01×10^{-4} mole dm ⁻³
Concentration of sulphanilic acid	<u>ca</u> 0.05 mole dm ⁻³
Temperature	: $60.0 \pm 0.2^\circ$
Wavelength of measurement	: 350 nm

Fig. 4.2 shows the extinction curve, Table 4.1 the data obtained therefrom and Fig. 4.3 shows the plot of $\log_{10}(A_t - A_\infty)$ vs time.

$$k_2(\text{obs}) = -2.303 \times \text{slope} / [\text{HNO}_3] \text{ dm}^3 \text{ mole}^{-1} \text{ s}^{-1}$$

$$k_2(\text{obs}) = 1.31 \times 10^{-2} \text{ dm}^3 \text{ mole}^{-1} \text{ s}^{-1}$$

Only the rate of the initial stage of the reaction was measured (Fig. 4.3) because of the curvature of the first-order plot. It was not possible to obtain kinetic data at all for the nitration of 1,3,5-trimethoxybenzene at lower acidities than 54% sulphuric acid because the rate of hydrolysis of 1,3,5-trimethoxybenzene to phloroglucinol becomes faster than nitration at these lower acidities. The spectral change (Fig. 4.4) of 1,3,5-trimethoxybenzene in 48% sulphuric acid ($H_o = -3.14$) at 60° was followed and the final spectrum was identical to that of phloroglucinol which was recorded under the same conditions and concentrations. The value of the rate constant ($k_{\text{obs}} = 2.71 \text{ s}^{-1}$) determined was in close agreement with that estimated⁹⁷ in perchloric acid ($H_o = -3.23$, $k_{\text{obs}} = 3.31 \text{ s}^{-1}$) at 60° .

In view of this hydrolysis, attention was concentrated on phloroglucinol.

4.312 PHLOROGLUCINOL

A typical determination of a rate coefficient:-

Concentration of sulphuric acid	: 53.9% w/w
Concentration of phloroglucinol	: $7.92 \times 10^{-5} \text{ mole dm}^{-3}$
Concentration of nitric acid	: $5.51 \times 10^{-2} \text{ mole dm}^{-3}$
Concentration of sulphanilic acid	<u>ca</u> $0.05 \text{ mole dm}^{-3}$
Temperature	: $40.0 \pm 0.2^\circ$
Wavelength of measurement	: 350 nm

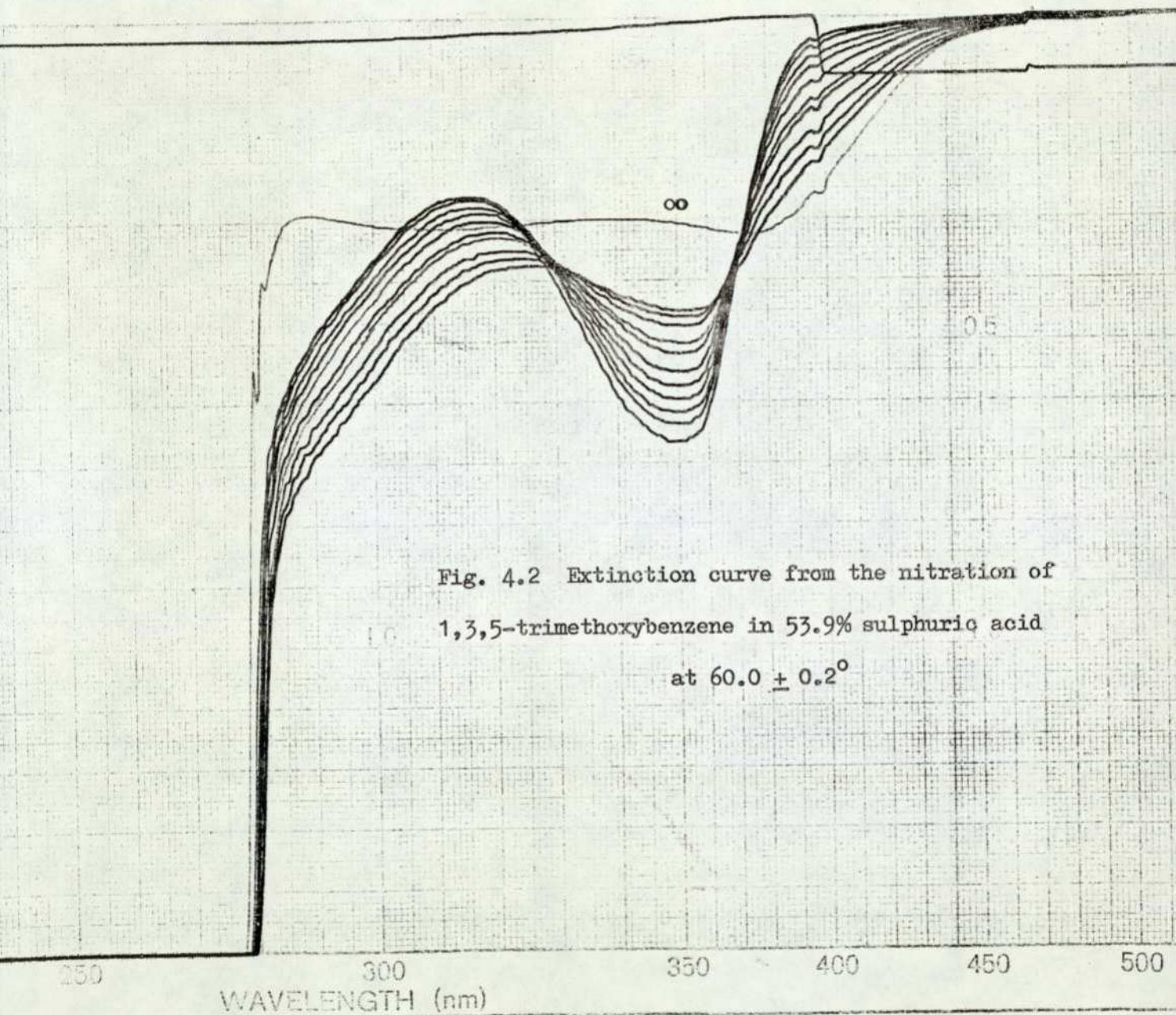


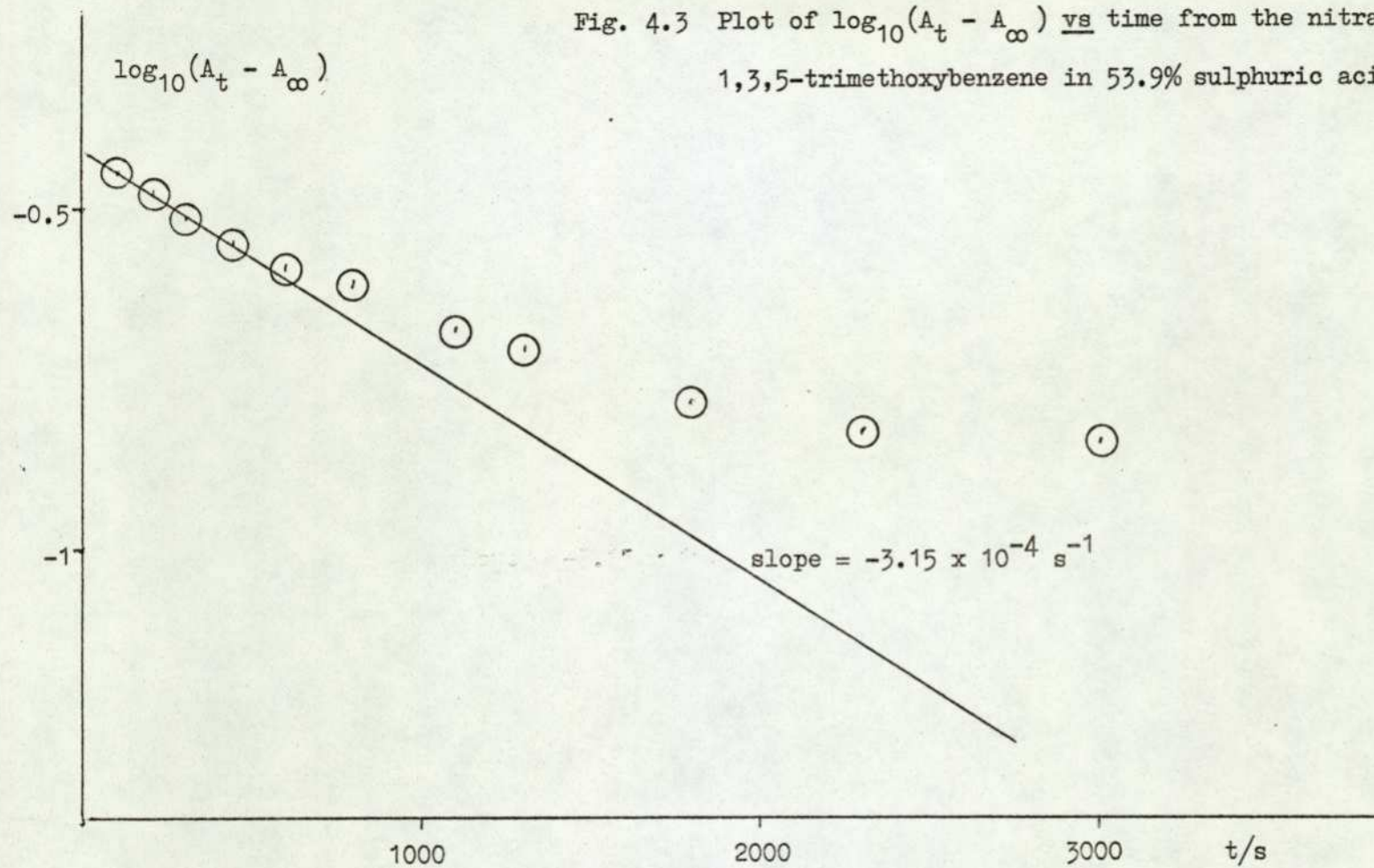
Table 4.1

Data from a typical determination of the rate
of nitration of 1,3,5-trimethoxybenzene in 53.9%
sulphuric acid at $60.0 \pm 0.2^\circ$

Time (t)	Absorbance	$\log_{10}(A_t - A_\infty)$
/s	A_t	
100	0.667	-0.45
200	0.638	-0.48
300	0.618	-0.51
450	0.597	-0.54
600	0.574	-0.68
800	0.551	-0.62
1100	0.521	-0.68
1280	0.505	-0.71
1800	0.474	-0.79
2300	0.460	-0.86
t_∞	0.310^a	

a) Calculated from the molar absorptivity of
1,3,5-trimethoxy-2-nitrobenzene in 53.9%
sulphuric acid.

Fig. 4.3 Plot of $\log_{10}(A_t - A_\infty)$ vs time from the nitration of
1,3,5-trimethoxybenzene in 53.9% sulphuric acid at $60.0 \pm 0.2^\circ$



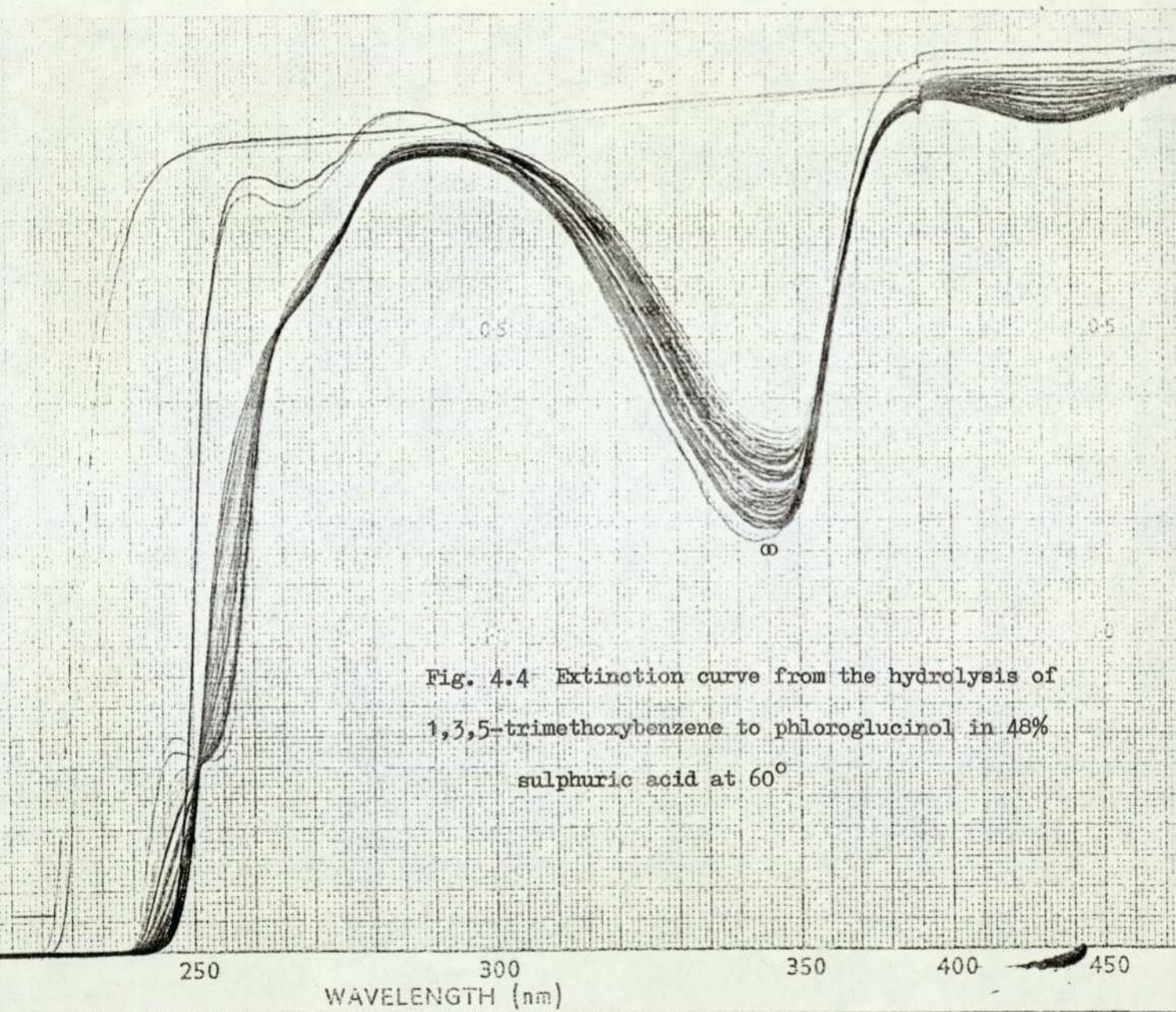


Fig. 4.5 shows the extinction curve, Table 4.2 the data obtained therefrom and Fig. 4.6 the plot of $\log_{10}(A_{\infty} - A_t)$ vs time.

$$k_2(\text{obs}) = -2.303 \times \text{slope} / [\text{HNO}_3] \text{ dm}^3 \text{ mole}^{-1} \text{ s}^{-1}$$

$$k_2(\text{obs}) = 1.47 \times 10^{-3} \text{ dm}^3 \text{ mole}^{-1} \text{ s}^{-1}$$

Second-order rate coefficients determined over range of percentages of sulphuric acid at various temperatures are given in Table 4.3 and Fig. 4.7 shows the plot of $\log_{10} k_2(\text{obs})$ vs % H_2SO_4 .

4.313 PHENOL

The results and subsequent calculations required for the determination of a typical rate coefficient for the formation of the nitronium ion from solute nitric acid at 25° are given below.

Concentration of sulphuric acid : 63.7% w/w

Concentration of nitric acid : $1.19 \times 10^{-4} \text{ mole dm}^{-3}$

Concentration of phenol : 0.1 mole dm^{-3}

Concentration of sulphamic acid ca $0.05 \text{ mole dm}^{-3}$

Temperature : $25.0 \pm 0.2^\circ$

Wavelength of measurement : 330 nm.

Fig. 4.8 shows the extinction curve, Table 4.4 the data obtained therefrom and Fig. 4.9 the plot of $\log_{10}(A_{\infty} - A_t)$ vs time.

$$k_1 = -2.303 \times \text{slope} \text{ s}^{-1}$$

$$k_1 = 5.91 \times 10^{-4} \text{ s}^{-1}$$

Rate constants for the formation of the nitronium ion were determined over a range of percentages of sulphuric acid and are given in Table 4.5

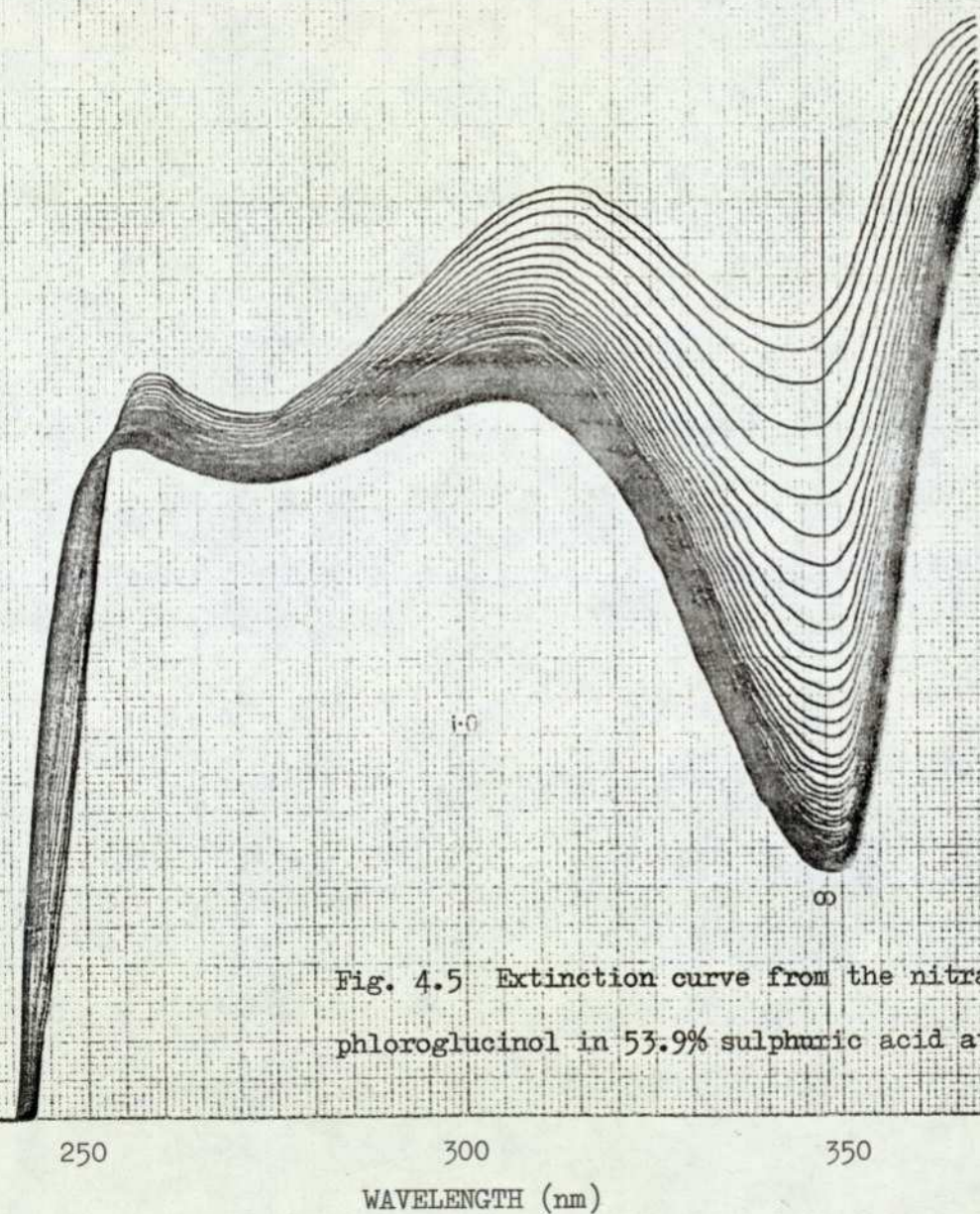


Fig. 4.5 Extinction curve from the nitration of phloroglucinol in 53.9% sulphuric acid at $40.0 \pm 0.2^\circ$

Table 4.2

Data from a typical determination of the rate
of nitration of phloroglucinol in 53.9%
sulphuric acid at $40.0 \pm 0.2^{\circ}$

Time (t) /mins.	Absorbance (A_t)	$\log_{10}(A_{\infty} - A_t)$
25	0.53	-0.19
65	0.65	-0.27
105	0.74	-0.36
145	0.82	-0.44
185	0.89	-0.54
225	0.94	-0.63
265	0.98	-0.71
305	1.02	-0.80
345	1.06	-0.91
385	1.08	-1.00
t_{∞}	1.18	

Fig. 4.6 Plot of $\log_{10}(A_{\infty} - A_t)$ vs time from the nitration of phloroglucinol in 53.9% sulphuric acid at $40.0 \pm 0.2^{\circ}$

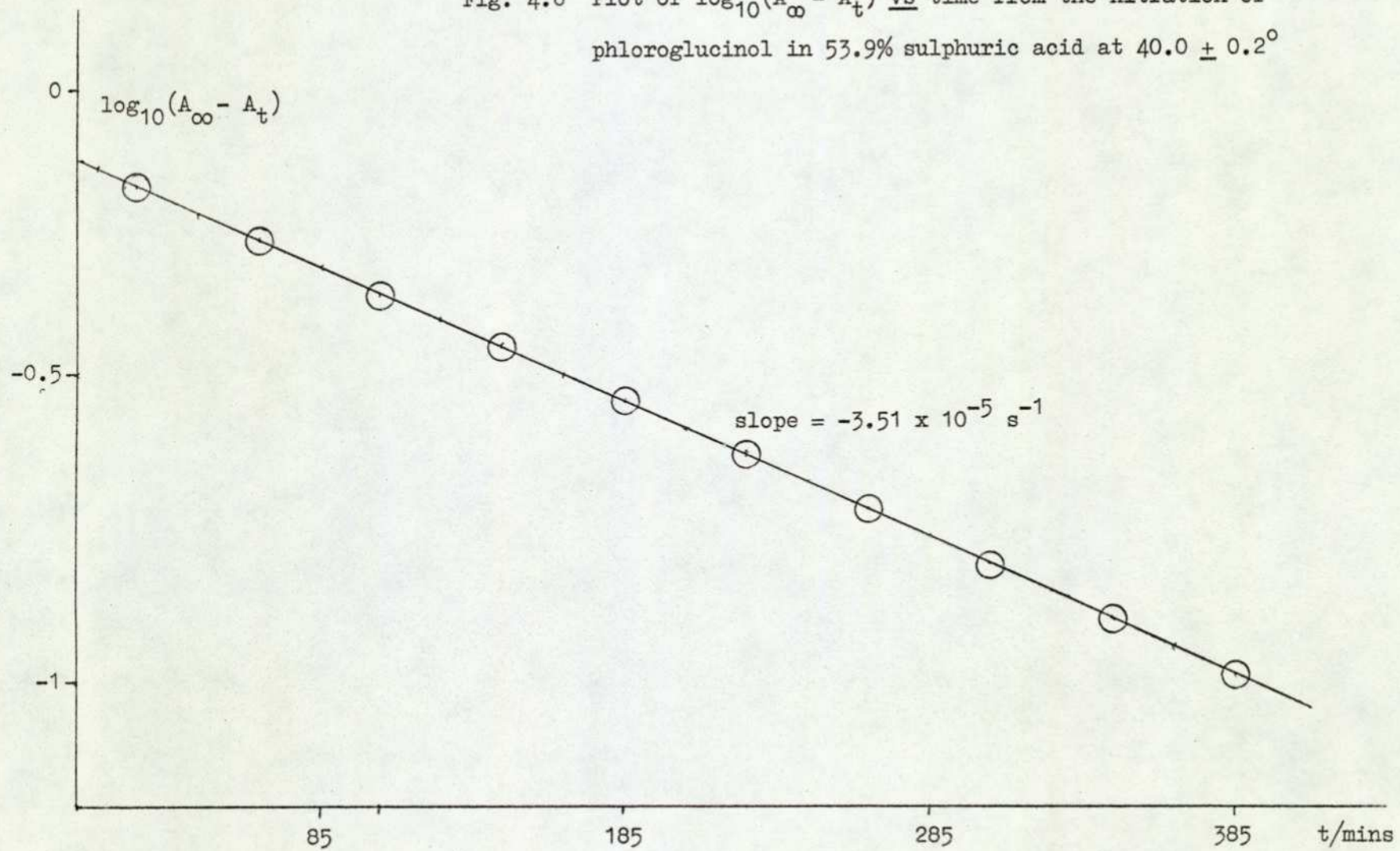


Table 4.3

Second-order rate coefficients for the nitration
of phloroglucinol^{a,b,c} in sulphuric acid.

H_2SO_4 (%) ^d	$-(H_R + \log_{10} a_{\text{H}_2\text{O}})^e$	$k_2(\text{obs})$ $/\text{dm}^3 \text{ mole}^{-1} \text{ s}^{-1}$
At $25.0 \pm 0.2^\circ\text{f}$		
69.1	13.04	1.36×10^{-2}
66.6	12.31	1.02×10^{-2}
63.6	11.60	6.27×10^{-3}
62.3	11.18	4.39×10^{-3}
59.6	10.44	1.95×10^{-3}
At $40.0 \pm 0.2^\circ\text{f}$		
63.6	10.60	3.21×10^{-2}
62.3	10.35	2.27×10^{-2}
59.6	9.53	1.16×10^{-2}
58.1	9.05	6.48×10^{-2}
56.1	8.48	3.84×10^{-2}
53.9	7.89	1.47×10^{-2}
At $60.0 \pm 0.2^\circ\text{g}$		
53.9	6.93	1.68×10^{-2}
52.0	6.56	8.36×10^{-3}
49.8	6.13	4.15×10^{-3}
48.2	5.79	2.36×10^{-3}

Table 4.3 (continued)

Second-order rate coefficients for the nitration
of phloroglucinol^{a,b,c} in sulphuric acid.

H_2SO_4 (%) ^d	$-(H_R + \log_{10} a_{\text{H}_2\text{O}})^e$	$k_2(\text{obs})$ /dm ³ mole ⁻¹ s ⁻¹
At $80.0 \pm 0.2^\circ\text{C}^g$		
48.2	4.71	2.06×10^{-2}
46.0	4.36	1.03×10^{-2}
44.3	4.13	6.00×10^{-3}
41.3	3.69	2.58×10^{-3}
39.2	3.41	1.34×10^{-3}

a) $[\text{ArH}] = 7.92 \times 10^{-5} \text{ mole dm}^{-3}$

b) Measurement at 350 nm

c) $[\text{HNO}_3] = 5.5 \times 10^{-2} \text{ mole dm}^{-3}$

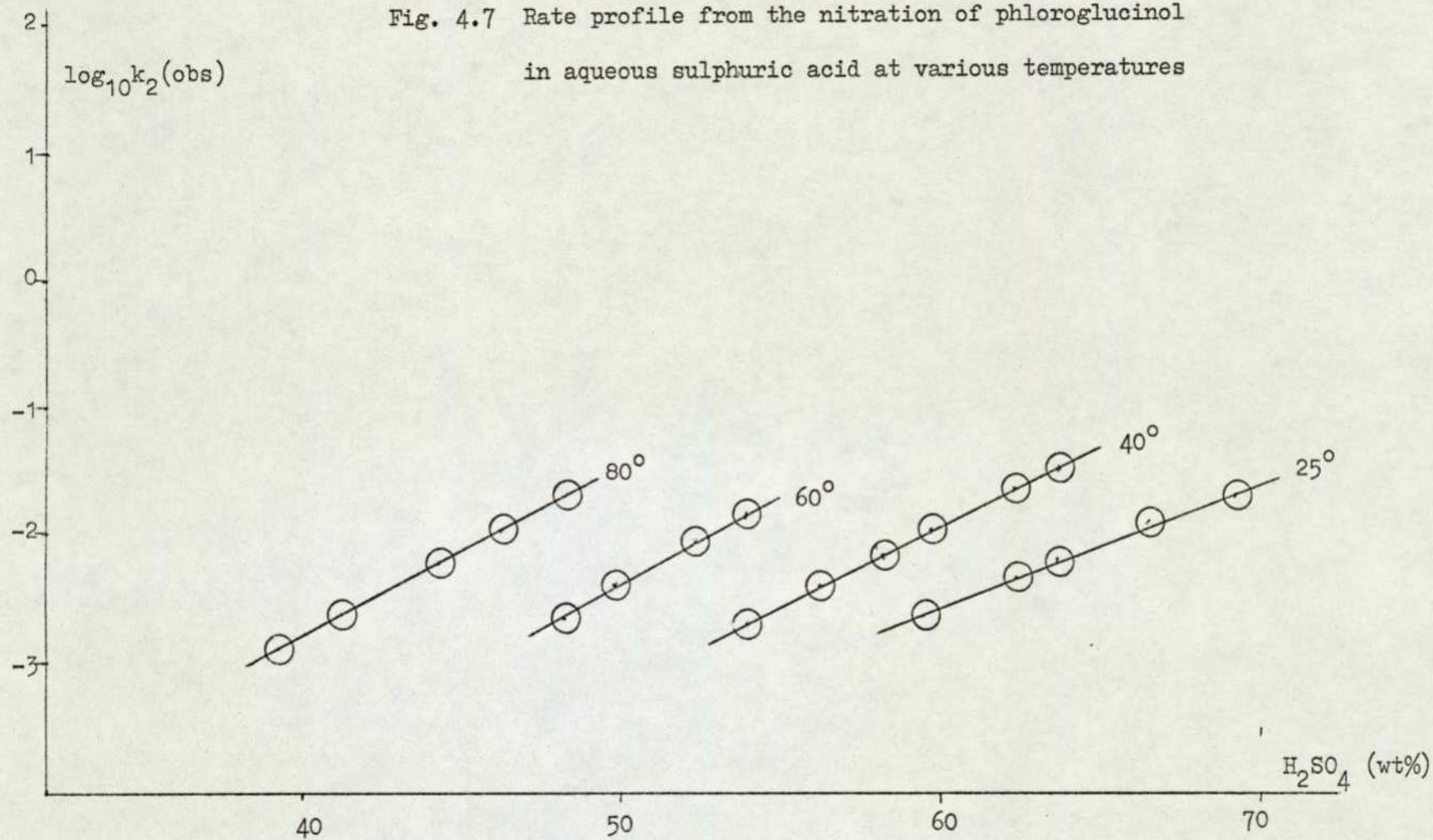
d) $\pm 0.1\% \text{ w/w}$

e) Ref. 88 and 96

f) $[\text{Sulphamic acid}] \text{ ca } 0.05 \text{ mole dm}^{-3}$

g) $[\text{Sulphanilic acid}] \text{ ca } 0.05 \text{ mole dm}^{-3}$

Fig. 4.7 Rate profile from the nitration of phloroglucinol
in aqueous sulphuric acid at various temperatures



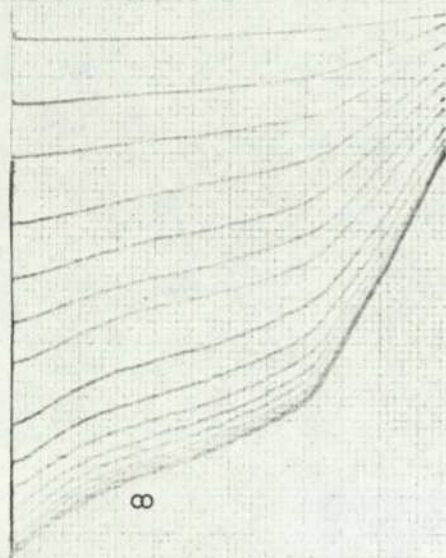


Fig. 4.8 Extinction curve from the 'zeroth order' nitration of phenol in 63.8% sulphuric acid at $25.0 \pm 0.2^\circ$

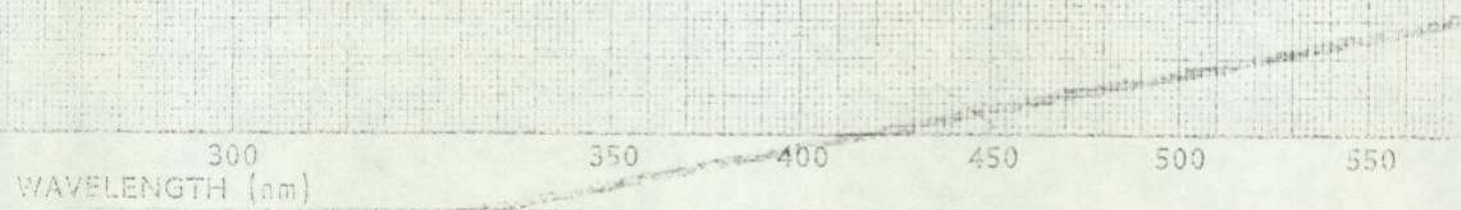


Table 4.4

Data from a typical determination of the rate
of formation of the nitronium ion from solute
nitric acid in 63.8% sulphuric acid at $25.0 \pm 0.2^\circ$

Time (t)	Absorbance	$\log_{10}(A_\infty - A_t)$
/mins	A_t	
1	0.15	-0.14
6	0.22	-0.29
10	0.28	-0.35
20	0.41	-0.50
30	0.50	-0.65
40	0.57	-0.81
50	0.62	-0.97
60	0.65	-1.12
70	0.67	-1.27
80	0.68	-1.42
t_∞	0.72	

Fig. 4.9 Plot of $\log_{10}(A_{\infty} - A_t)$ vs time from the 'zeroth order' nitration of phenol in 63.8% sulphuric acid at $25.0 \pm 0.2^{\circ}$

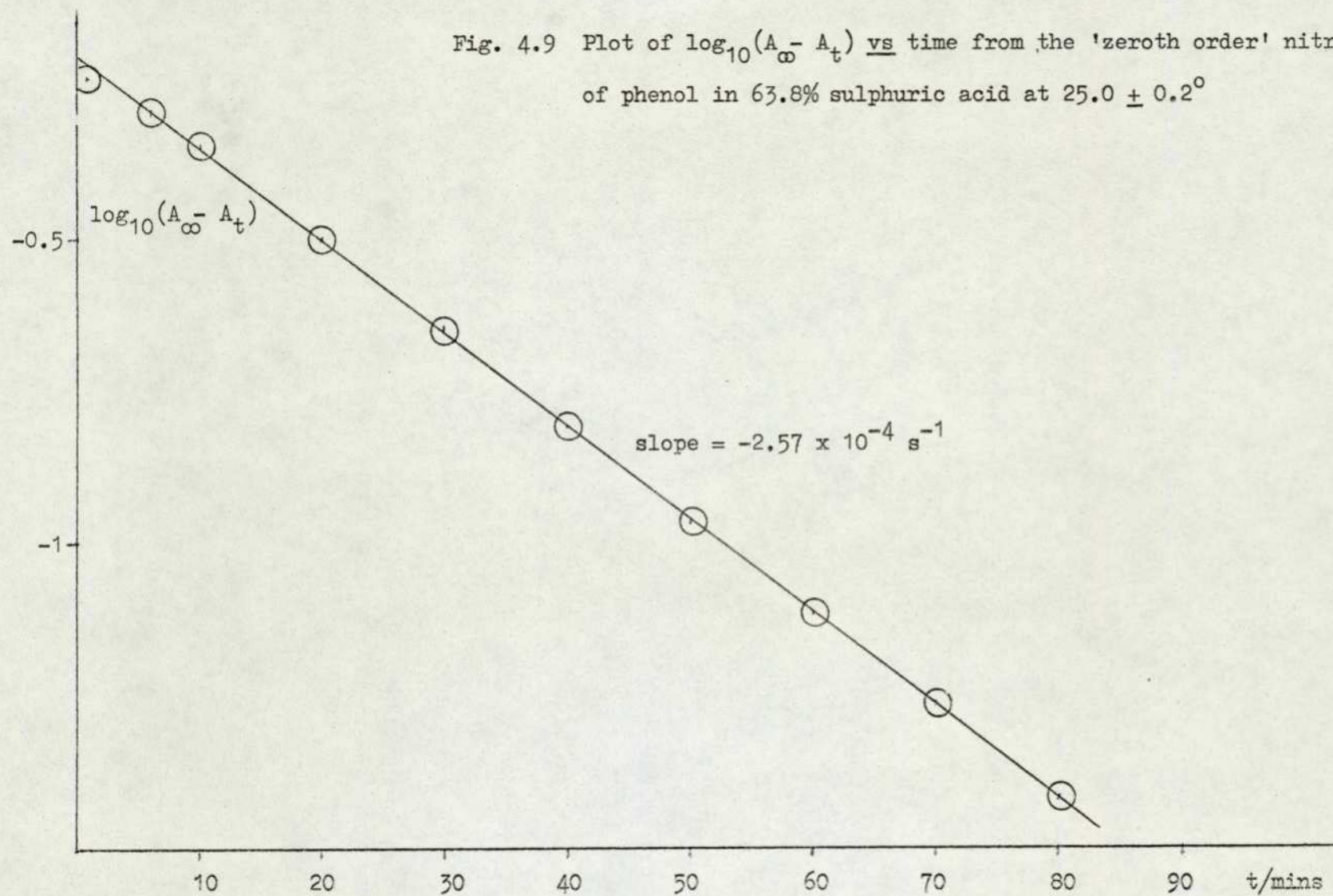


Table 4.5

Rate coefficients for the formation of the nitronium ion
from solute nitric acid in sulphuric acid at $25.0 \pm 0.2^\circ$

H_2SO_4 (%) ^a	Phenol ^{b,c,d} mole dm^{-3}	-Ho	k_1/s^{-1}
58.1	0.15	4.32	2.88×10^{-5}
59.6	0.15	4.51	9.59×10^{-5}
62.2	0.15	4.83	2.94×10^{-4}
63.7	0.1	5.05	5.91×10^{-4}
66.3	0.1	5.30	9.50×10^{-4}
68.5	0.1	5.67	5.41×10^{-3}
70.8	0.1	5.84	1.22×10^{-2}

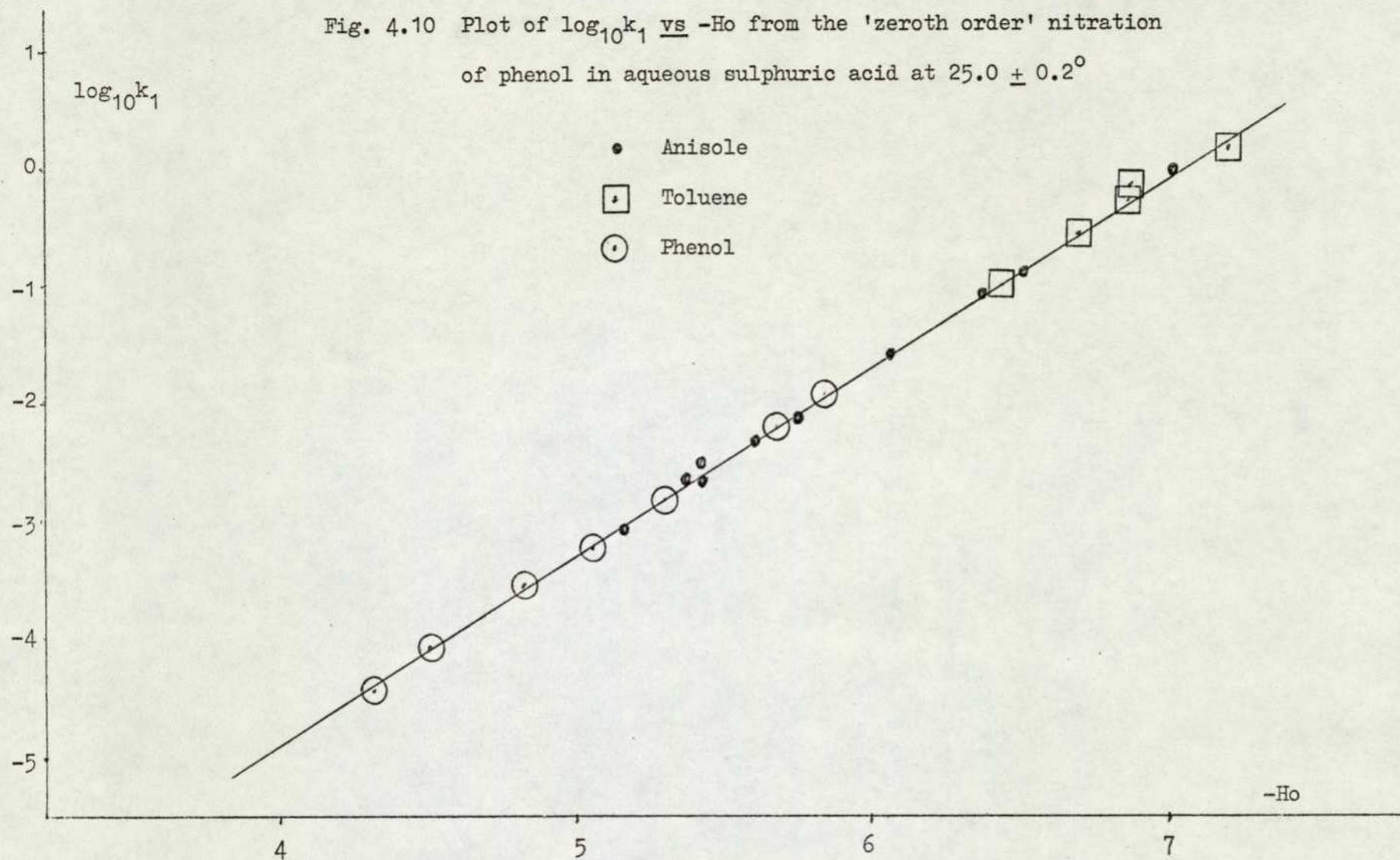
a) $\pm 0.1\%$ w/w

b) $[\text{HNO}_3] = 1.19 \times 10^{-4} \text{ mole dm}^{-3}$

c) $[\text{Sulphamic acid}] \text{ ca } 0.05 \text{ mole dm}^{-3}$

d) Measurement at 330 nm

Fig. 4.10 Plot of $\log_{10} k_1$ vs $-H_o$ from the 'zeroth order' nitration of phenol in aqueous sulphuric acid at $25.0 \pm 0.2^\circ$



and a plot of $\log_{10} k_1$ vs $-H_0$ (acidity function) is shown in Fig. 4.10 together with some data obtained²⁴ for anisole and toluene.

4.32 PRODUCTS

4.321 PHLOROGLUCINOL

With phloroglucinol which is potentially a very reactive substrate, particular care was taken to show that the rate of mono-nitration was being followed by comparing the observed UV extinction curve of the product ($\lambda_{\max} = 350 \text{ nm}$) with that of a spectrum of nitrophloroglucinol ($\lambda_{\max} = 350 \text{ nm}$). As a further check the spectral change for the nitration of nitrophloroglucinol in 44.3% sulphuric acid was followed. No change in the UV spectrum was observed, therefore dinitration would not interfere with the kinetic runs quoted ($\lambda_{\max}$ for dinitrophloroglucinol 300 nm)⁹⁵.

4.322 PHENOL

Products from the nitration of phenol have previously been reported⁶⁶.

4.4 DISCUSSION

4.41 PHLOROGLUCINOL

Phloroglucinol has been shown to undergo reversible protonation⁹⁹ in aqueous acids, to give the protonated species below:-

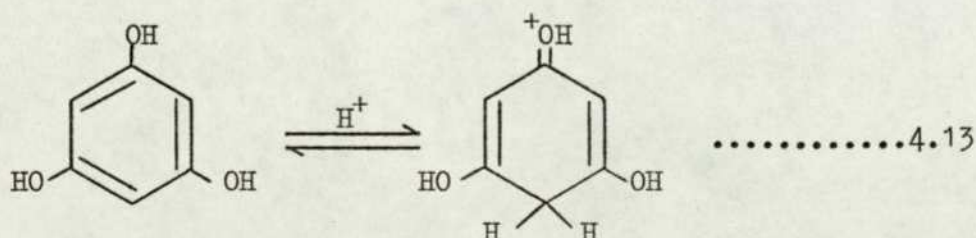


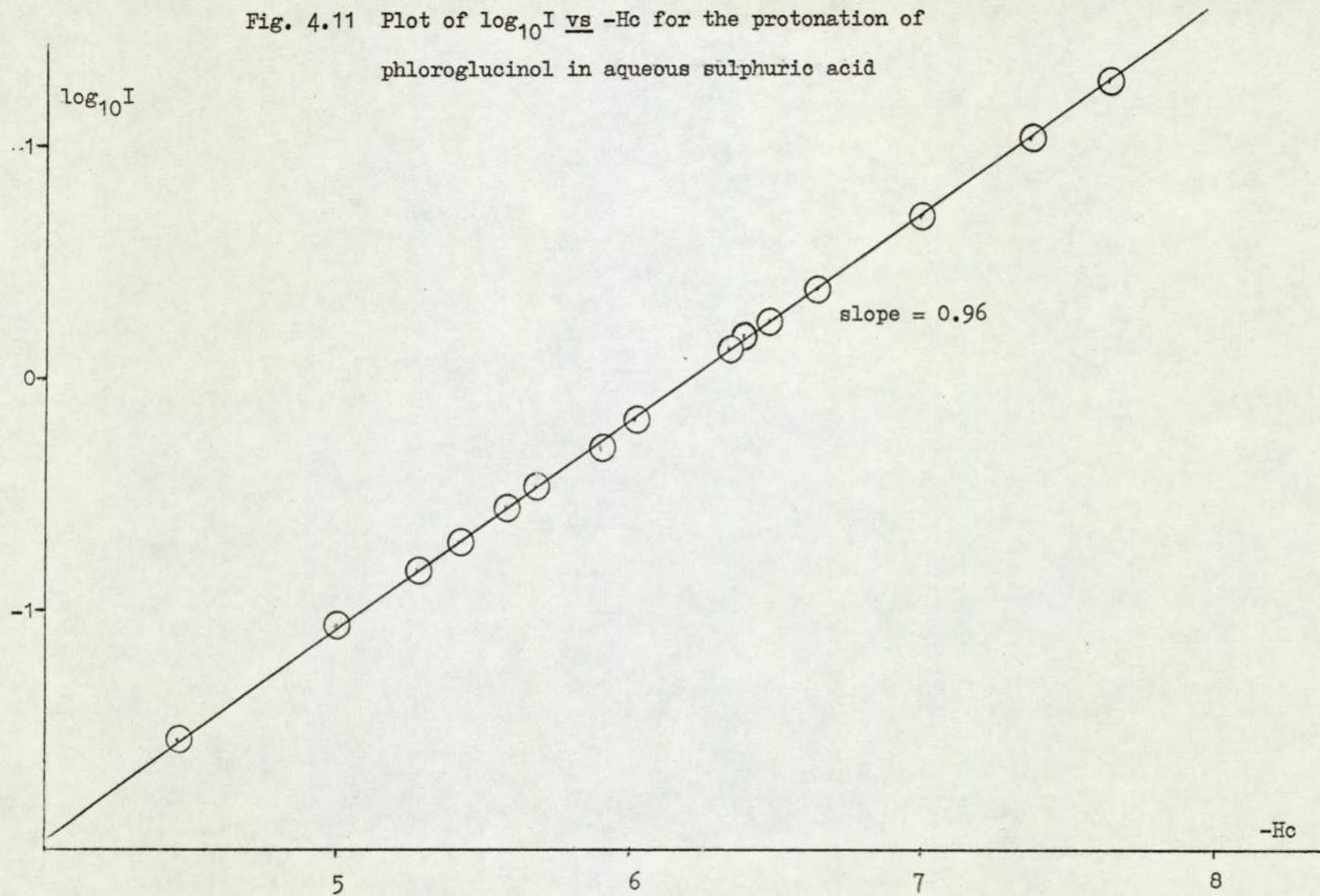
Table 4.6 gives the values of $\log_{10} I$ (indicator ratio, Equ. 4.14) of phloroglucinol in aqueous sulphuric acid and Fig. 4.11 shows the

Table 4.6

Indicator ratios for the protonation of
phloroglucinol in aqueous sulphuric acid

H_2SO_4 (%)	$-\text{Hc}^{98}$	$\log_{10} \text{I}^{99}$
44.2	4.47	-1.53
46.8	5.03	-1.03
48.2	5.32	-0.78
49.3	5.42	-0.72
50.7	5.66	-0.49
51.9	5.84	-0.29
53.0	6.02	-0.17
54.8	6.33	0.12
55.3	6.43	0.20
56.6	6.66	0.40
58.4	7.00	0.69
60.3	7.31	0.97
61.7	7.58	1.21

Fig. 4.11 Plot of $\log_{10} I$ vs $-H_c$ for the protonation of
phloroglucinol in aqueous sulphuric acid



plot of $\log_{10} I$ vs the acidity function $-H_c$ (where H_c is based on the protonation of certain aromatic bases such as azulene). From this plot which has a slope of 0.96 the indicator ratio can be determined for a given concentration of sulphuric acid. The indicator ratio I can be used to find the amount of unprotonated species from the following equation:-

$$I = \frac{[BH^+]}{[B]} \dots\dots\dots 4.14$$

Where I : indicator ratio

$[BH^+]$: concentration of protonated species

$[B]$: concentration of aromatic base

Thus for 52.0% sulphuric acid

$$I = 0.85$$

$$\text{and as \% unprotonated} = \frac{100}{I + 1}$$

$$\text{then} \quad \% B = 54.0$$

Protonation of phloroglucinol caused the observed rate of nitration to be lower than might have been expected, as the protonated species will be unreactive to electrophilic aromatic substitution and the increase in rate with increasing acidity was less than that found for unprotonated compounds. The observed rate of nitration for phloroglucinol and the degree of protonation can be used to calculate the rate of nitration for the unprotonated species from the equation:-

$$k_2(B) = \frac{100}{\%B} \times k_2(\text{obs})$$

Thus for nitration in 52.0% sulphuric acid at 60.0°

$$k_2(B) = \frac{100}{54.0} \times 8.36 \times 10^{-3} \text{ dm}^3 \text{ mole}^{-1} \text{ s}^{-1}$$

$$k_2(B) = 1.55 \times 10^{-2} \text{ dm}^3 \text{ mole}^{-1} \text{ s}^{-1}$$

Table 4.7 gives the calculated rates of reaction for the unprotonated species B, and Fig. 4.12 shows the plot of $\log_{10} k_2(B)$ vs acidity with a plot for mesitylene⁶⁶ as a comparison. From Fig. 4.12 it can be seen that the calculated second-order rate coefficients for the unprotonated species are very close to those for mesitylene. This type of rate profile is characteristic of some compounds that are nitrated at the encounter limit (see Section 2.42).

This Chapter is concerned with the search for electrophiles other than the nitronium ion, for the nitration of reactive aromatic compounds at low acidities. The operation of other electrophiles would be expected to change the slope of a plot of $\log_{10} k_2(\text{obs})$ vs $-(H_R + \log_{10} a_{H_2O})$, see Fig. 4.1. A plot of $\log_{10} k_2(B)$ vs $-(H_R + \log_{10} a_{H_2O})$ for phloroglucinol is shown in Fig. 4.13. The values of H_R used and their temperature dependence were those determined by Katritzky and co-workers¹⁰⁰. In this study the activity of water (a_{H_2O}) has been assumed to be constant with temperature (see discussion in Ref. 100). From Fig. 4.13 it can be seen that the rate profiles for phloroglucinol at various temperatures are parallel straight lines. The slopes were approximately 1 and the variation in slope with temperature is given in Table 4.8. The small variations are perhaps due to the change in a_{H_2O} with temperature and the inadequacy of the acidity function, but it is clear that there is no significant change in the slope of the profiles at low acidities. From this study there is no evidence for a change in electrophile from the nitronium ion for phloroglucinol in as low as 39% sulphuric acid.

The fact that the nitronium ion is the effective electrophile is truly remarkable when it is noted (see below) that only 10^{-17} of the nitric acid is present as NO_2^+ and the reactivity of the nitronium ion is lowered for this substrate by about 10^{12} because of the

Table 4.7

Second-order rate coefficients for the nitration of
phloroglucinol in sulphuric acid at various temperatures

H_2SO_4 (%)	$-(\text{H}_\text{R} + \log_{10} a_{\text{H}_2\text{O}})$	$k_2(\text{obs})$ $/\text{dm}^3 \text{ mole}^{-1} \text{ s}^{-1}$	% (B)	$k_2(\text{B})$ $/\text{dm}^3 \text{ mole}^{-1} \text{ s}^{-1}$
39.2 ^a	3.41	1.34×10^{-3}	96.72	1.38×10^{-3}
41.3 ^a	3.69	2.56×10^{-3}	94.34	2.76×10^{-3}
44.3 ^a	4.13	5.99×10^{-3}	89.04	6.72×10^{-3}
46.0 ^a	4.36	1.03×10^{-2}	84.03	1.22×10^{-3}
48.2 ^a	4.71	2.06×10^{-2}	75.58	2.72×10^{-3}
48.2 ^b	5.79	2.36×10^{-3}	75.58	3.12×10^{-3}
49.8 ^b	6.13	4.15×10^{-3}	67.11	6.18×10^{-3}
52.0 ^b	6.56	8.36×10^{-3}	54.05	1.55×10^{-2}
53.9 ^b	6.93	1.69×10^{-2}	42.73	3.93×10^{-2}
53.9 ^c	7.89	1.47×10^{-3}	42.73	3.43×10^{-3}
56.1 ^c	8.48	3.84×10^{-3}	29.94	1.28×10^{-2}
58.1 ^c	9.08	5.48×10^{-3}	19.37	3.34×10^{-2}
59.6 ^c	9.53	1.63×10^{-2}	14.81	7.83×10^{-2}
59.6 ^d	10.44	1.95×10^{-3}	14.81	1.31×10^{-2}
62.3 ^c	10.35	2.27×10^{-3}	7.05	0.322
62.3 ^d	11.18	4.39×10^{-3}	7.05	6.22×10^{-2}
63.6 ^c	10.60	3.21×10^{-2}	4.98	0.644
63.6 ^d	11.60	6.27×10^{-3}	4.98	0.125
66.6 ^d	12.31	1.02×10^{-2}	1.09	0.506
69.1 ^d	13.04	1.37×10^{-2}	0.72	1.88

a) $80.0 \pm 0.2^\circ$; b) $60.0 \pm 0.2^\circ$;

c) $40.0 \pm 0.2^\circ$; d) $25.0 \pm 0.2^\circ$

Fig. 4.12 Rate profiles from the nitration of phloroglucinol
in aqueous sulphuric acid at various temperatures

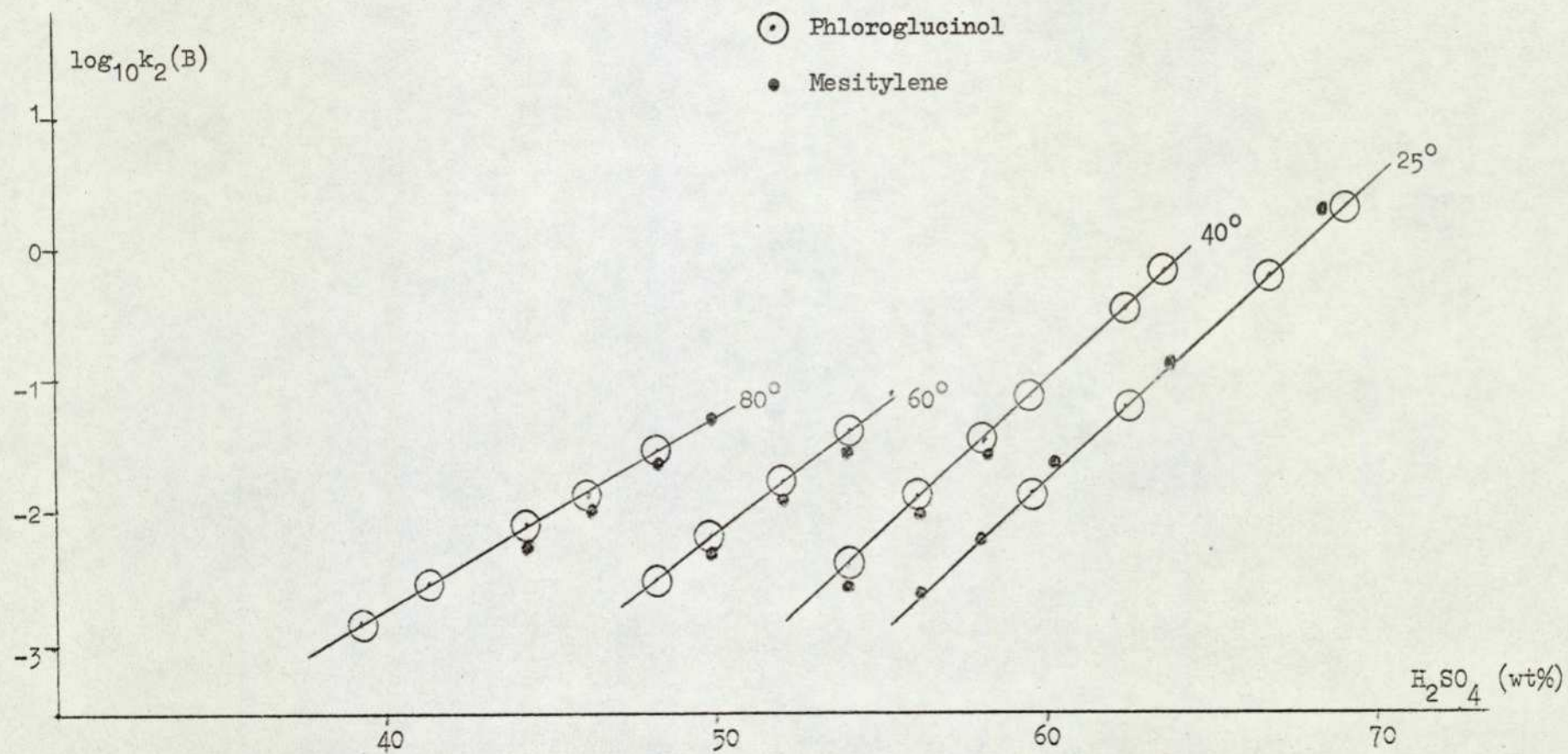
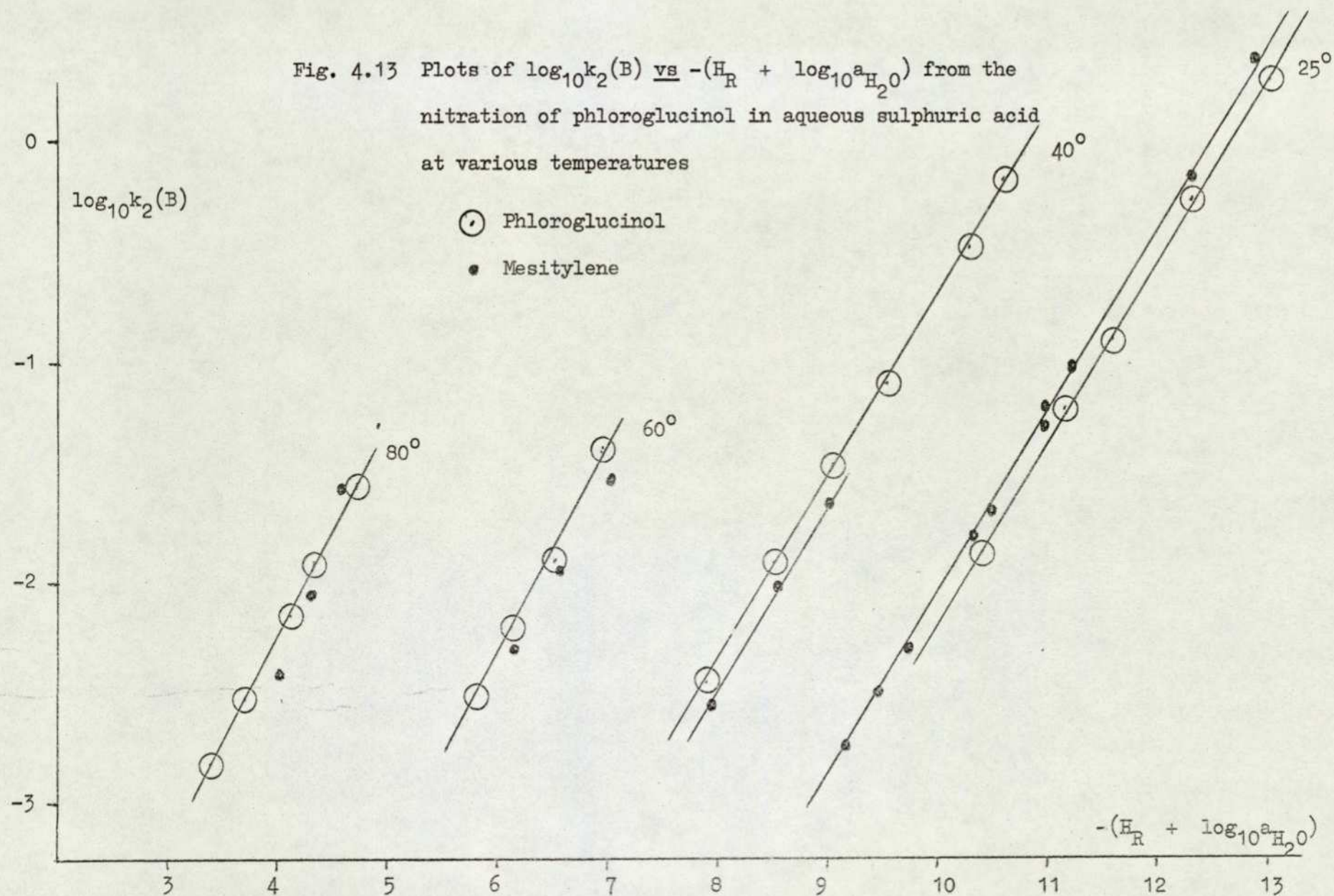


Fig. 4.13 Plots of $\log_{10} k_2(B)$ vs $-(H_R + \log_{10} a_{H_2O})$ from the nitration of phloroglucinol in aqueous sulphuric acid at various temperatures



operation of the encounter limit. It is now clear that the search for another electrophile is very unlikely to be successful when there is any possibility of nitronium ion formation.

Table 4.9 gives the Arrhenius activation parameters for the nitration of phloroglucinol calculated from the following expression:-

$$\log_{10} \frac{k_2^2(\text{obs})}{k_2^1(\text{obs})} = \frac{E}{2.303 R} \times \frac{(T_2 - T_1)}{(T_1 \times T_2)} \dots\dots\dots 4.16$$

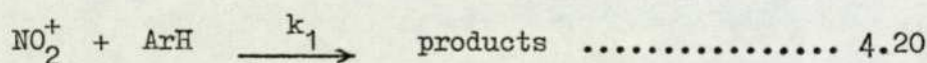
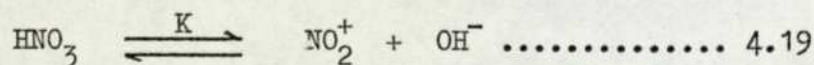
Where $k_2^1(\text{obs})$: the rate constant at temperature T_1

$k_2^2(\text{obs})$: the rate constant at temperature T_2

R : gas constant

E : activation energy

The activation energies for the nitration of phloroglucinol as for mesitylene tend to increase with decreasing acidity. The enthalpy of dissociation of nitric acid to the nitronium ion and hydroxide ion has been shown to decrease with increasing acidity²², i.e. 45.4 kJ mole⁻¹ in 68.3% sulphuric acid and 21.3 kJ mole⁻¹ in 79.2% sulphuric acid. The mechanism of nitration is thought to be:-



If the second step is an encounter-controlled process, its apparent activation energy arising from the temperature coefficient of the viscosity of the medium should be 25 - 29 kJ mole⁻¹ in 68.3% sulphuric acid, thus, the expected activation energy for encounter controlled nitration at this acidity would be 75 kJ mole⁻¹, and this value would be expected to increase with decreasing acidity due to the larger

Table 4.9

Activation parameters for the nitration
of phloroglucinol^a in sulphuric acid

H ₂ SO ₄ (%) ^b	Temp. range (°C)	E _A /kJ mole ⁻¹
62.3	25 - 40	87
53.9	40 - 60	105
48.2	60 - 80	122

a) [Phloroglucinol] = 7.92×10^{-5} mole dm⁻³

b) $\pm 0.1\%$ w/w

contribution of the first process. The activation energies obtained for phloroglucinol as for mesitylene⁶⁶ are consistent with this theory.

4.42 PHENOL

With $[\text{Phenol}] \gg [\text{HNO}_3]$ the reaction followed a first-order course with rate constant k_1 .

From Fig. 4.10 it can be seen that the k_1 values obtained for phenol are in good agreement with the values obtained²⁴ from studies of anisole and toluene. A straight line is obtained with slope 1.5. Extrapolation of this line down to $H_0 = -2.4$ (i.e. 40% sulphuric acid) gives:-

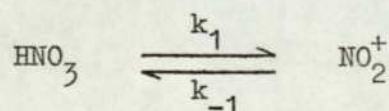
$$k_1^{40} = 3.98 \times 10^{-8} \text{ s}^{-1}$$

For benzene⁶⁶ $k_2(\text{obs})$ in 40% sulphuric acid at 25° is $5.62 \times 10^{-10} \text{ dm}^3 \text{ mole}^{-1} \text{ s}^{-1}$ (by extrapolation). For *p*-dichlorobenzene, $k_2(\text{obs})$ in 40% sulphuric acid at 25° , assuming it to be 6×10^{-4} as reactive as benzene¹², is $3.37 \times 10^{-13} \text{ dm}^3 \text{ mole}^{-1} \text{ s}^{-1}$. For *p*-dichlorobenzene¹², $k_2(\text{obs})$ in 90% sulphuric acid, in which all the nitric acid is converted to the nitronium ion, is $1.20 \times 10^4 \text{ dm}^3 \text{ mole}^{-1} \text{ s}^{-1}$, and so if the assumption is made that the drop in nitration rate for *p*-dichlorobenzene is solely due to the lowering of the nitronium ion concentration, then:-

$$\frac{[\text{NO}_2^+]}{[\text{HNO}_3]} \text{ in 40\% sulphuric acid is : } \frac{3.37 \times 10^{-13}}{1.20 \times 10^4} = R$$

$$\therefore R = 2.8 \times 10^{-17}$$

Now from the equilibrium:



$$R = \frac{k_1}{k_{-1}}$$

$$\therefore k_{-1} = \frac{k_1}{R} = \frac{3.98 \times 10^{-8}}{2.80 \times 10^{-17}} = 1.4 \times 10^9 \text{ s}^{-1} \text{ in } 40\% \text{ H}_2\text{SO}_4$$

$$\therefore \text{Half-life of } [\text{NO}_2^+] = \frac{0.69}{k_{-1}} = 5 \times 10^{-10} \text{ s}^{-1} \text{ in } 40\% \text{ H}_2\text{SO}_4$$

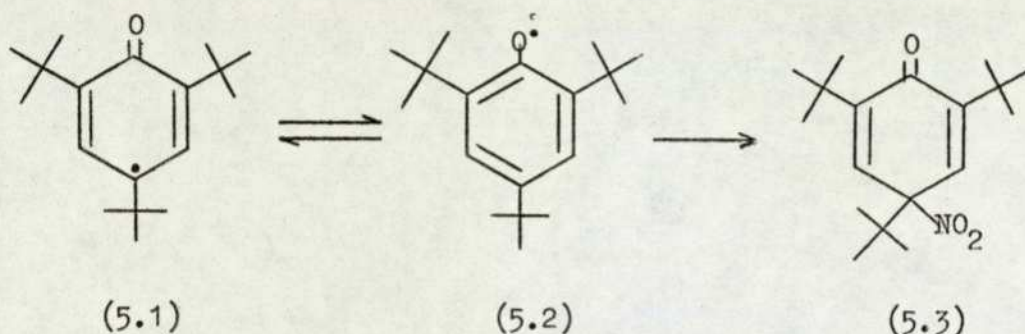
The nitration of phloroglucinol (which is reactive enough to react upon encounter in 40% sulphuric acid) was carried out at 80° in this acidity. At this temperature the acidity of the medium is less than that at 25° (due to temperature dependence of H_R^{100}) and therefore it is a reasonable assumption that the half-life of the nitronium ion is even less than that calculated above. A pre-association mechanism (Scheme 1.2, page 15) is then suggested for the nitration of phloroglucinol in less than 40% sulphuric acid, although no consequence of this appears in the rate profile. An analogous calculation to the above gives the half-life of the nitronium ion in 68% sulphuric acid as $4 \times 10^{-7} \text{ s}^{-1}$, indicating that the generally accepted interpretation is satisfactory at this acidity, where many comparisons of reactivity have been made.

CHAPTER 5

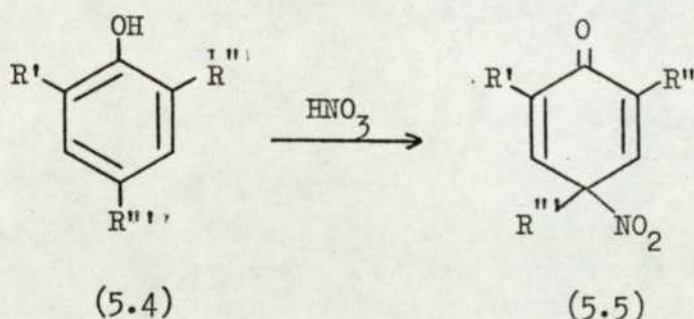
A STUDY OF THE BEHAVIOUR OF SOME CYCLOHEXA-2,5-DIENONES IN SULPHURIC ACID

5.1 INTRODUCTION

Cyclohexadienones are known as products of nitration of phenols, where reactive positions are blocked by alkyl substituents⁸¹. Cook and Woodworth¹⁰² have shown that the reaction of the 2,4,6-tri-t-butylphenoxy radical (5.2) with nitrogen dioxide leads to the formation of 2,4,6-tri-t-butyl-4-nitrocyclohexa-2,5-dienone (5.3), which had a UV absorption at 241 nm (cyclohexane).



Ershov and Zlobina¹⁰³ found that the nitration of 2,4,6-trialkylphenols in organic media by nitric acid, gave the 'quinonitroles' (2,4,6-trialkyl-4-nitrocyclohexa-2,5-dien-1-ones) (5.5). These compounds had UV absorptions in the range 233 - 240 nm. The data of



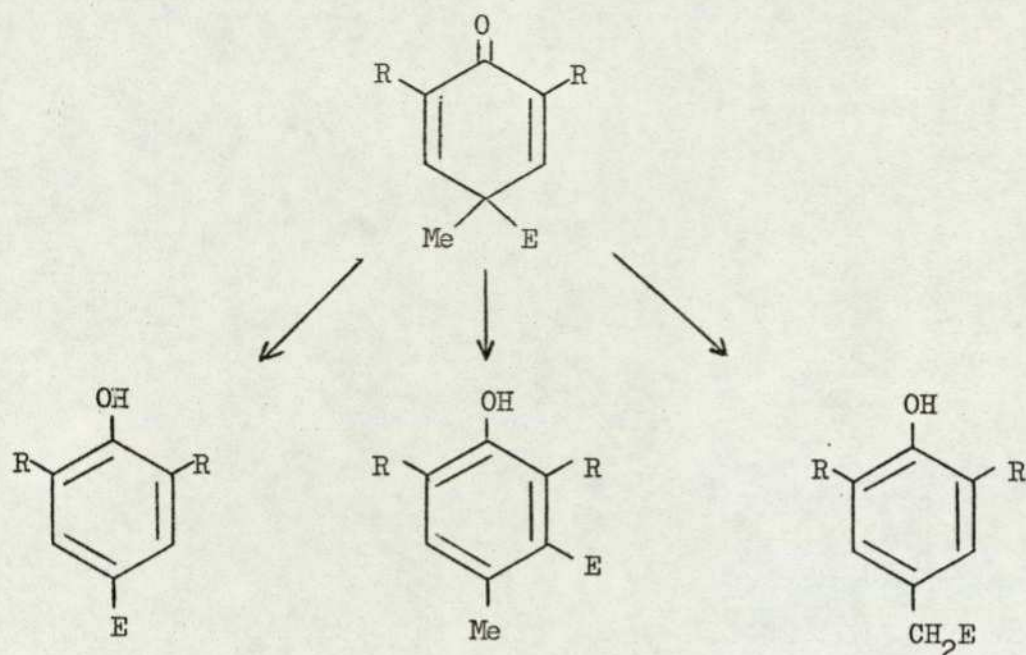
these workers are summarised in Table 5.1. In many reactions dienones, although not actually isolated, are thought to be reaction intermediates^{104,105,81}. Scheme 5.1 shows some possible modes of decomposition of such intermediates.

Table 5.1

The UV absorptions¹⁰³ for a series of
trialkyl-substituted "quinonitroles"

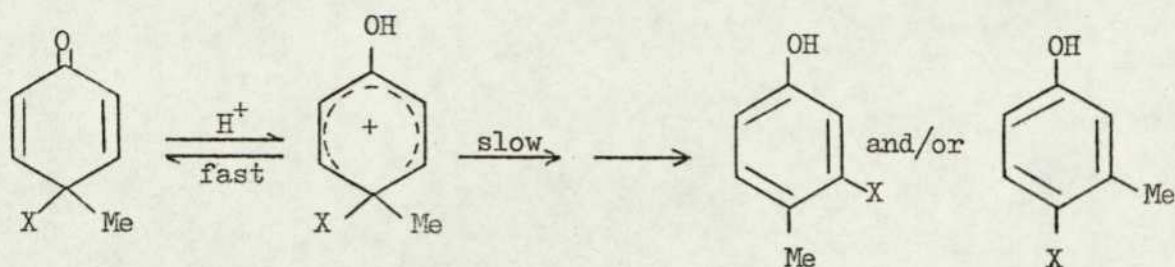
R'	R''	R'''	$\lambda_{\text{max}}/\text{nm}^a$
$\text{C}(\text{CH}_3)_3$	$\text{C}(\text{CH}_3)_3$	$\text{C}(\text{CH}_3)_3$	239
$\text{C}(\text{CH}_3)_3$	$\text{C}(\text{CH}_3)_3$	CH_3	233
C_6H_{11}	C_6H_{11}	CH_3	240
CH_3	CH_3	CH_3	230
CH_3	$\text{C}(\text{CH}_3)_3$	CH_3	233
CH_3	$\text{C}(\text{CH}_3)_3$	$\text{C}(\text{CH}_3)_3$	238

a) n-Hexane was used as the solvent in all cases.



Scheme 5.1

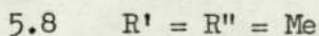
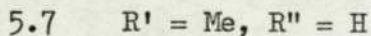
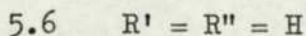
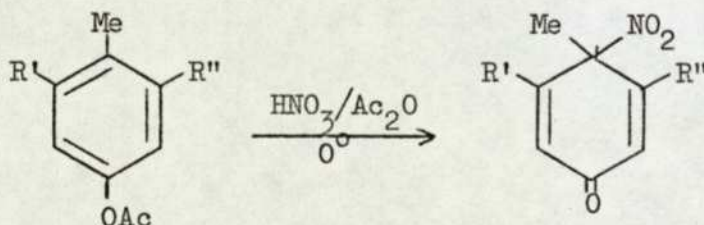
Dienone-phenol and related rearrangements are of continuing active interest^{51,81,106}. All the results thus far obtained¹⁰⁷⁻¹¹² for the rearrangements under acidic conditions of 4-X-4-methylcyclohexadienones (X = Me, Et, OAc, OH, Cl, OMe, Ph) provide substantial support for the mechanism outlined in Scheme 5.2. First-order kinetics were observed in all cases and the value of $\log_{10} k_1$ was found to vary with the acidity function $-H_o$, the rate profiles being parallel with slopes ~ 0.7 . This is consistent with a slow rate-limiting reaction of the small equilibrium concentration of the species formed by protonation on oxygen as the plots of the ionization ratios in aqueous sulphuric acid for the protonation of these dienones, against the acidity function $-H_o$ gave straight lines with similar slopes (~ 0.6)¹⁰⁹. All these rearrangements were found to occur with 1,2-migration of Me or X, depending on the nature of X, under acidic conditions (sulphuric or perchloric acid) and no



Scheme 5.2

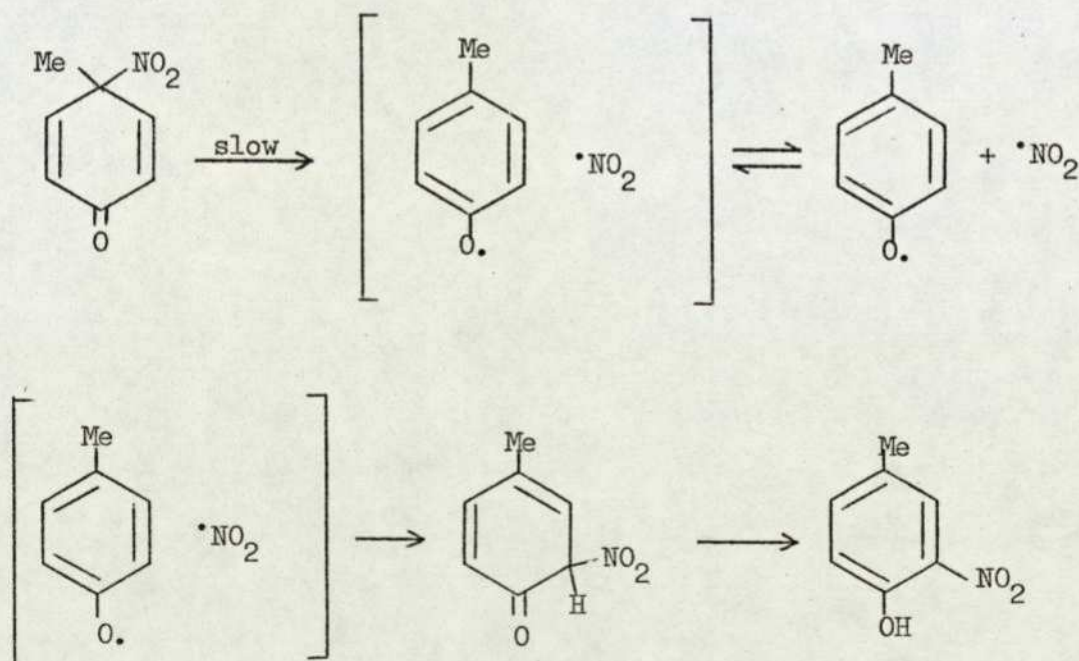
1,3-rearrangement products were found to be present.

4-Methyl-4-nitrocyclohexa-2,5-dien-1-one was isolated and characterised by Hartshorn and coworkers¹³¹ from *p*-bromotoluene, *p*-methylanisole and 4-methylphenyl acetate on reaction with nitric acid in acetic anhydride at 0°. Several 4-methyl-4-nitrocyclohexa-2,5-dienones have been prepared¹⁰⁶ in good yield by the nitration of 4-methylphenyl acetate, 3,4-dimethylphenyl acetate and 3,4,5-trimethylphenyl acetate with nitric acid in acetic anhydride at 0°. In



agreement with earlier reports^{35,49,71}, all the 4-methyl-4-nitrocyclohexadienones (5.6, 5.7, 5.8) were found to rearomatise at moderate temperatures in various solvents to give *o*-nitrophenols. In contrast to 1,2-shifts mentioned earlier and 1,2-shifts of nitro groups observed⁴⁵ with 4-alkyl-4-nitrocyclohexadienyl cations, no

1,2-shift products were detected. Well-behaved first-order kinetics were observed and Table 5.2 lists some kinetic data collected together with activation parameters. The reaction had the following characteristics: (1) Rates of product formation were equal to rates of reactant disappearance. (2) Reaction rates decreased as the polarity or hydrogen bonding ability of the solvent increased. (3) Activation entropies were small but positive. (4) Added radical scavengers did not alter reaction rates but reduced the yield of nitrophenol products and increased the yields of alkylphenol products. (5) The reactivity order $5.6 > 5.7 > 5.8$ was observed. These results were held to indicate a radical dissociation-recombination mechanism as shown in Scheme 5.3, where dissociation is rate limiting. Formation of 3,4-dimethylphenol when 5.7 is allowed to react in the presence of hydroquinone reflected some diffusion of the radical pair from the solvent cage.



Scheme 5.3

Table 5.2

First-order rate coefficients for reaction
of 5.6, 5.7 and 5.8 in various solvents^a

Solvent	Temperature /°C	$10^4 k_1 / \text{s}^{-1}$		
		Compound		
		5.6	5.7	5.8
Hexane	45.0	—	18.8	—
	40.0	31.1	10.5 ^{b,c}	0.42
	30.0	8.9	3.0	—
	15.0	—	0.34	—
Acetic acid	45.0	—	11.8	—
	40.0	—	5.7 ^c	—
	30.0	4.7	1.6	—
	15.0	—	0.16	—
Ethanol	40.0	—	8.7 ^b	—
	30.0	7.46	—	—
Water	40.0	—	2.0	—
	30.0	1.57	—	—
Dimethyl sulphoxide	40.0	—	1.0	—

Table 5.2 (continued)

Activation parameters for the rearomatisation
of 5.6 and 5.7 in various solvents

		Compound		
		5.6	5.7	
$\Delta H_{298}^\ddagger$	(hexane)	97.4	98.3	kJ mole^{-1}
$\Delta H_{298}^\ddagger$	(acetic acid)		105.8	kJ mole^{-1}
$\Delta S_{298}^\ddagger$	(hexane)	17.2	10.5	$\text{J deg}^{-1} \text{ mole}^{-1}$
$\Delta S_{298}^\ddagger$	(acetic acid)		30.2	$\text{J deg}^{-1} \text{ mole}^{-1}$

a) Measurement at 360 nm

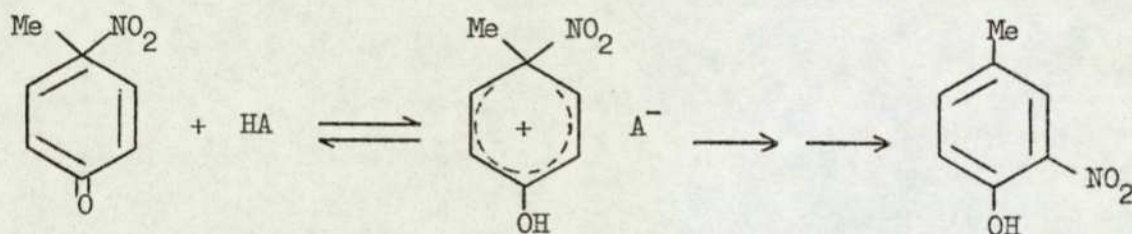
b) Measurement at 230 nm

c) Addition of hydroquinone (ca 2×10^{-4} M) reduced

A_∞ (360 nm) by about 50%, but rates were unchanged.

The Scheme 5.3 was tested by allowing an equimolar mixture of 5.7 and (^{15}N)-2,6- d_2 -3,4-dimethyl-4-nitrocyclohexa-2,5-dien-1-one to react in n-hexane under kinetic conditions. The extent of scrambling conformed to the results obtained with radical scavengers.

The rates of rearomatization of 5.6 and 5.7 in aqueous sulphuric acid gave evidence of acid catalysis in solutions that exceed 50 weight percent and it was assumed that under these strongly acidic conditions, reaction occurred through the conjugate acid involving protonation on oxygen¹⁰⁶ (Scheme 5.4). Products from the acid-catalysed rearrangement of 5.6 and 5.7 were said to include *o*-nitrophenols, phenols and dinitro-



Scheme 5.4

phenols. In a personal communication received while our work was in progress, Myhre has reported the rate profile for the rearrangement of 5.7 in sulphuric acid (Fig. 5.1 and 5.2) and the products were now recorded as, 3,4-dimethyl-6-nitrophenol (65%), 3,4-dimethyl-2-nitrophenol (22%) and 3,4-dimethylphenol (11%), in 67.5% sulphuric acid.

Cross-over experiments for the reaction of the cyclohexadienone (5.6) in sulphuric acid suggested that the rearomatization of this dienone occurs via an intramolecular process. This rearrangement mechanism is presumably the same as that observed for 4-methyl-4-nitrocyclohexadienone during the nitration of *p*-cresol (see Section 1.53).

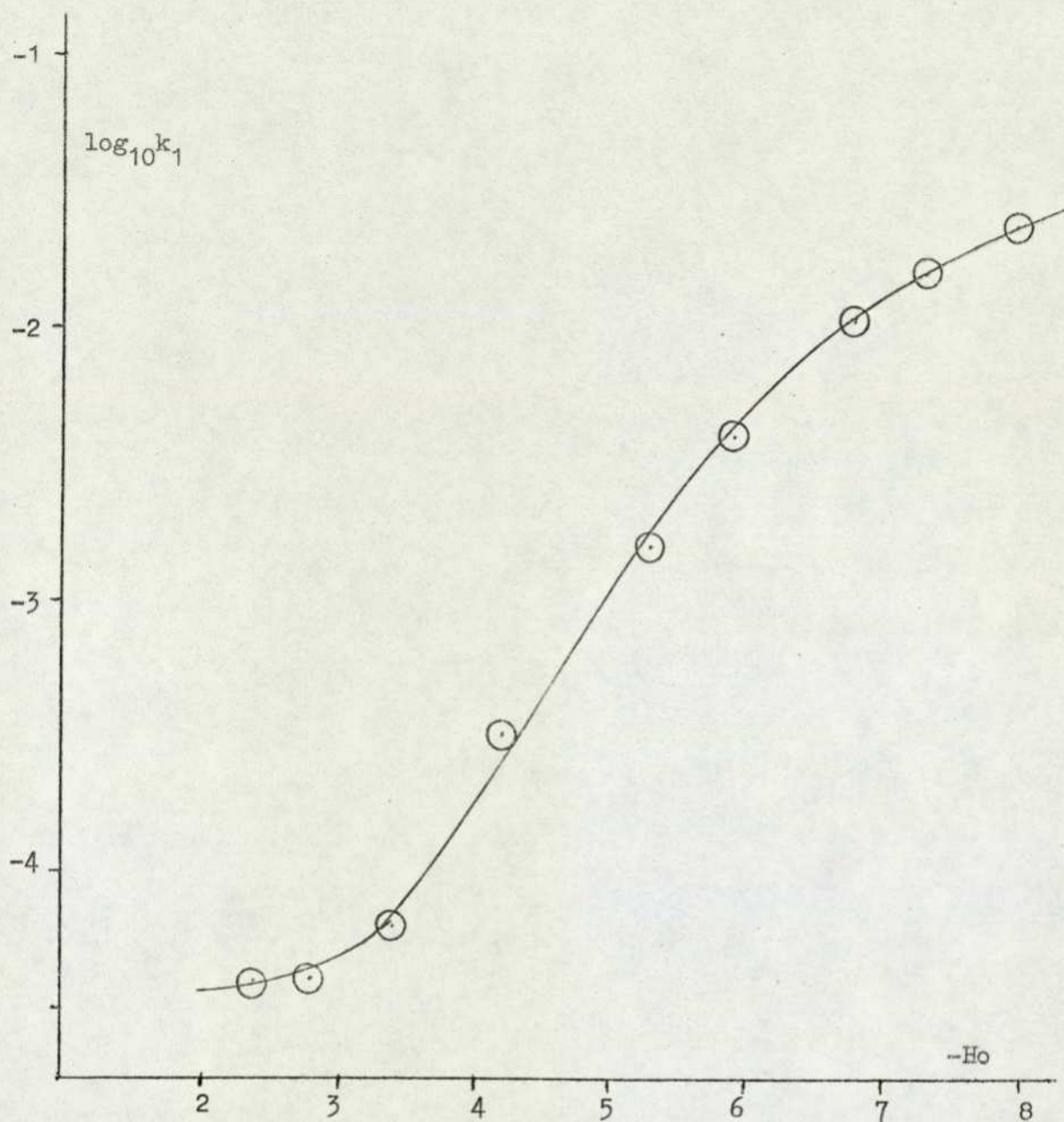


Fig. 5.1 Rate profile for the rearomatization of 3,4-dimethyl-4-nitrocyclohexa-2,5-dien-1-one in sulphuric acid at 30°

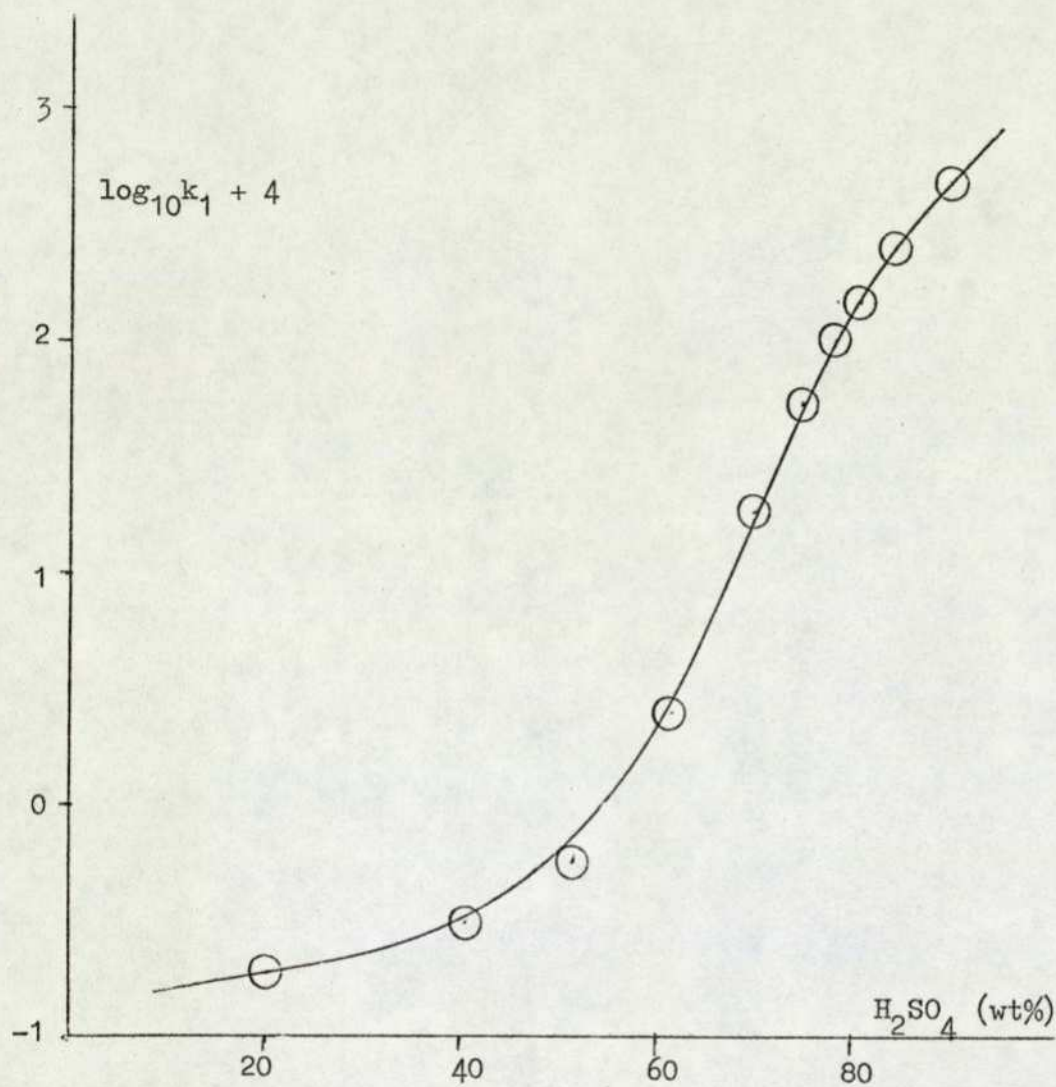


Fig. 5.2

Rate profile for the rearomatization of 3,4-dimethyl-4-nitrocyclohexa-2,5-dien-1-one in sulphuric acid at 30°

In this Chapter 4-methyl-4-nitrocyclohexadienone and some cyclohexadienones from Table 5.1 were isolated and characterized. Kinetic and product studies for the reaction of 4-methyl-4-nitrocyclohexa-2,5-dien-1-one and 2,4,6-trimethyl-4-nitrocyclohexa-2,5-dien-1-one in various concentrations of sulphuric acid were carried out.

5.2 EXPERIMENTAL

5.21 MATERIALS

These were as described in Section 7.2 with the addition of the following: 4-Methyl-2-nitrophenol, 2-methyl-3-nitrophenol and 3,5-dimethyl-4-hydroxybenzaldehyde were commercial reagents purified by crystallization. Nitric acid used was AnalaR, the reagent (d 1.52) distilled twice at 20° under vacuum from 98% sulphuric acid.

5.211 NITROMESITOL

2,4,6-Trimethylaniline (5 ml) was dissolved in 98% sulphuric acid (50 ml). The solution was cooled down to 0° and 70% nitric acid (2 ml) was added slowly with continuous stirring. The reaction mixture was then poured into 300g of ice and neutralized with sodium hydroxide pellets. The yellow flakes obtained by filtration were recrystallized from ethanol (4.3g); m.p. 71° (lit.¹¹³ 73 - 75°).

¹H.n.m.r.(CDCl₃): τ 3.20(1H, s, ArH), 6.36(2H, s, NH₂), 7.84(6H, s, Ar-2-CH₃, Ar-4-CH₃), 7.96(3H, s, Ar-6-CH₃).

The nitromesidine (3g) obtained above was placed in a 800 ml beaker and a cold mixture of water (70 ml) and 98% sulphuric acid (50 ml) was added with continuous stirring and then about 100g of ice were added. A solution of sodium nitrite (1g) in water (25 ml) was added slowly until a permanent colour was given to starch iodide paper, the temperature being kept at 0 - 5°. The reaction mixture was then poured into a solution of 70% sulphuric acid (175 ml) which was

previously heated at 160°. When the evolution of nitrogen ceased, the dark brown crystals were filtered by suction, washed with ice water and then recrystallized from methanol/water, to give yellow crystals; m.p. 63 - 64° (lit.¹¹⁴ 64°).

¹H.n.m.r.(CDCl₃): τ 3.20(1H, s, ArH), 5.28(3H, s, OH), 8.80(3H, s, Ar-2-CH₃), 8.84(3H, s, Ar-4-CH₃), 8.88(3H, s, Ar-6-CH₃).

5.212 2,4,6-TRIMETHYL-4-NITROCYCLOHEXA-2,5-DIEN-1-ONE.

To a solution of 2,4,6-trimethylphenol (2g) in hexane (50 ml) at 20°, nitric acid (2.3 ml, d.1.5) was added with continuous stirring. The reaction mixture was left stirring for one hour and then washed with water and dried over anhydrous magnesium sulphate. Half of the hexane was removed under vacuum and the remainder was left to stand at -70°. The colourless crystals were filtered off (1.5g); m.p. 43° (lit.¹⁰³ 43°); unstable at room temperature (2 days);

¹H.n.m.r.(CCl₄): τ 3.26(2H, s, ArH), 8.04(6H, s, Ar-2,6-CH₃), 8.20(3H, s, Ar-4-CH₃).

The ¹H.n.m.r. spectrum in CCl₄ was recorded again after 48 hours and the bands due to the dienone disappeared and new bands at τ 3.04(2H, s), 4.84(2H, s), 5.36(1H, s) and 7.74(6H, s) appeared, which are thought to be due to 2,6-dimethyl-4-nitromethylphenol. Attempts to isolate and characterise this compound were unsuccessful.

5.213 2,6-DI-*t*-BUTYL-4-METHYL-4-NITROCYCLOHEXA-2,5-DIEN-1-ONE

As in 5.212; yield 2.5g; stable at room temperature (6 weeks); m.p. 95 - 96° (lit.¹⁰³ 97°);

¹H.n.m.r.(CCl₄): τ 3.28(2H, s, ArH), 8.20(3H, s, ArMe), 8.76(18H, s, Ar-2,6-*t*-Bu).

5.214 2,4-DIMETHYL-6-*t*-BUTYL-4-NITROCYCLOHEXA-2,5-DIEN-1-ONE

As in 5.212; yield 1.2g; unstable at room temperature (1 week);

m.p. 63° (lit.¹⁰³ 63 - 65°);

¹H.n.m.r.(CCl₄): τ 3.28(2H, s, ArH), 7.98(3H, s, Ar-2-Me),

8.22(3H, s, Ar-4-Me), 8.75(9H, s, Ar-*t*-Bu).

5.215 4-METHYL-4-NITROCYCLOHEXA-2,5-DIEN-1-ONE

Nitric acid (1 ml, d 1.52) in acetic anhydride (10 ml) was added during 30 minutes to a stirred solution of 4-methylphenyl acetate (5g) (prepared by the acetylation of *p*-cresol with acetic anhydride in a basic aqueous solution) in acetic anhydride (10 ml) at 0°. The reaction mixture was stirred at 0° for 2 hours after which the solvent was removed at 5mmHg and 20° during 5 hours. The dark yellow residue was then adsorbed onto a column of 10% deactivated alumina (200g) which was cooled externally to -20° by an ethanol thermostat, to reduce decomposition of the desired product to a minimum. Elution with light petroleum/ether (10:1) (cooled to the desired temperature) gave a mixture of 4-methyl-2-nitrophenyl acetate and 2,6-dinitro-4-methylphenyl acetate. Elution with light petroleum/ether (30:1) gave a pale yellow oil after removal of the solvent, under vacuum at 20°. The product was found to be unstable at room temperature (6 hours) but it was stable at -30° for one week.

¹H.n.m.r.(CDCl₃): τ 2.76(2H, d, J_{2,3}=J_{6,5}=10Hz, 2- and 6-H),

3.56(2H, d, J_{3,2}=J_{5,6}=10Hz, 3- and 5-H),

8.08(3H, s, 4-Me).

The ¹H.n.m.r. values quoted here are at variance with those reported¹³¹ previously, but are in close agreement with those reported³⁴ for similar compounds.

5.22 KINETIC MEASUREMENTS

A standard solution of the cyclohexadienone in acetic acid was freshly prepared on each occasion and typically contained $0.05 \text{ mole dm}^{-3}$ of substrate. Sulphuric acid (25 ml) of the appropriate concentration, in a 50 ml volumetric flask was thermostatted at $25.0 \pm 0.2^\circ$. An aliquot (typically 0.1 ml) of the standard solution in acetic acid was added to the sulphuric acid solution and after mixing, a sample was rapidly transferred to a 10 mm silica cell in the thermostatted cell compartment of a PERKIN-ELMER 402 UV spectrophotometer. The change in absorbance with time, at a selected wavelength close to the maximum in the UV extinction curve of the products, was measured. Linear first-order kinetic plots were thus obtained during several half-lives of the reaction

5.23 PRODUCTS

About 0.1g of the cyclohexadienone was added to 100 ml of sulphuric acid of the appropriate concentration, with continuous stirring at 25° and the solution was left to react for 10 half-lives (determined from the first-order rate coefficients), after which it was quenched with distilled water (250 ml). The reaction mixture was then extracted with chloroform, dried over anhydrous magnesium sulphate and the chloroform was removed under vacuum. Deuteriochloroform (0.5 ml) was then added and the $^1\text{H.n.m.r.}$ spectrum at 100 MHz was recorded. Finally the reaction extracts were subjected to t.l.c. and h.p.l.c. analysis. The t.l.c. conditions were, silica gel, 10% MeCN/1,2-dichloroethane for 2,4,6-trimethyl-4-nitrocyclohexadienone and 15% EtOAc/cyclohexane for 4-methyl-4-nitrocyclohexadienone. The h.p.l.c. conditions were as described in Table 5.3 and Table 5.4 respectively and the products were identified from their retention times. In the

Table 5.3

H.p.l.c. conditions for the separation of m-nitromesitol,
3,5-dimethyl-4-hydroxybenzaldehyde and other unidentified
products

Column : 25 cm x $\frac{1}{4}$ " Merkosorb SI60
Solvent : 5% MeCN/1,2-dichloromethane
Flow rate : 3 ml/min
Wavelength : 260 nm
Detector : Cecil 272
Pump : Waters Associates, model 6000A
Temperature : Ambient

Compound	Retention times/s
3,5-dimethyl-4-hydroxybenzaldehyde	192
<u>m</u> -nitromesitol	280

Table 5.4

H.p.l.c. conditions for the quantitative
estimation of 4-methyl-2-nitrophenol

Column : 25 cm x $\frac{1}{4}$ " Merkosorb SI60
Solvent : 10% EtOAc/cyclohexane
Flow rate : 2 ml/min
Wavelength : 280 nm
Detector : Cecil 272
Pump : Waters Associates, model 6000A
Temperature : Ambient

Compound	Retention times/s
4-methyl-2-nitrophenol	172
2-methyl-3-nitrophenol (standard)	545

former case the combined extracts from a series of reactions were adsorbed onto a preparative silica gel plate and m-nitromesitol and 3,5-dimethyl-4-hydroxybenzaldehyde were separated as described above. Their identity was confirmed by their $^1\text{H.n.m.r.}$ spectra which were identical to those of the authentic samples.

$^1\text{H.n.m.r.}$ spectrum of 3,5-dimethyl-4-hydroxybenzaldehyde in CDCl_3 : τ 0.15(1H, s, CHO), 2.26(2H, s, ArH), 4.40(1H, s, OH), 8.52(6H, s, 3- and 5-Me).

5.3 RESULTS

5.31 KINETICS

5.311 2,4,6-TRIMETHYL-4-NITROCYCLOHEXA-2,5-DIEN-1-ONE

At higher acidities (e.g. 70% sulphuric acid) several changes in the UV spectrum occur; one is relatively fast and very difficult to follow and this followed by one or more changes which are very slow and take about 48 hours to complete. The first change becomes slower at lower acidities (e.g. at 60% sulphuric acid) and one can then isolate this stage, which gives well behaved first-order kinetics.

The results and subsequent calculations required for a typical determination of a rate coefficient for the reaction of this dienone in sulphuric acid at $25.0 \pm 0.2^\circ$ are given below:-

Concentration of sulphuric acid	: 53.9% w/w
Concentration of substrate	: 9.21×10^{-5} mole dm^{-3}
Temperature	: $25.0 \pm 0.2^\circ$
Wavelength of measurement	: 300 nm

Fig. 5.3 shows the extinction curve obtained, Table 5.5 gives the data obtained therefrom and Fig. 5.4 shows the plot of $\log_{10}(A_{\infty} - A_t)$ vs time.

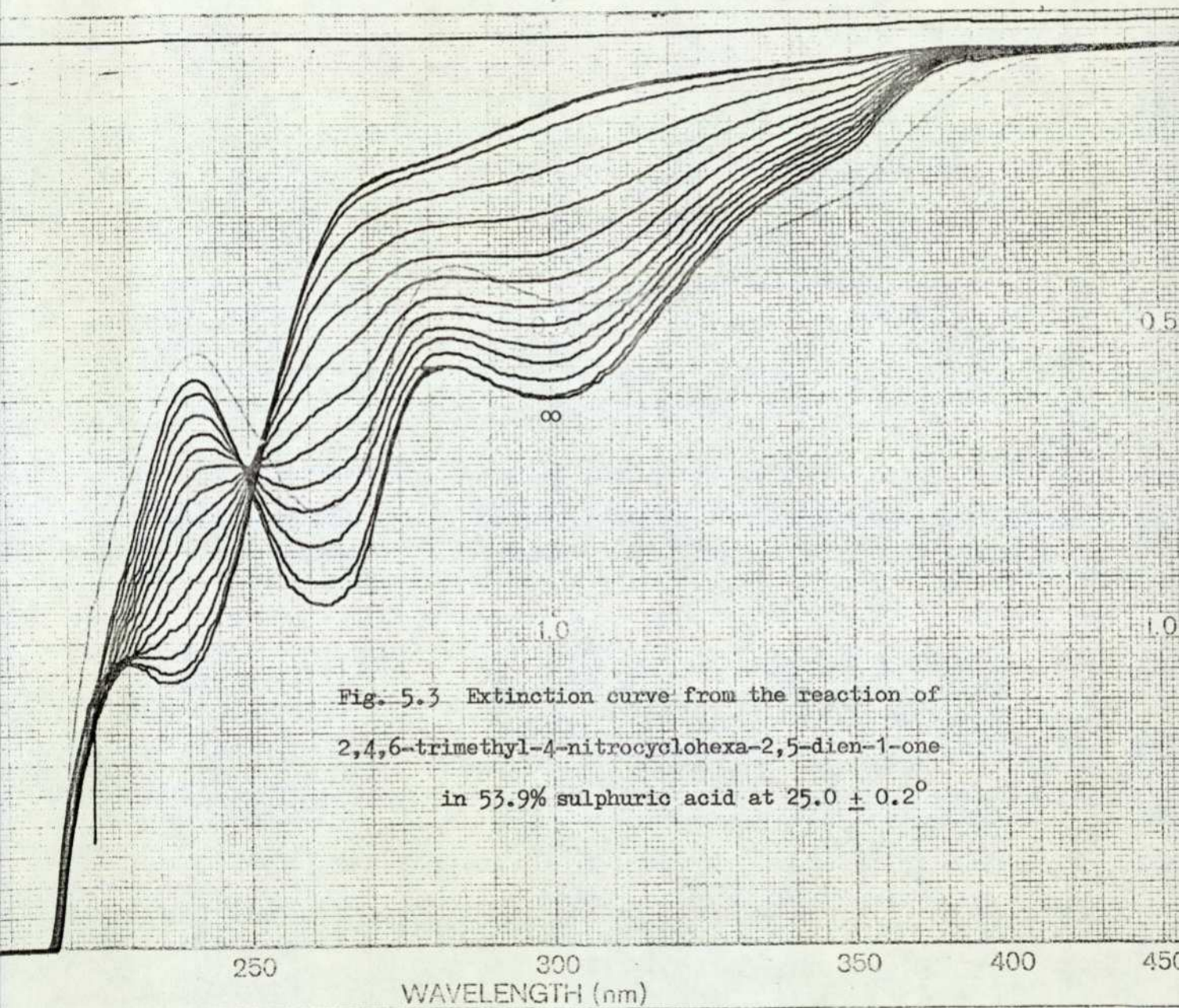


Table 5.5

Data from a typical determination of a the rate
coefficient for the reaction of 2,4,6-trimethyl-
4-nitrocyclohexa-2,5-dien-1-one in 53.9% sulphuric
acid at $25.0 \pm 0.2^{\circ}$

Time	Absorbance	$\log_{10}(A_{\infty} - A_t)$
/s	A_t	
100	0.125	-0.31
200	0.130	-0.32
400	0.157	-0.34
700	0.225	-0.41
1000	0.290	-0.49
1400	0.363	-0.60
1800	0.409	-0.69
2300	0.450	-0.78
2800	0.480	-0.89
3400	0.518	-1.01
4000	0.542	-1.13
t_{∞}	0.610	

Fig. 5.4 Plot of $\log_{10}(A_{\infty} - A_t)$ vs time from the reaction of 2,4,6-trimethyl-4-nitrocyclohexa-2,5-dien-1-one in 53.9% sulphuric acid at $25.0 \pm 0.2^{\circ}$.

220

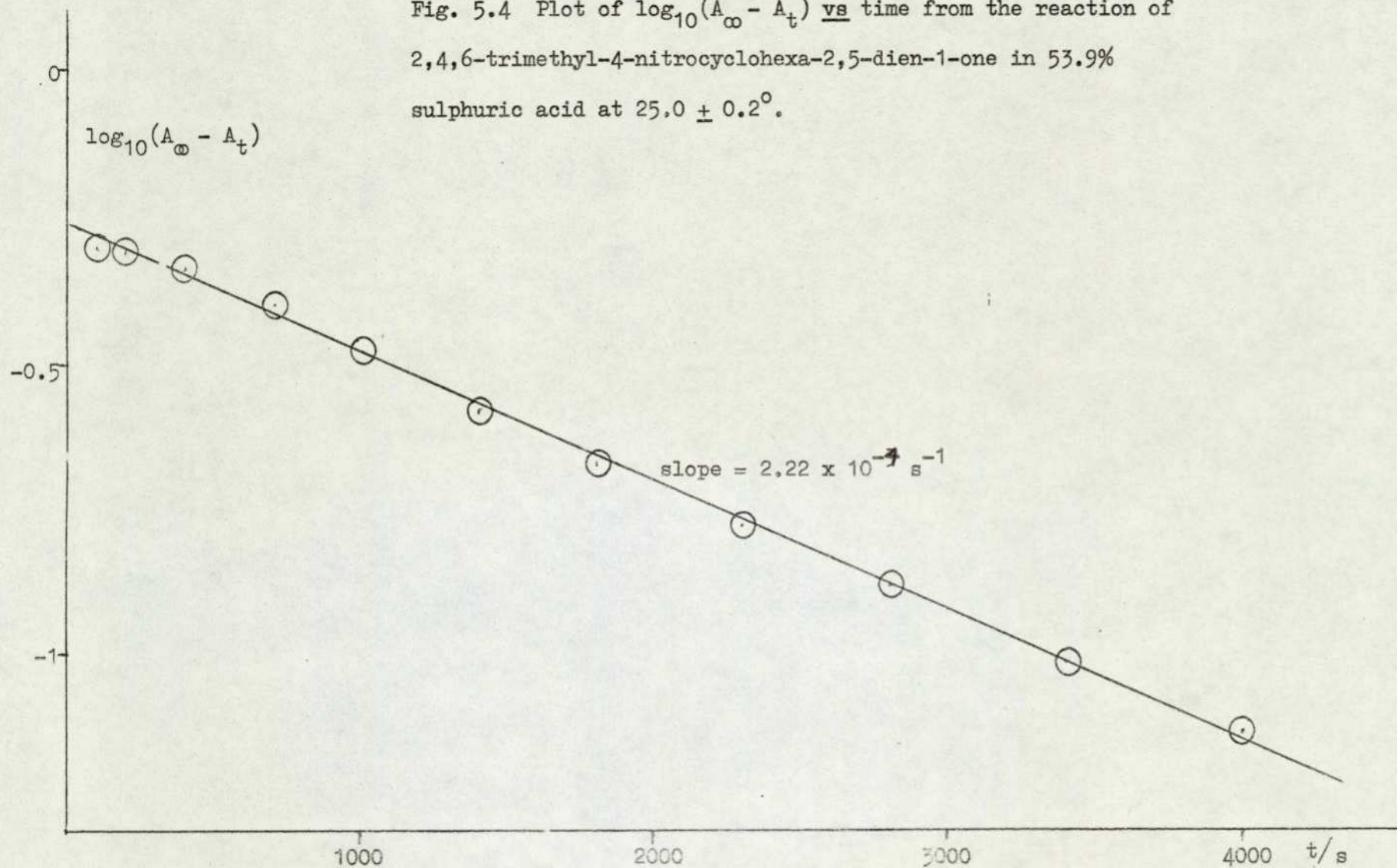


Table 5.6

First-order rate coefficients for the reaction of
2,4,6-trimethyl-4-nitrocyclohexa-2,5-dien-1-one^{a,b}
in sulphuric acid at $25.0 \pm 0.2^\circ$

H_2SO_4 (%) ^c	$-\text{Ho}^{116}$	$k(\text{obs})$ $/\text{s}^{-1}$
64.3	5.00	2.85×10^{-3}
62.3	4.76	2.30×10^{-3}
60.1	4.49	1.61×10^{-3}
58.1	4.25	1.20×10^{-3}
56.1	4.02	9.04×10^{-4}
53.9	3.78	5.12×10^{-4}
52.0	3.57	4.12×10^{-4}
49.8	3.34	2.46×10^{-4}
48.2	3.17	2.02×10^{-4}
46.0	2.95	1.02×10^{-4}
44.3	2.76	9.33×10^{-5}
38.8	2.30	6.65×10^{-5}
36.7	2.16	6.25×10^{-5}

a) $[\text{ArH}] = 9.21 \times 10^{-5} \text{ mole dm}^{-3}$

b) Measurement at 300 nm

c) $\pm 0.1\% \text{ w/w}$

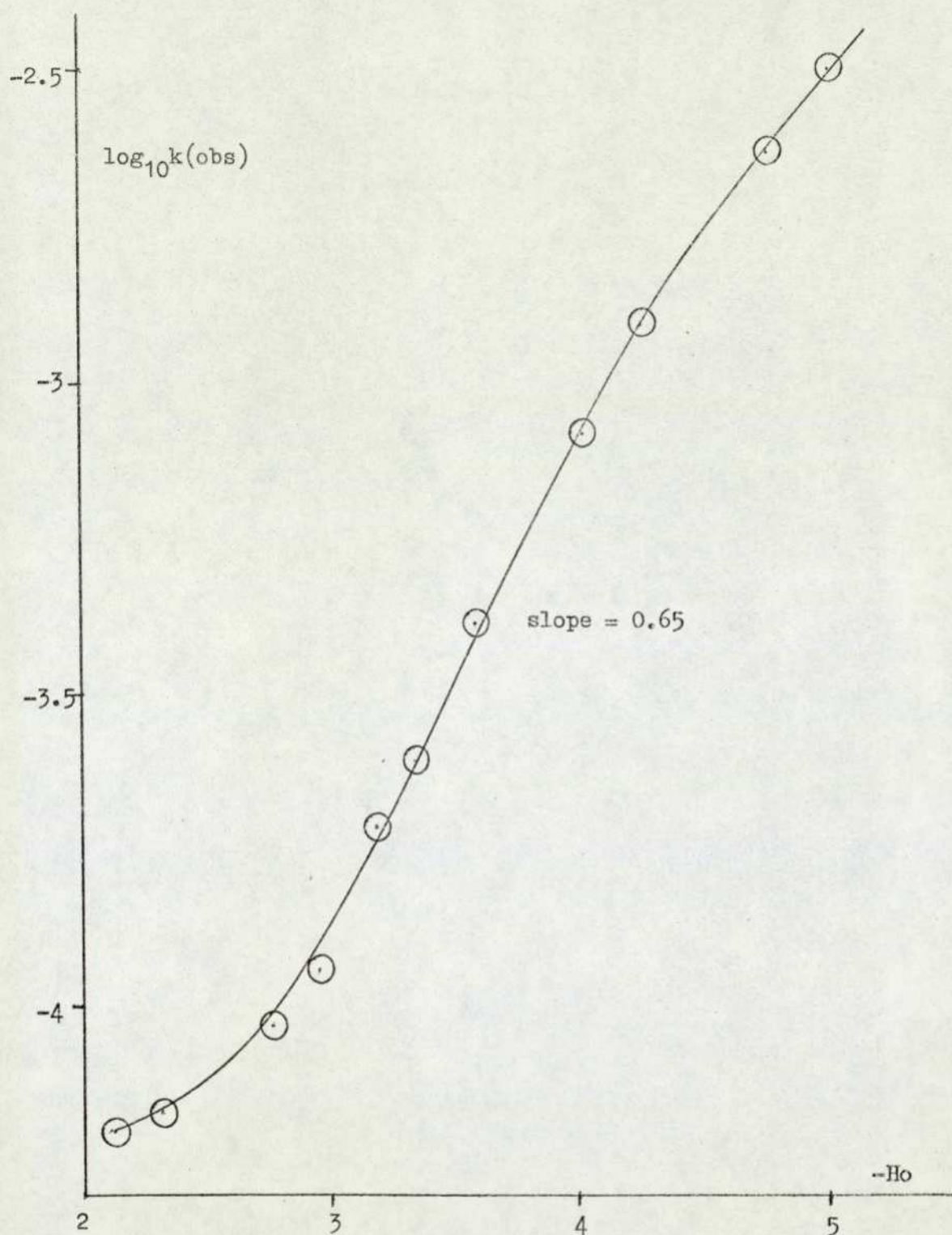


Fig. 5.5

Rate profile from the reaction of 2,4,6-trimethyl-
4-nitrocyclohexa-2,5-dien-1-one in sulphuric acid
at $25.0 \pm 0.2^\circ$

$$k(\text{obs}) = -2.303 \times \text{slope} \text{ s}^{-1}$$

$$k(\text{obs}) = 5.12 \times 10^{-4} \text{ s}^{-1}$$

A summary of the kinetic data for reaction of 2,4,6-trimethyl-4-nitrocyclohexa-2,5-dien-1-one in aqueous sulphuric acid is given in Table 5.6 and Fig. 5.5 shows the plot of $\log_{10} k(\text{obs})$ vs the acidity function $-H_o$.

5.312 4-METHYL-4-NITROCYCLOHEXA-2,5-DIEN-1-ONE

The results and subsequent calculations required for a typical determination of a rate coefficient for the reaction of this cyclohexadienone in sulphuric acid at $25.0 \pm 0.2^\circ$ are given below:-

Concentration of sulphuric acid : 66.3% w/w

Concentration of substrate : $9.41 \times 10^{-5} \text{ mole dm}^{-3}$

Temperature : $25.0 \pm 0.2^\circ$

Wavelength of measurement : 235 nm

Fig. 5.6 shows the extinction curve obtained, Table 5.7 the data obtained therefrom and Fig. 5.7 the plot of $\log_{10}(A_t - A_\infty)$ vs time.

$$k(\text{obs}) = -2.303 \times \text{slope} \text{ s}^{-1}$$

$$k(\text{obs}) = 1.21 \times 10^{-3} \text{ s}^{-1}$$

A summary of the kinetic data for reaction of 4-methyl-4-nitrocyclohexa-2,5-dien-1-one in aqueous sulphuric acid is given in Table 5.8 and Fig. 5.8 shows the plot of $\log_{10} k(\text{obs})$ vs the acidity function $-H_o$. The values obtained from the rate of disappearance of the intermediate formed during the nitration of *p*-cresol^{66,81} in sulphuric acid at 25° , are also shown on this plot. Using high concentrations of nitric acid (ca $1.2 \times 10^{-2} \text{ mole dm}^{-3}$), a rate coefficient for the disappearance of the same intermediate, formed during the nitration of *p*-methyl-anisole, in 70.6% sulphuric acid at $25.0 \pm 0.2^\circ$, was also determined using an approximate infinity absorbance, at λ_{max} 235 nm. This value

Fig. 5.6 Extinction curve from the reaction of
4-methyl-4-nitrocyclohexa-2,5-dien-1-one in 66.3%
sulphuric acid at $25.0 \pm 0.2^\circ$

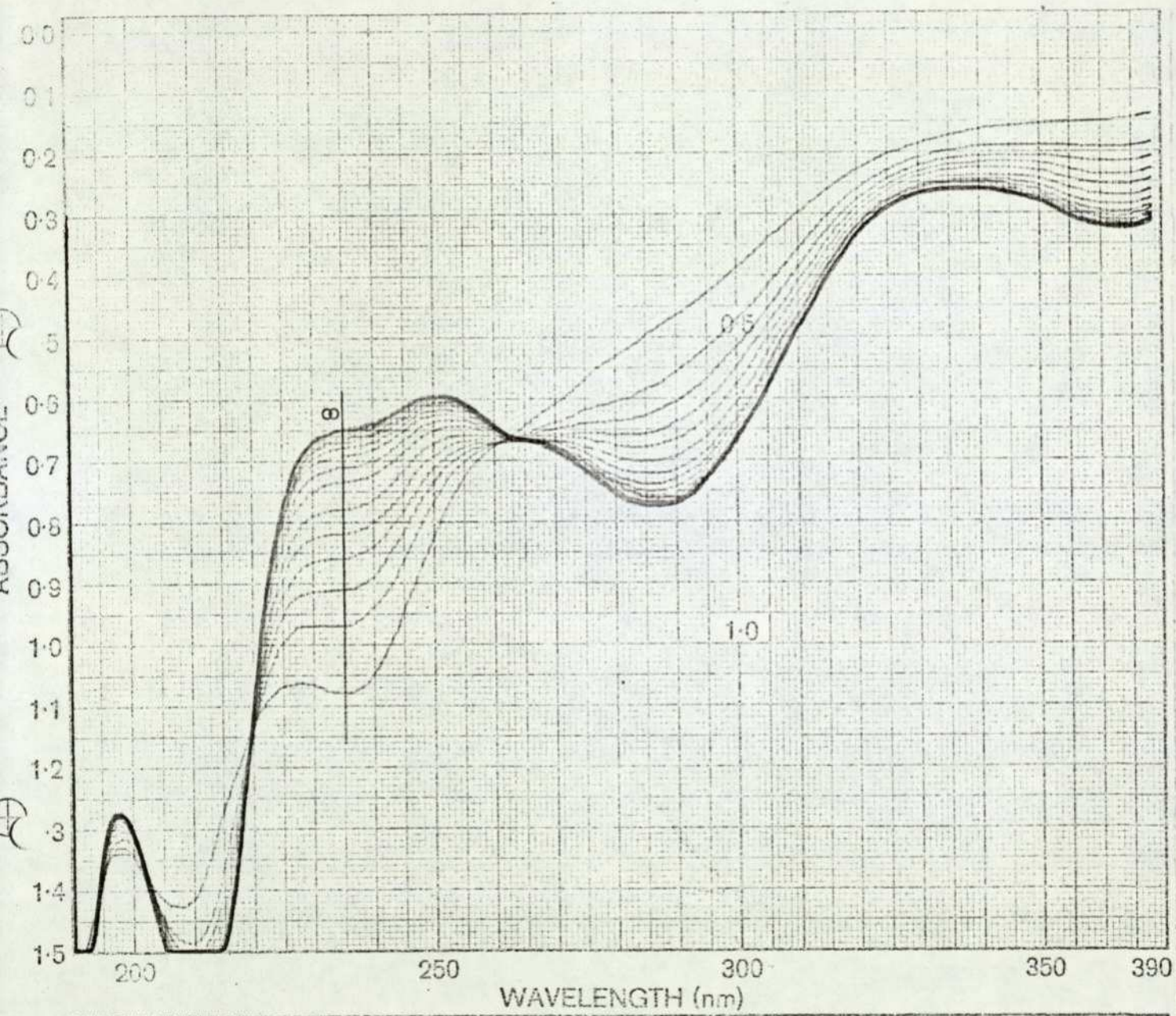


Table 5.7

Data from a typical determination of the rate of
reaction of 4-methyl-4-nitrocyclohexa-2,5-dienone
in 66.3% sulphuric acid at $25.0 \pm 0.2^{\circ}$

Time /min	Absorbance A_t	$\log_{10}(A_t - A_{\infty})$
3	1.079	-0.37
7	0.969	-0.49
10	0.910	-0.58
13	0.860	-0.68
16	0.820	-0.77
20	0.779	-0.89
25	0.734	-1.08
30	0.710	-1.21
35	0.692	-1.38
40	0.679	-1.54
t_{∞}	0.650	

Fig. 5.7 Plot of $\log_{10}(A_t - A_\infty)$ vs time from the reaction of 4-methyl-4-nitrocyclohexa-2,5-dien-1-one in 66.3% sulphuric acid at $25.0 \pm 0.2^\circ$

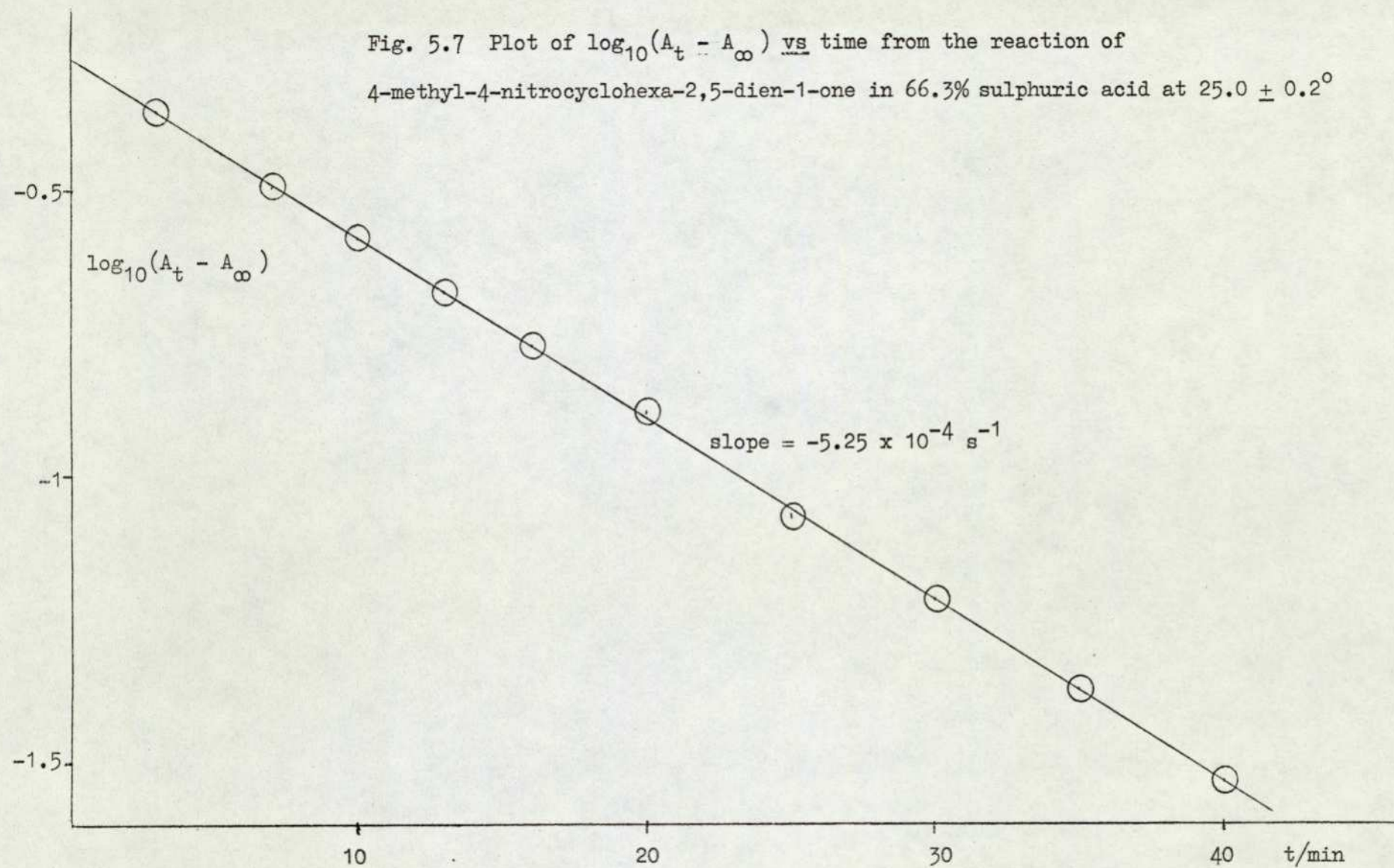


Table 5.8

First-order rate coefficients for the reaction of
4-methyl-4-nitrocyclohexa-2,5-dien-1-one^{b,c} in
sulphuric acid at $25.0 \pm 0.2^\circ$

H_2SO_4 (%) ^a	$-\text{H}_0^{\text{d}}$	$k(\text{obs})$ $/\text{s}^{-1}$
72.7	6.20	6.14×10^{-3}
70.6	5.99	3.81×10^{-3}
68.5	5.65	2.05×10^{-3}
66.3	5.27	1.21×10^{-3}
63.8	4.93	7.67×10^{-4}
62.2	4.76	6.40×10^{-4}
59.6	4.48	3.83×10^{-4}
58.1	4.25	2.83×10^{-4}
56.1	4.02	2.21×10^{-4}
53.9	3.78	1.79×10^{-4}
52.0	3.57	1.58×10^{-4}
49.8	3.34	1.47×10^{-4}
48.2	3.17	1.34×10^{-4}
46.0	2.95	1.28×10^{-4}
44.3	2.76	1.02×10^{-4}
38.8	2.30	9.09×10^{-5}
36.7	2.16	8.91×10^{-5}

a) $\pm 0.1\%$ w/w

b) $[\text{ArH}] = 9.41 \times 10^{-5} \text{ mole dm}^{-3}$

c) Measurement at 235 or 290 nm

d) Ref. 116

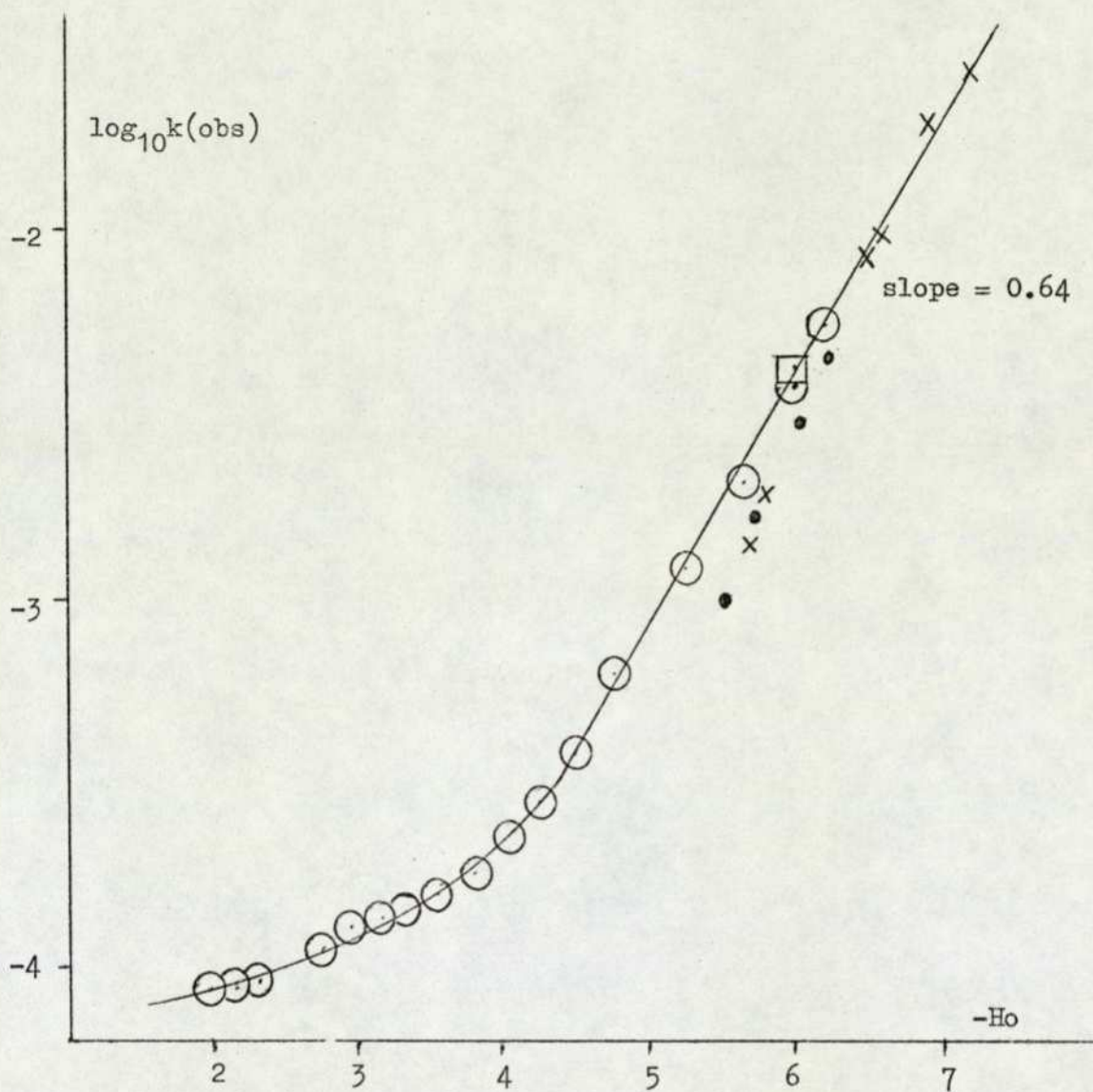


Fig. 5.8

Rate profile from the reaction of 4-methyl-4-nitrocyclohexa-2,5-dien-1-one in sulphuric acid at $25.0 \pm 0.2^\circ$

⊙ : from 4-methyl-4-nitrocyclohexa-2,5-dien-1-one

o : from p-cresol^{66,81}

□ : from p-methylanisole

x : from p-methylanisole¹³³

($k_1 = 0.004 \text{ s}^{-1}$) is shown on Fig. 5.8 together with the values obtained¹³³ independently from the rate of disappearance of the same intermediate, formed during the nitration of p-methylanisole at higher acidities.

5.32 PRODUCTS

5.321 2,4,6-TRIMETHYL-4-NITROCYCLOHEXA-2,5-DIEN-1ONE

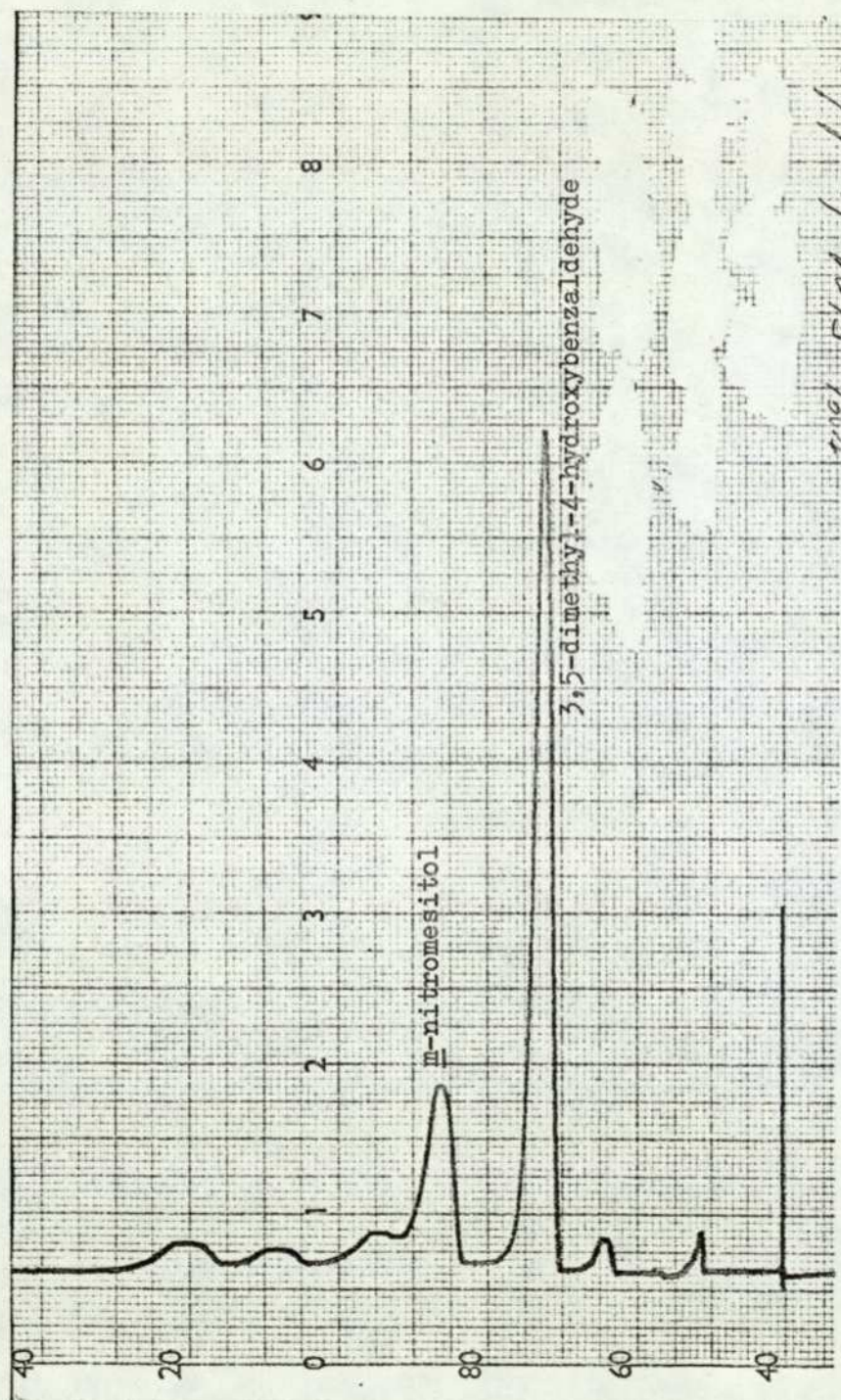
The recorded $^1\text{H.n.m.r.}$ spectrum of the reaction mixture in CDCl_3 indicated amongst other products, the presence of 3,5-dimethyl-4-hydroxybenzaldehyde as the major product and m-nitromesitol to a lesser extent; the amount of the 3,5-dimethyl-4-hydroxybenzaldehyde increasing with increasing acidity and the amount of m-nitromesitol remaining approximately constant. Thin layer chromatography of the reaction mixture (t.l.c. conditions as described in Section 5.23) showed a minimum of seven spots, two corresponding to 3,5-dimethyl-4-hydroxybenzaldehyde ($R_f = 0.86$) and m-nitromesitol ($R_f = 0.72$) which were eluted alongside for comparison.

H.p.l.c. (conditions as Table 5.3) showed the presence of six components (Fig. 5.9), the major ones corresponding to 3,5-dimethyl-4-hydroxybenzaldehyde ($\sim 50\%$) and m-nitromesitol ($\sim 15\%$). No quantitative studies were carried out since not all the products were identified and 3,5-dimethyl-4-hydroxybenzaldehyde could not be extracted quantitatively from the reaction mixture. The maximum amount of 3,5-dimethyl-4-hydroxybenzaldehyde recovered from a 63.8% sulphuric acid solution ($\sim 3 \times 10^{-3} \text{ mole dm}^{-3}$) was 78%.

5.322 4-METHYL-4-NITROCYCLOHEXA-2,5-DIEN-1-ONE

The $^1\text{H.n.m.r.}$ spectrum of the reaction mixture in CDCl_3 was identical to the spectrum of an authentic sample of 4-methyl-2-nitrophenol; τ -0.5(1H, s, OH), 1.97 - 2.95(3H, m, ArH), 7.82(3H, s, ArMe).

Fig. 5.9 Chromatogram of the products from the reaction
of 2,4,6-trimethyl-4-nitrocyclohexa-2,5-dien-1-one in 59.6%
sulphuric acid



Thin layer chromatography of the reaction mixture (t.l.c. conditions as described in Section 5.23), showed only one spot which corresponded to that of 4-methyl-2-nitrophenol ($R_f = 0.91$) which was eluted alongside for comparison.

An example of the h.p.l.c. method for calculating the yield of 4-methyl-2-nitrophenol from the reaction of 4-methyl-4-nitrocyclohexa-2,5-dien-1-one in sulphuric acid is given below:-

Concentration of sulphuric acid	: 59.6% w/w
Amount of cyclohexadienone	: 6.55×10^{-4} moles
Amount of reference standard	
2-methyl-3-nitrophenol	: 8.12×10^{-4} moles

Fig. 5.10 shows the chromatogram obtained (h.p.l.c. conditions as in Table 5.4).

Peak weights from chromatogram

Compound	Weight/g
4-methyl-2-nitrophenol	0.0180
2-methyl-3-nitrophenol (standard)	0.0150

The method of relative response factors as described in Section 7.5 was used:

$$c_x/c_s = A_x/A_s \times f$$

Factor f for 4-methyl-2-nitrophenol : 0.64

Amount of 4-methyl-2-nitrophenol =

$$\begin{aligned}
 &= \frac{0.0180}{0.0150} \times 8.12 \times 10^{-5} \times 0.64 \text{ moles} \\
 &= 6.25 \times 10^{-4} \text{ moles}
 \end{aligned}$$

$$\begin{aligned}
 \% \text{ of 4-methyl-2-nitrophenol} &= \frac{6.25 \times 10^{-4}}{6.55 \times 10^{-4}} \times 100 \\
 &= 95.4 \%
 \end{aligned}$$

Fig. 5.10 Chromatogram of the products from the reaction
of 4-methyl-4-nitrocyclohexa-2,5-dien-1-one in 59.6%
sulphuric acid

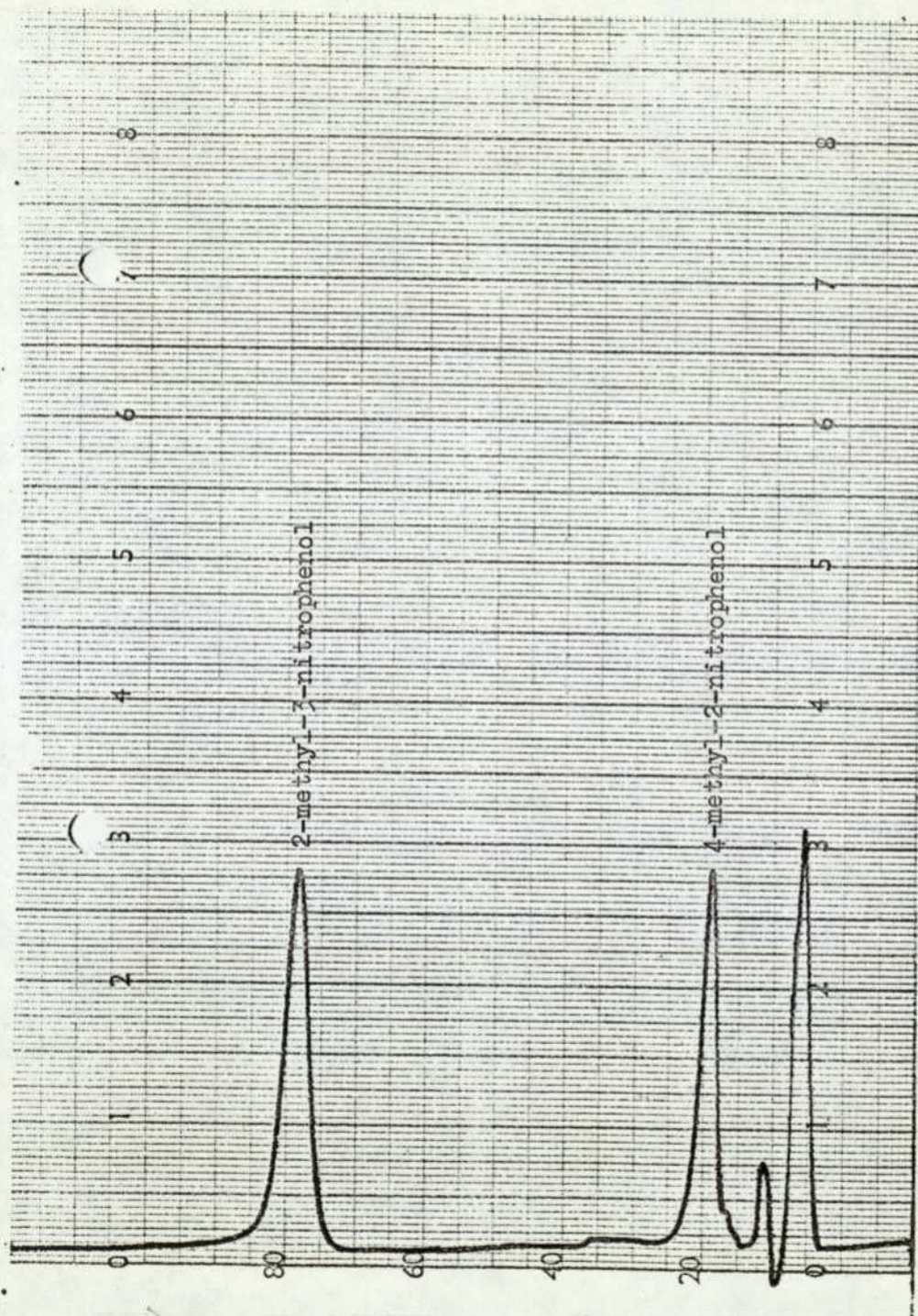


Table 5.9

Yields of 4-methyl-2-nitrophenol from the reaction of
4-methyl-4-nitrocyclohexa-2,5-dien-1-one^b in sulphuric
acid at $25.0 \pm 0.2^{\circ}$

H_2SO_4 (%) ^a	4-methyl-2-nitro- phenol (%) ^c
66.3	95.9
59.6	95.4
53.9	97.3
48.2	97.1
44.3	98.0

a) $\pm 0.1\%$ w/w

b) $[\text{ArH}] = 6.55 \times 10^{-3} \text{ mole dm}^{-3}$

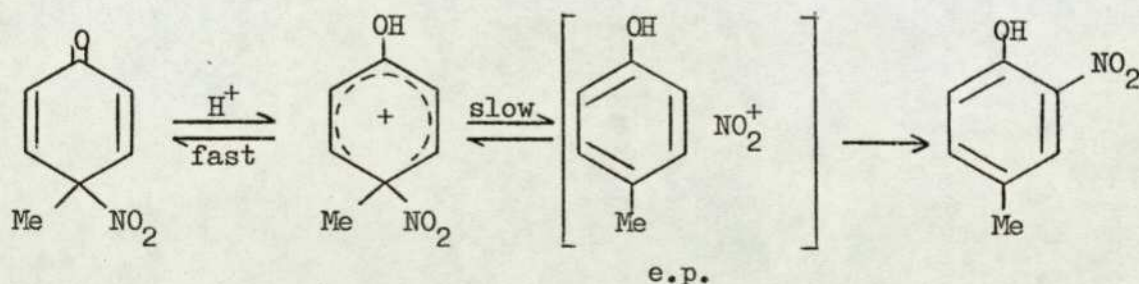
c) $\pm 2\%$

Table 5.9 gives the yields of 4-methyl-2-nitrophenol from the reaction of 4-methyl-4-nitrocyclohexa-2,5-dien-1-one in various concentrations of sulphuric acid at $25.0 \pm 0.2^\circ$.

5.4 DISCUSSION

5.41 RATE PROFILES

4-Methyl-4-nitrocyclohexa-2,5-dien-1-one has been postulated as an intermediate in the nitration of *p*-cresol^{66,81} and should also be present in the nitration of *p*-methylanisole⁵⁰ in aqueous sulphuric acid (see Section 1.53). The rate of reaction of this intermediate in sulphuric acid was determined for both *p*-cresol^{66,81} and *p*-methylanisole¹³³ and the results are shown in plotted in Fig. 5.8 together with the results in this study. The three sets of results agree reasonably well and strong support for the previous deduction is provided. Above 56% sulphuric acid the rate profile (*vs* -*H*₀) for the reaction is a straight line with slope 0.64. Similar slopes of rate profiles have been obtained in the rearomatization of some 4-X-4-methylcyclohexa-2,5-dien-1-ones¹⁰⁷⁻¹¹² in sulphuric acid and it seems reasonable to assume in the present case also that under these strongly acidic conditions the oxygen conjugate acid is the reactant, but reacting via the pathway shown in Scheme 5.5.



Scheme 5.5

Myhre has studied the rearomatization of 3,4-dimethyl-4-nitrocyclohexa-2,5-dien-1-one in sulphuric acid and a similar rate profile was obtained (see Fig. 5.1 and 5.2). Above 75% sulphuric acid the

slope of the rate profile gradually decreased (Fig. 5.1) which is presumably due to complete protonation of the cyclohexadienone at high acidities. Cross-over experiments for the reaction of this cyclohexadienone in sulphuric acid suggested that the rearomatization of this dienone occurs via an intramolecular process as would be expected for a mechanism similar to that of Scheme 5.5 as the phenol is sufficiently reactive for the nitronium ion not to be expected to diffuse from the solvent cage (see also below in Section 5.422).

Below 56% sulphuric acid the slope of the rate profile (Fig. 5.8) gradually decreases and finally the profile levels out below ca 35% sulphuric acid, as does that for the dienone studied by Myhre (Fig. 5.1). At these low acidities the radical dissociation-recombination mechanism as shown in Scheme 5.3 becomes dominant and there is good agreement with the limiting minimum rate from Fig. 5.8 ($8 \times 10^{-5} \text{ s}^{-1}$) and that estimated from Myhre's in water solution ($6 \times 10^{-5} \text{ s}^{-1}$).

A similar rate profile (Fig. 5.5) was obtained for the reaction of 2,4,6-trimethyl-4-nitrocyclohexa-2,5-dien-1-one in sulphuric acid, although in this case the products were complicated (see Section 5.421), and it seems therefore that here also the protonated form is the reacting species. The higher reactivity of this dienone compared to the 4-methyl-4-nitro- and 3,4-dimethyl-4-nitrocyclohexa-2,5-dien-1-ones is presumably due to its higher basicity induced by the two extra methyl groups at 2- and 6-positions. The effect, however, is small (a rate factor of 3). The similarity in rates of rearrangement of the other two cyclohexadienones must mean that the increased reactivity conferred by the additional methyl group is countered by a decreased rate of rearrangement.

The mechanistic suggestions made above rely on the cyclohexadienones having a $-H_o$ value for half protonation of >7 for the

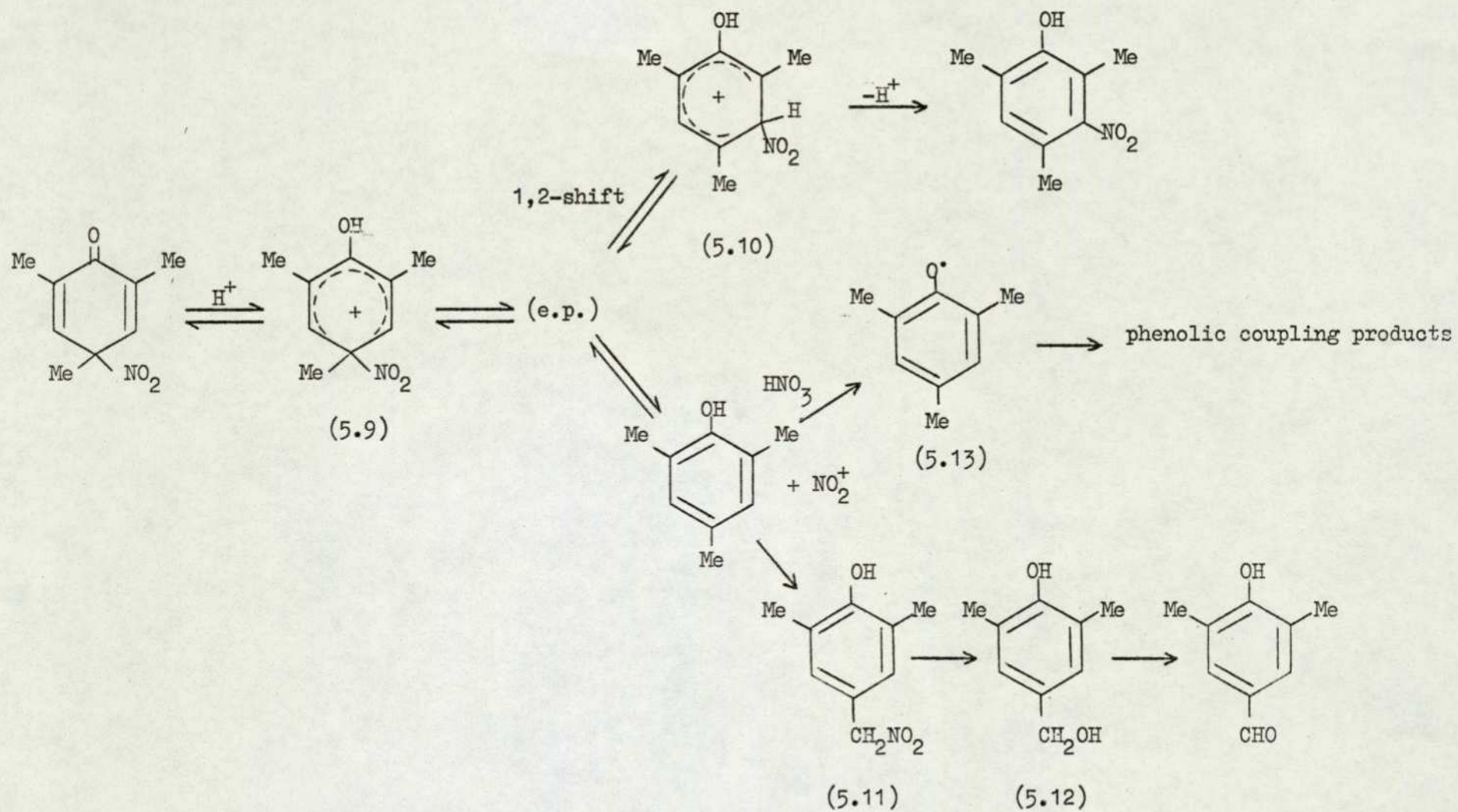
4-methyl-4-nitro compound, > 5 for the 2,4,6-trimethyl-4-nitro compound and $> 7.5 - 8$ for the 3,4-dimethyl-4-nitro compound. Values of this quantity for other compounds (e.g. for 4-X-4-methylcyclohexa-2,5-dienone, where $X = \text{CCl}_3$), and for the variation with X^{107} suggest that such values are very reasonable. It was not possible to study the rates of reaction in the present study at high enough acidities to observe the expected decrease in slope caused by nearing the acidities where the bulk of the dienone is protonated (cf Fig. 5.1).

The 2,4,6-trimethyl-4-nitrocyclohexa-2,5-dienone also shows the levelling off of the rate rate decrease at low acidities attributed to the radical process becoming dominant. This process shows a lack of sensitivity to the substituent effects of the methyl group.

5.42 PRODUCTS

5.421 2,4,6-TRIMETHYL-4-NITROCYCLOHEXA-2,5-DIEN-1-ONE

3,5-Dimethyl-4-hydroxybenzaldehyde and m-nitromesitol have been established amongst other products as the major products of the reaction of this dienone in 54 - 64% sulphuric acid. The formation of m-nitromesitol could be explained by an intramolecular 1,2-shift of the nitro group in the protonated conjugate acid (5.9) to give the Wheland intermediate (5.10) and subsequent protonloss to give m-nitromesitol (Scheme 5.6). This pathway is relatively unfavourable since the formation of the Wheland intermediate (5.10) is disfavoured by the m-OH group and this is probably the reason why m-nitromesitol is formed at relatively low yields ($\sim 10 - 20\%$). The formation of 3,5-dimethyl-4-hydroxybenzaldehyde which is the major product ($\sim 50\%$), could involve the oxidation of compounds (5.11) and (5.12) by nitric acid. Side chain nitration is known from some nitration reactions^{36,38} although the methyl group is usually activated to proton loss by



Scheme 5.6

ipso-substitution para to it. Hindered phenols have been known to undergo oxidation^{102,115} and mesitol here could be oxidized by nitric acid to give phenolic coupling products through the phenoxy radical 5.13.

5.422 4-METHYL-4-NITROCYCLOHEXA-2,5-DIEN-1-ONE

4-Methyl-2-nitrophenol was formed quantitatively from the reaction of this dienone in 44 - 66% sulphuric acid (Table 5.9). As discussed above the likely pathway involves rate limiting reversion of the protonated conjugate acid to the encounter pair, fast formation of the Wheland intermediate and subsequent proton loss (Scheme 5.5). Possible nucleophilic capture of the protonated conjugate acid at low acidities by water, is precluded by the quantitative yields of 4-methyl-2-nitrophenol, which was also the only product of the reaction of this dienone in non-acidic media¹⁰⁶.

This rearrangement has one puzzling feature. Some isotopic labelling experiments have been interpreted as showing that some leakage from the encounter pair must occur in 68.8% but not in 71.3% sulphuric acid⁵¹. p-Cresol is expected to be a very reactive substrate, the rate of which is subjected to the encounter limit. Escape from the encounter pair is therefore not to be expected.

CHAPTER 6

THE NITRATION OF DIPHENYLMETHANE AND
OF DIPHENYLETHER

6.1 INTRODUCTION

The nitration of diphenylmethane in acetic anhydride¹¹⁷ has been found to yield the 2- and 4-nitro isomers and the partial rate factors have been determined as $f_o = 13$ and $f_p = 32$. The rate of nitration relative to benzene has been found to be 19.5^{23} . The benzyl group appears to be marginally less activating than the methyl group. Gehring and Reddy¹¹⁸ studied the nitration of diphenylmethane with nitric acid and were able to identify six products using $^1\text{H.n.m.r.}$. Their results are summarized in Table 6.1. J.G. Golding studied the nitration of diphenylmethane in aqueous sulphuric acid and good first-order kinetics were obtained. Some of his kinetic results are shown in Table 6.6. The method of Gehring and Reddy¹¹⁸ was used by Golding for the identification and quantitative estimation of the products with the results shown in Table 6.2. In spite of the spread of results, the inconsistencies in some of them, the unknown extraction behaviour of any of the compounds, and the inability to separate completely the $^1\text{H.n.m.r.}$ peaks for 2-nitrodiphenylmethane and 4,4'-dinitrodiphenylmethane, it appeared that there was some evidence for an anomalous amount of dinitration. This was particularly so in view of the kinetic studies, which indicated that the mononitro compounds were less reactive than the parent hydrocarbon.

The nitration of diphenylether in acetic anhydride/nitric acid mixture has been studied by Suter¹¹⁹ who found that the ratio of the 2- to the 4-nitro isomer is approximately 1. Dinitration was also observed, the amount of which was found to increase with increasing nitric acid concentration. The nitration of diphenylether in acetic anhydride was also reported by Dewar and Urch¹¹⁷ who again observed that the 2- to 4-nitro isomer ratio was approximately 1. The partial

Table 6.1

Nitro-products from the nitration of
diphenylmethane by nitric acid¹¹⁸

Compound	Mole % found
Diphenylmethane	1-2
4-Nitrodiphenylmethane	1-2
4,4'-Dinitrodiphenylmethane	20
2,4'-Dinitrodiphenylmethane	25
2,2',4-Trinitrodiphenylmethane	22
2,4',4-Trinitrodiphenylmethane	27
2,2',4,4'-Tetranitrodiphenylmethane	4

No 2-nitrodiphenylmethane or 2,2'-dinitrodiphenylmethane
was detected.

Table 6.2

Yields of nitro compounds from the nitration of diphenylmethane^{a,b,c} in sulphuric acid

H_2SO_4 (%)	Diphenyl- methane	4-Nitro- diphenyl- methane	2-nitrodiphenyl- methane and 4,4'-dinitro- diphenylmethane	2,4'-Dinitro- diphenyl- methane	2,2'-Dinitro- diphenyl- methane	Σ of rings containing nitro-groups (%) ^e
66.6 ^d	11	3	35	33	17	154
69.1	33	17	25	18	8	106
72.2	19	33	27	14	7	114
75.2	29	24	27	15	6	105
77.1	13	11	35	29	12	145
84.1	19	11	30	31	9	134
84.1	18	12	34	30	6	133

Table 6.2 (continued)

- a) $[\text{ArH}] = 5.8 \times 10^{-5} \text{ mole dm}^{-3}$
- b) $[\text{Sulphamic acid}] = 0.02 \text{ mole dm}^{-3}$
- c) $[\text{HNO}_3] = 5.9 \times 10^{-5} \text{ mole dm}^{-3}$
- d) $[\text{HNO}_3] = 4.5 \times 10^{-2} \text{ mole dm}^{-3}$
- e) The amounts of 2-nitrodiphenylmethane and
4,4'-dinitrodiphenylmethane were assumed to be equal.

rate factors were determined as $f_o = 117$ and $f_p = 23$ and the rate of nitration relative to benzene was 156.

In this Chapter the nitration of diphenylmethane in sulphuric acid is reinvestigated and the nitration of diphenylether has also been studied. These unsubstituted compounds are studied as they are relevant to projected studies of selectivity between two aromatic rings (see Section 1.343, page 19).

6.2 EXPERIMENTAL

6.21 MATERIALS

These were as described in Section 7.2 with the addition of the following: Diphenylmethane, diphenylether, 4,4'-dinitrodiphenylmethane, 2-nitrodiphenylether, 4-nitrodiphenylether, p-nitroanisole and p-nitroethylbenzene were commercial reagents purified by distillation or recrystallization as necessary.

6.211 2-NITRODIPHENYLMETHANE¹²⁰

o-Nitrobenzylchloride (20g) was dissolved in dry benzene (100 ml) and aluminium chloride (10g) was added gradually with warming on a water-bath. The solution went dark-brown and a black resin separated. The entire contents of the flask were shaken with the same volume of water, the benzene layer was separated and benzene was removed under vacuum leaving behind the impure 2-nitrodiphenylmethane as a dark-yellow oil. The product was purified by preparative t.l.c. (20% EtOAc/cyclohexane, silica gel) which gave a pale-yellow oil.

¹H.n.m.r. (CDCl₃): τ 2.24 (1H, d, H-3), 2.60 (8H, m, H-4,-5,-6,-2',-3',-5',-6'), 5.76 (2H, s, Ph-CH₂-Ar).

6.212 3-NITRODIPHENYLMETHANE

The same method as described above was followed using m-nitrobenzylchloride and dry benzene. The final product was purified by

preparative t.l.c. (silica gel, 20% EtOAc/cyclohexane) which gave a viscous yellow oil.

$^1\text{H.n.m.r.}(\text{CDCl}_3): \tau$ 2.22 - 2.30(2H, m, H-2,-4), 2.85 - 3.10(7H, m, H-5, -6,-2',-3',-4',-5',-6'), 6.13(2H, s, Ph-CH₂-Ar).

6.213 4-NITRODIPHENYLMETHANE

p-Nitrobenzyl alcohol (5g) was suspended in dry benzene (100 ml) and concentrated sulphuric acid (50 ml) was added with shaking. The whole mixture was transferred into a separating funnel and was shaken for 10 minutes until all the p-nitrobenzyl alcohol was dissolved and the sulphuric acid layer went dark-brown. The sulphuric acid layer was run off and diluted four times its volume with distilled water. Then it was extracted with benzene and the benzene extracts were combined and benzene was removed under vacuum leaving the impure 4-nitrodiphenylmethane as a light-brown oil. The product was purified by preparative t.l.c. (silica gel, 20% EtOAc/cyclohexane) which gave a viscous pale-yellow oil.

$^1\text{H.n.m.r.}(\text{CDCl}_3): \tau$ 2.06(2H, d, $J_{2,3}=J_{6,5}=4.7\text{Hz}$, H-3 and -5), 2.80 - 3.00(7H, m, H-2,-6,-2',-3',-4',-5',-6'), 6.00(2H, s, Ph-CH₂-Ar).

6.214 2,2'-DINITRODIPHENYLMETHANE

4,4'-Diamino-2,2'-dinitrodiphenylmethane (5g) was added in portions with vigorous stirring to a solution of sodium nitrite (3.35g) in concentrated sulphuric acid (35 ml) maintained below 20°. Glacial acetic acid (45 ml) was then added slowly at <20° and after 2 hours the solution was run into a vigorously stirred suspension of cuprous oxide (13g) in ethanol (100 ml) during 5 mins; the temperature quickly rose to 70° and it was kept at that temperature for further 30 mins. The hot mixture was filtered and the residue was washed with hot ethanol.

The crude deamination product was then adsorbed onto a column of alumina and was eluted with benzene. The yellow solid recovered from the first yellow band was then crystallised from methanol-water mixture which yielded 2,2'-dinitrodiphenylmethane as pale-yellow needles; m.p. 82 - 83° (lit.¹²¹ 84°).

¹H.n.m.r.(CDCl₃): τ 1.90 - 2.00(2H, d, H-3,-3'), 2.40 - 2.80(6H, m, H-4,-5,-6,-4',-5',-6'), 5.32(2H, s, Ar-CH₂-Ar').

6.215 2,4'-DINITRODIPHENYLMETHANE

Diphenylmethane (15g) was added slowly to nitric acid (300 ml, d 1.42) with stirring and heating to boiling until no more red fumes were given off. The nitrated product which crystallised on cooling, was filtered giving 13g of product which was crystallised from ethanol giving a crystalline product. The product gave two spots on t.l.c. (silica gel, 20% EtOAc/cyclohexane) and preparative t.l.c. gave two bands; the product recovered from the first band was identical to the commercially available 4,4'-dinitrodiphenylmethane and the product recovered from the second band was 2,4'-dinitrodiphenylmethane which on recrystallization from ethanol gave a pale-yellow crystalline solid; m.p. 116° (lit.¹²² 118°).

¹H.n.m.r.(CDCl₃): τ 1.84(2H, d, J_{2',3'}=J_{6',5'}= 4.5Hz, H-3', -5'), 2.05(1H, d, J_{4,3'}= 4.2Hz, H-3), 2.60 - 2.95(5H, m, H-4, -5, -6, -2', -6'), 5.64(2H, s, Ar-CH₂-Ar').

6.216 2,2'-, 2,4'- and 4,4'-DINITRODIPHENYLEETHERS

A solution in dimethylformamide (30 ml) of equimolar amounts of the appropriate sodium nitrophenoxide (0.05 moles) and the appropriate chloronitrobenzene (0.05 moles) was refluxed for 20 hours and then poured into ice (200g). The precipitates formed, were filtered, air-dried and then all three dinitrodiphenylethers were recrystallised from ethanol to give the desired pure products.

2,2'-Dinitrodiphenylether: yellow needles; m.p. 114° (lit.¹²³ 116°);

¹H.n.m.r.(CDCl₃): τ 2.08(2H, d, H-3, -3'), 2.50(2H, t, H-4, -4'),

2.78(2H, t, H-5, -5'), 3.05(2H, d, H-6, -6').

2,4'-Dinitrodiphenylether: light-brown needles; m.p. 101° (lit.¹²³ 104°);

¹H.n.m.r.(CDCl₃): τ 1.98 - 3.15(3H, m, H-3, -3', -5'), 2.52(1H, t, H-4),

2.80(1H, t, H-5), 3.00 - 3.12(3H, m, H-6, -2', -6').

4,4'-Dinitrodiphenylether: brown needles; m.p. $139 - 140^{\circ}$ (lit.¹²³ 142°);

¹H.n.m.r.(CDCl₃): τ 2.02(4H, d, $J_{2,3}=J_{6,5}=4.2\text{Hz}$, H-3, -5, -3', -5'),

3.10(4H, d, $J_{3,2}=J_{5,6}=4.2\text{Hz}$, H-2, -6, -2', -6').

6.22 KINETIC MEASUREMENTS

The kinetics for diphenylmethane and diphenylether were determined as described in Section 7.3.

6.23 PRODUCT ANALYSIS

6.231 DIPHENYLMETHANE

The conventional h.p.l.c. method as described in Section 7.4 (ii) was used, with the exception that 250 ml of sulphuric acid was used and the half-lives of the reactions were determined from the pre-determined second-order rate coefficients in Table 5.6 of Ref. 66. Table 6.3 gives the h.p.l.c. conditions.

6.232 DIPHENYLETHER

The conventional h.p.l.c. method as described in Section 7.4(i) was used for the determination of the yields of mononitrodiphenylethers below 66% sulphuric acid, with the exception that 250 ml of sulphuric acid was used and the reaction was terminated after about 2 half-lives as calculated from the kinetic data. Table 6.4 gives the h.p.l.c. conditions.

Table 6.3

H.p.l.c. conditions for the separation of 2-, 3-
and 4-nitrodiphenylmethane and 2,2'-, 2,4', and
4,4'-dinitrodiphenylmethane

Column : 25cm x $\frac{1}{4}$ " Merkosorb SI60
Solvent : 1% EtOAc/cyclohexane; changed to 5% EtOAc/
cyclohexane after 10 minutes
Flow rate : 0.8 ml/min; changed to 5 ml/min after 10 minutes
Wavelength : 295 nm
Detector : Cecil 272
Pump : Waters Associates, Model 6000A
Temperature : Ambient

Compound	Retention times/s
2-nitrodiphenylmethane	390
3-nitrodiphenylmethane	440
4-nitrodiphenylmethane	470
2,2'-dinitrodiphenylmethane	665
2,4'-dinitrodiphenylmethane	840
4,4'-dinitrodiphenylmethane	1230
p-nitroethylbenzene (reference standard)	250

Table 6.4

H.p.l.c. conditions for the separation of 2- and
4-nitrodiphenylether and 2,2'-, 2,4'- and 4,4'-
dinitrodiphenylether

Column : 25cm x $\frac{1}{4}$ " Merkosorb SI60
Solvent : 5% EtOAc/cyclohexane
Flow rate : 2 ml/min
Wavelength : 300 nm
Detector : Cecil 272
Pump : Waters Associates, Model 6000A
Temperature : Ambient

Compound	Retention times/s
2-nitrodiphenylether	235
4-nitrodiphenylether	156
2,2'-dinitrodiphenylether	198
2,4'-dinitrodiphenylether	640
4,4'-dinitrodiphenylether	930
p-nitroanisole (reference standard)	370

6.3 RESULTS

6.31 KINETICS

6.311 DIPHENYLMETHANE

Some kinetic results for this substrate have been described previously⁶⁶. Some further values were obtained in the present study and the results and subsequent calculations required for the determination of a second-order rate coefficient are given below:-

Concentration of sulphuric acid : 72.4% w/w

Concentration of nitric acid : 8.98×10^{-4} mole dm^{-3}

Concentration of diphenylmethane : 1.23×10^{-4} mole dm^{-3}

Concentration of sulphamic acid ca 0.05 mole dm^{-3}

Temperature : $25.0 \pm 0.2^\circ$

Wavelength of measurement : 290 nm

Fig. 6.1 shows the extinction curve obtained, Table 6.5 the data obtained therefrom and Fig. 6.2 shows the plot of $\log_{10}(A_\infty - A_t)$ vs time.

$$k_2(\text{obs}) = -2.303 \times \text{slope} / [\text{HNO}_3] \text{ dm}^3 \text{ mole}^{-1} \text{ s}^{-1}$$

$$k_2(\text{obs}) = 1.83 \text{ dm}^3 \text{ mole}^{-1} \text{ s}^{-1}$$

Table 6.6 gives the second-order rate coefficients for the nitration of diphenylmethane, 2-nitrodiphenylmethane, 3-nitrodiphenylmethane and 4-nitrodiphenylmethane together with some values from Ref. 66. The runs labelled 'd' were carried out with the substrate at the same concentration as used in the product studies (see below).

The values of the ratios of the absorbances of the final extinction curves to the absorbances of the initial curves at 273 nm (where measurements for the nitration of diphenylmethane were made⁶⁶) for the nitration of 2-, 3- and 4-nitrodiphenylmethanes were determined and were found to be 1.98, 1.91 and 1.90 respectively.

Fig. 6.1 Extinction curve from the nitration of
diphenylmethane in 72.4% sulphuric acid at $25.0 \pm 0.2^\circ$

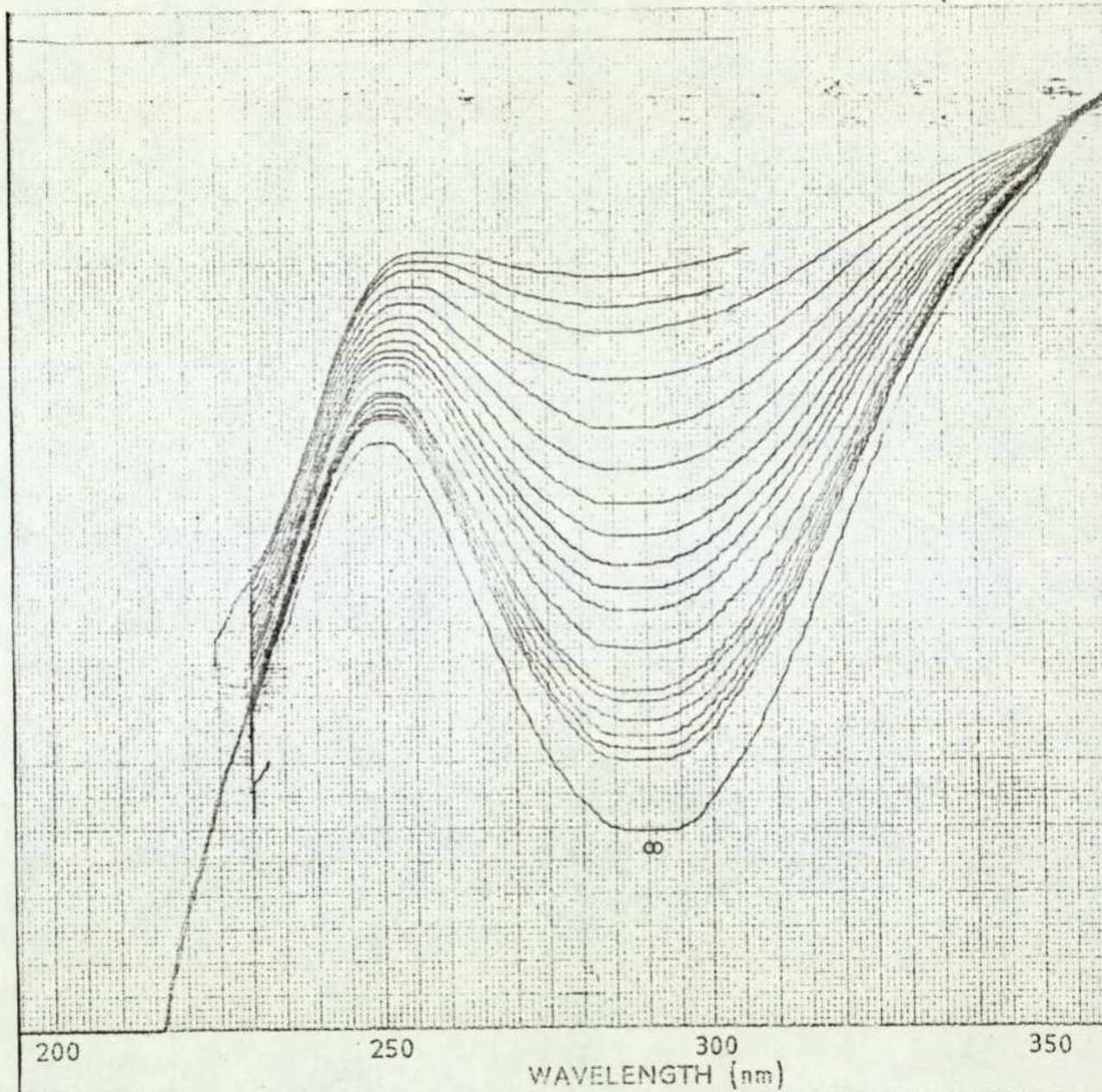


Table 6.5

Data from the determination of the rate of nitration
of diphenylmethane in 72.4% sulphuric acid at $25.0 \pm 0.2^\circ$

Time(t) /min	Absorbance A_t	$\log_{10}(A_\infty - A_t)$
1	0.364	-0.07
2	0.492	-0.14
4	0.599	-0.21
6	0.712	-0.30
10	0.873	-0.47
12	0.931	-0.55
15	0.993	-0.66
16	1.010	-0.70
18	1.040	-0.77
20	1.061	-0.83
22	1.081	-0.89
24	1.099	-0.95
t_∞	1.210	

Fig. 6.2 Plot of $\log_{10}(A_{\infty} - A_t)$ vs time from the nitration of diphenylmethane in 72.4% sulphuric acid at $25.0 \pm 0.2^{\circ}$.

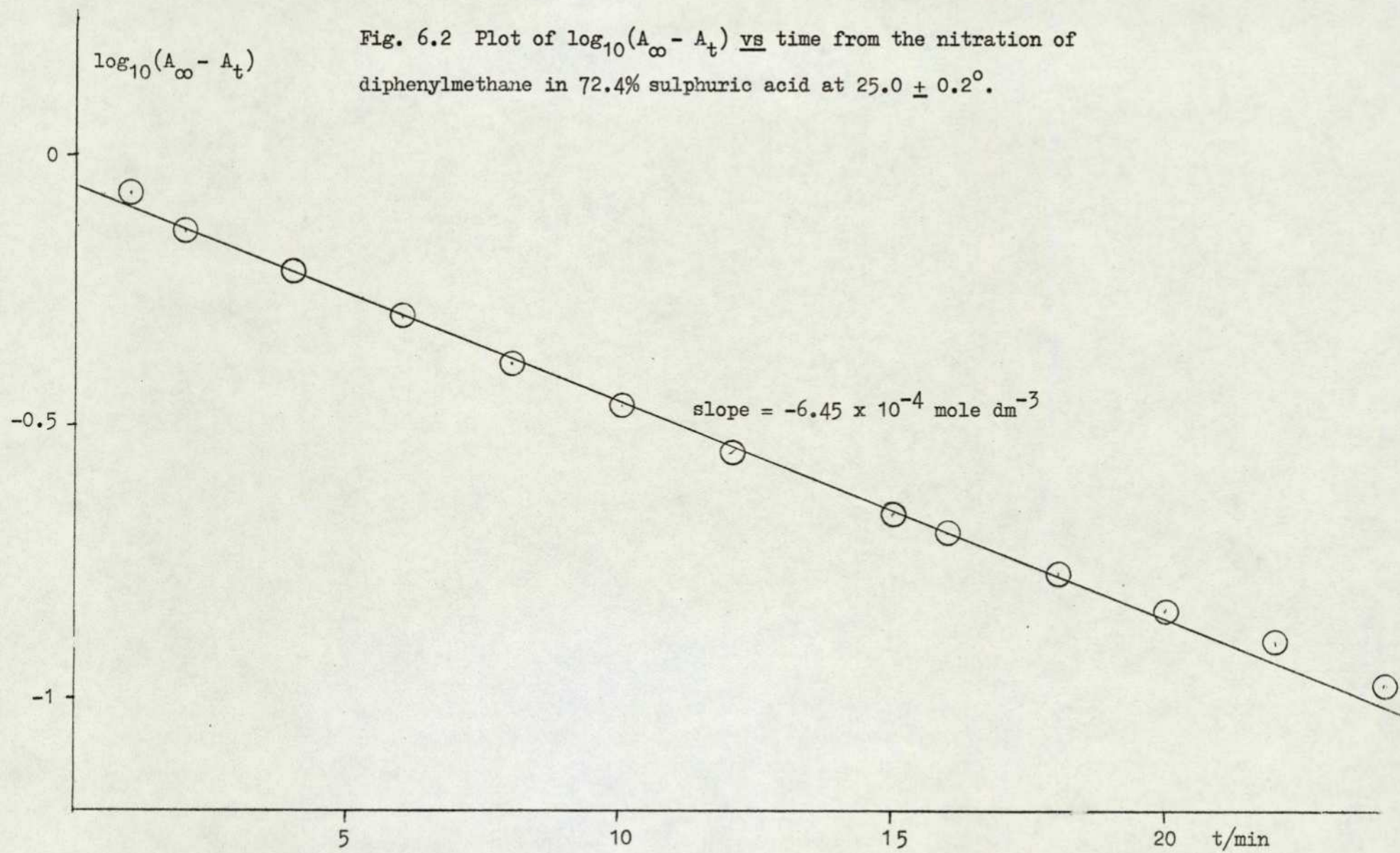


Table 6.6

Second-order rate coefficients for the nitration of
diphenylmethane in sulphuric acid at $25.0 \pm 0.2^\circ$

H_2SO_4 (%) ^{a,k}	$10^2 [\text{HNO}_3]$ /mole dm ⁻³	$k_2(\text{obs})$ /dm ³ mole ⁻¹ s ⁻¹
Diphenylmethane ^{b,f}		
63.2 ^c	0.77	2.5×10^{-3}
66.1 ^c	0.17	1.7×10^{-2}
68.3 ^c	0.09	0.12
70.4 ^c	0.09	0.53
72.4 ^d	0.09	1.83
72.5 ^c	0.09	2.30
74.4 ^c	0.05	13.9
74.4 ^{d,e}	0.013	21.6
2-Nitrodiphenylmethane ^{g,h}		
68.4	0.09	0.15
70.5	0.09	0.69
3-Nitrodiphenylmethane ^{i,f}		
68.4	0.09	0.12
70.5	0.09	0.63
4-Nitrodiphenylmethane ^{j,f}		
68.4	0.09	0.11
70.5	0.09	0.54

Table 6.6 (continued)

- a) $\pm 0.1\%$ w/w
- b) $[\text{ArH}] = 4.9 \times 10^{-5} \text{ mole dm}^{-3}$
- c) Table 5.6 of Ref. 66
- d) $[\text{ArH}] = 1.23 \times 10^{-4} \text{ mole dm}^{-3}$
- e) This run was carried out under equimolar conditions using the standard rate equation: $1/c - 1/c_0 = kt$ where c_0 is the initial concentration and c is the concentration at time t .
- f) Measurement at 290 nm
- g) $[\text{ArH}] = 8.92 \times 10^{-5} \text{ mole dm}^{-3}$
- h) Measurement at 287 nm
- i) $[\text{ArH}] = 5.16 \times 10^{-5} \text{ mole dm}^{-3}$
- j) $[\text{ArH}] = 5.03 \times 10^{-5} \text{ mole dm}^{-3}$
- k) $[\text{Sulphamic acid}] \text{ ca } 0.05 \text{ mole dm}^{-3}$

6.312 DIPHENYLETHER

A typical determination of a rate coefficient:-

Concentration of sulphuric acid	: 70.6% w/w
Concentration of nitric acid	: $2.33 \times 10^{-2} \text{ mole dm}^{-3}$
Concentration of diphenylether	: $1.33 \times 10^{-4} \text{ mole dm}^{-3}$
Concentration of sulphamic acid	<u>ca</u> $0.05 \text{ mole dm}^{-3}$
Temperature	: $25.0 \pm 0.2^{\circ}$
Wavelength of measurement	: 320 nm

Fig. 6.3 shows the extinction curve obtained, Table 6.7 gives the data obtained therefrom and Fig. 6.4 shows the plot of $\log_{10}(A_{\infty} - A_t)$ vs time.

$$k_2(\text{obs}) = -2.303 \times \text{slope} / [\text{HNO}_3] \text{ dm}^3 \text{ mole}^{-1} \text{ s}^{-1}$$

$$k_2(\text{obs}) = 2.75 \times 10^{-2} \text{ dm}^3 \text{ mole}^{-1} \text{ s}^{-1}$$

At lower acidities (*i.e.* 62 - 66% H_2SO_4) a two stage process was observed and the rate coefficient for the faster first stage is recorded and corresponds to the formation of the mononitro compound. The second slower stage is recorded in Table 6.9 as the rate of dinitration.

At higher acidities (*i.e.* 70 - 75% H_2SO_4) independent measurement of the rates of nitration of 2-nitro and 4-nitrodiphenylethers (table 6.9) shows that these are nitrated at a rate faster than the observed rate of nitration of diphenylether itself.

The rate profile for nitration of diphenylether (data from Table 6.8) is shown in Fig. 6.5. Also shown here is a rate profile for dinitration which includes data from Table 6.9 concerning 2-nitro and 4-nitrodiphenylethers, which are nitrated at a similar rate, and also, at lower acidities, data from the second stage of diphenylether nitration.

Fig. 6.3 Extinction curve from the nitration of diphenylether in 70.6% sulphuric acid at $25.0 \pm 0.2^\circ$

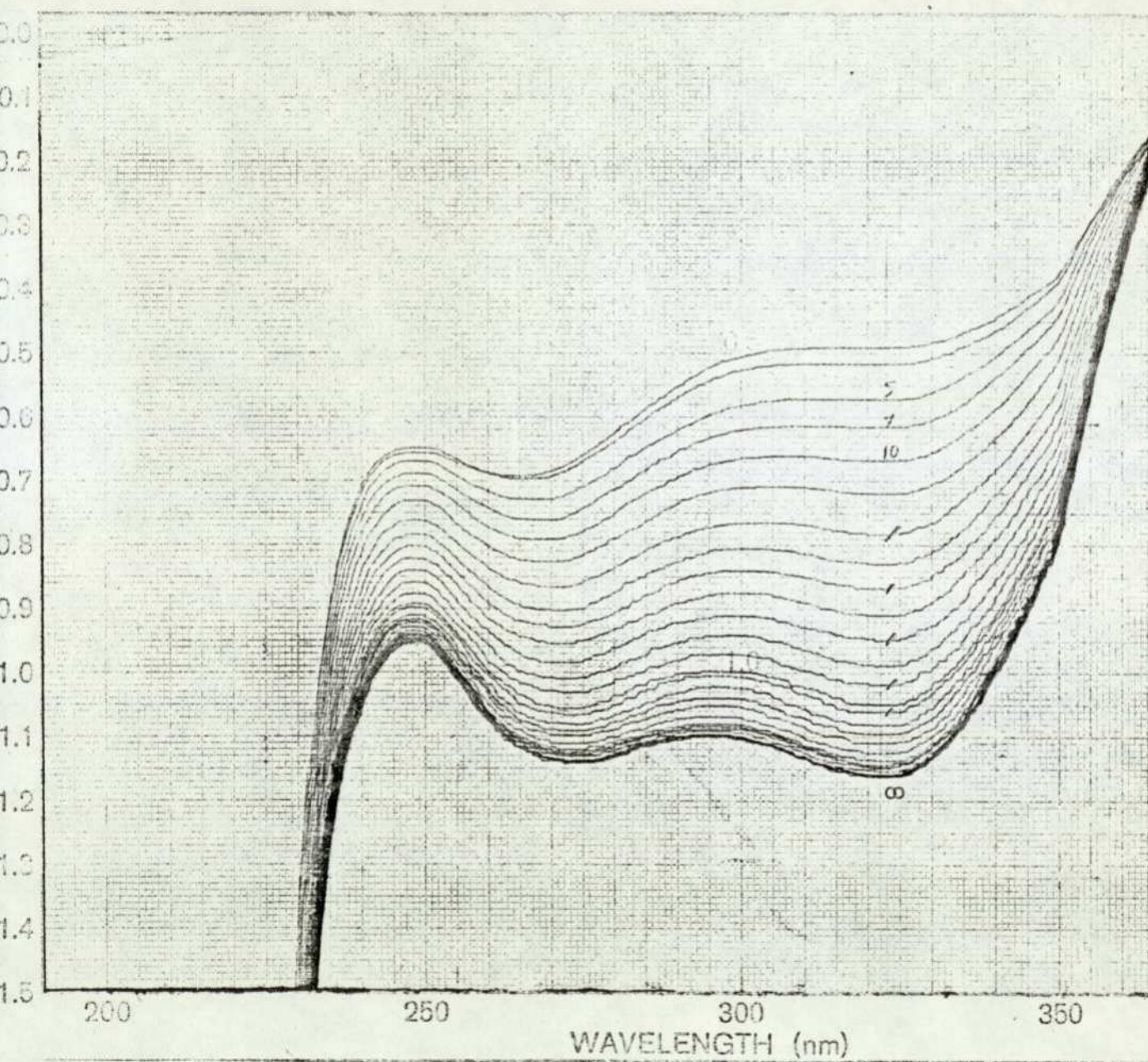


Table 6.7

Data from the determination of the rate of nitration
of diphenylether in 70.6% sulphuric acid at $25.0 \pm 0.2^{\circ}$

Time(t) /min	Absorbance A_t	$\log_{10}(A_{\infty} - A_t)$
5	0.571	-0.22
7	0.617	-0.26
10	0.668	-0.30
20	0.781	-0.41
30	0.869	-0.55
40	0.950	-0.68
50	1.018	-0.82
60	1.061	-0.96
70	1.097	-1.11
t_{∞}	1.170	

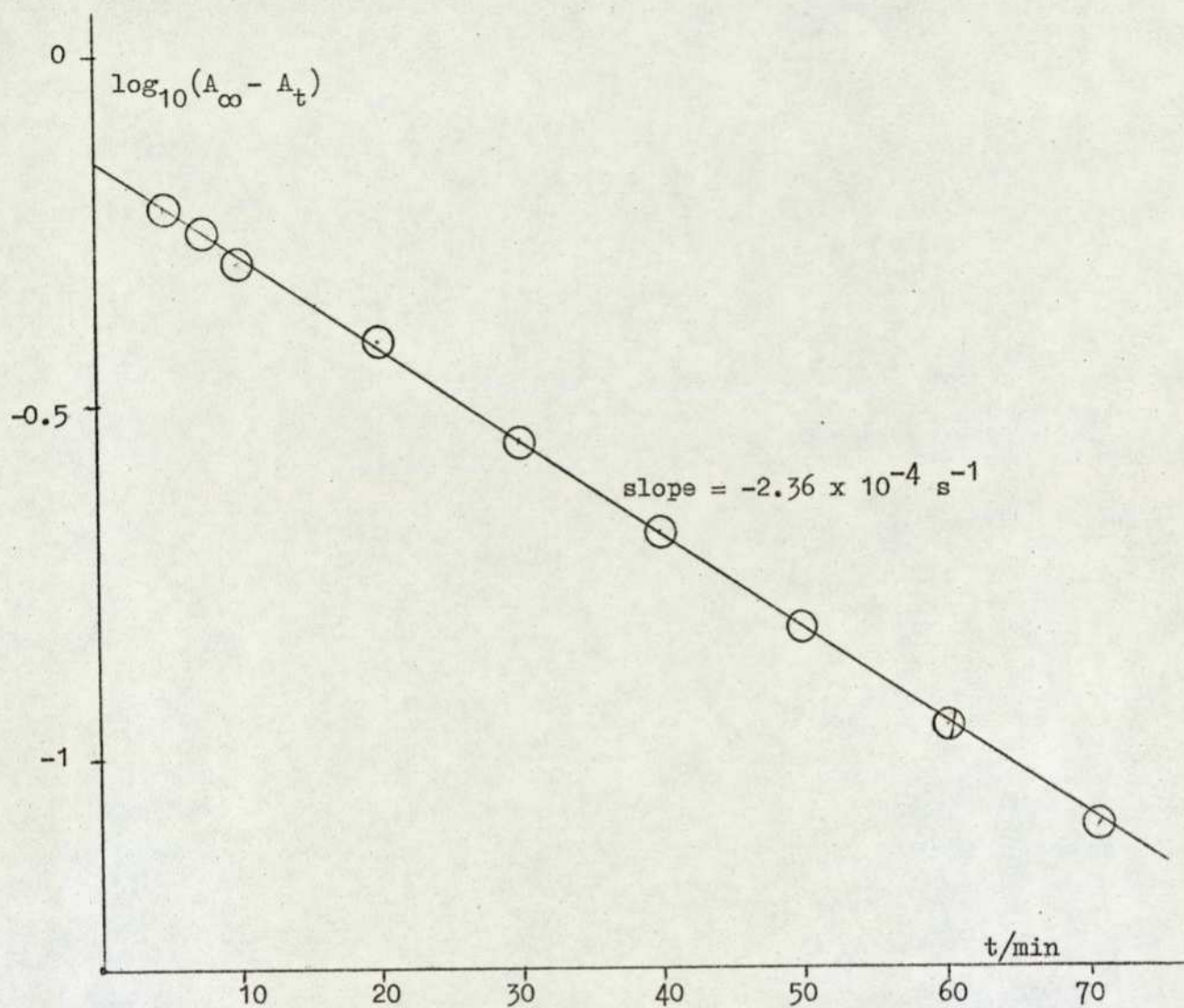


Fig. 6.4 Plot of $\log_{10}(A_{\infty} - A_t)$ vs time from the nitration of diphenylether in 70.6% sulphuric acid at $25.0 \pm 0.2^{\circ}$

Table 6.8

Second-order rate coefficients for the nitration of
diphenylether^{b,c,d} in sulphuric acid at $25.0 \pm 0.2^\circ$

H_2SO_4 (%) ^a	$10^2[\text{HNO}_3]$ /mole dm ⁻³	$k_2(\text{obs})$ /dm ³ mole ⁻¹ s ⁻¹
59.6	5.5	2.24×10^{-3}
62.2	2.3	7.31×10^{-3}
63.8	2.3	1.39×10^{-2}
66.3	2.3	2.51×10^{-2}
70.5	2.3	2.75×10^{-2}
72.7	2.3	3.31×10^{-2}
74.3	2.3	3.34×10^{-2}
77.7	2.3	3.34×10^{-2}

a) $\pm 0.1\%$ w/w

b) $[\text{ArH}] = 1.33 \times 10^{-4}$ mole dm⁻³

c) $[\text{Sulphamic acid}]$ ca 0.05 mole dm⁻³

d) Measurement at 320 nm

Table 6.9

Second-order rate coefficients for the dinitration
of diphenylether in sulphuric acid at $25.0 \pm 0.2^\circ$

H_2SO_4 (%) ^a	$10^2[\text{HNO}_3]$ /mole dm^{-3}	$k_2(\text{obs})$ / $\text{dm}^3 \text{ mole}^{-1} \text{ s}^{-1}$
Diphenylether (second stage) ^{b,c,d}		
62.2	2.3	1.20×10^{-3}
63.8	2.3	2.58×10^{-3}
66.3	2.3	1.15×10^{-2}
2-Nitrodiphenylether ^{c,e,f}		
66.3	2.3	1.25×10^{-2}
68.4	2.3	0.10
70.5	0.09	0.50
72.7	0.09	3.48
4-Nitrodiphenylether ^{c,d,g}		
66.3	2.3	1.19×10^{-2}
68.4	2.3	9.55×10^{-2}
70.5	0.09	0.52
72.7	0.09	3.51

a) $\pm 0.1\%$ w/w

b) $[\text{ArH}] = 1.33 \times 10^{-4} \text{ mole dm}^{-3}$

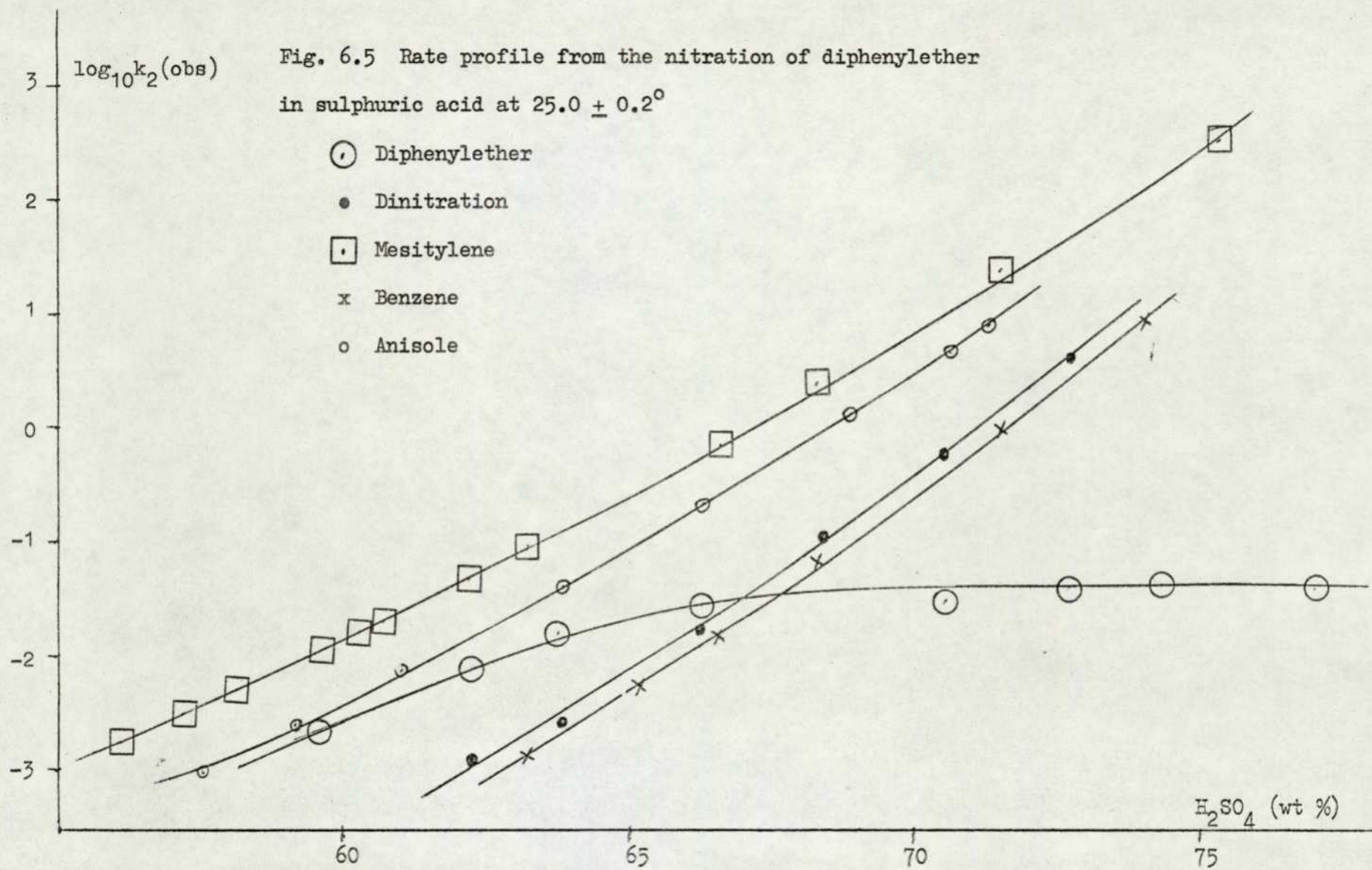
c) $[\text{Sulphamic acid}] \text{ ca } 0.05 \text{ mole dm}^{-3}$

d) Measurement at 320 nm

e) $[\text{ArH}] = 1.21 \times 10^{-4} \text{ mole dm}^{-3}$

f) Measurement at 300 nm

g) $[\text{ArH}] = 1.41 \times 10^{-4} \text{ mole dm}^{-3}$



6.32 YIELDS OF NITRO COMPOUNDS

6.321 DIPHENYLMETHANE

An example of the method for calculating the yields of nitro compounds from the nitration of diphenylmethane in sulphuric acid is given below:-

Concentration of sulphuric acid	: 68.3% w/w
Amount of diphenylmethane	: 3.07×10^{-5} moles
Amount of nitric acid	: 3.12×10^{-5} moles
Concentration of sulphamic acid	<u>ca</u> $0.05 \text{ mole dm}^{-3}$
Amount of reference standard	
<u>p</u> -nitroethylbenzene	: 1.15×10^{-5} moles

Fig. 6.6 shows the chromatogram obtained (h.p.l.c. conditions as in Table 6.3).

Peak weights from chromatogram

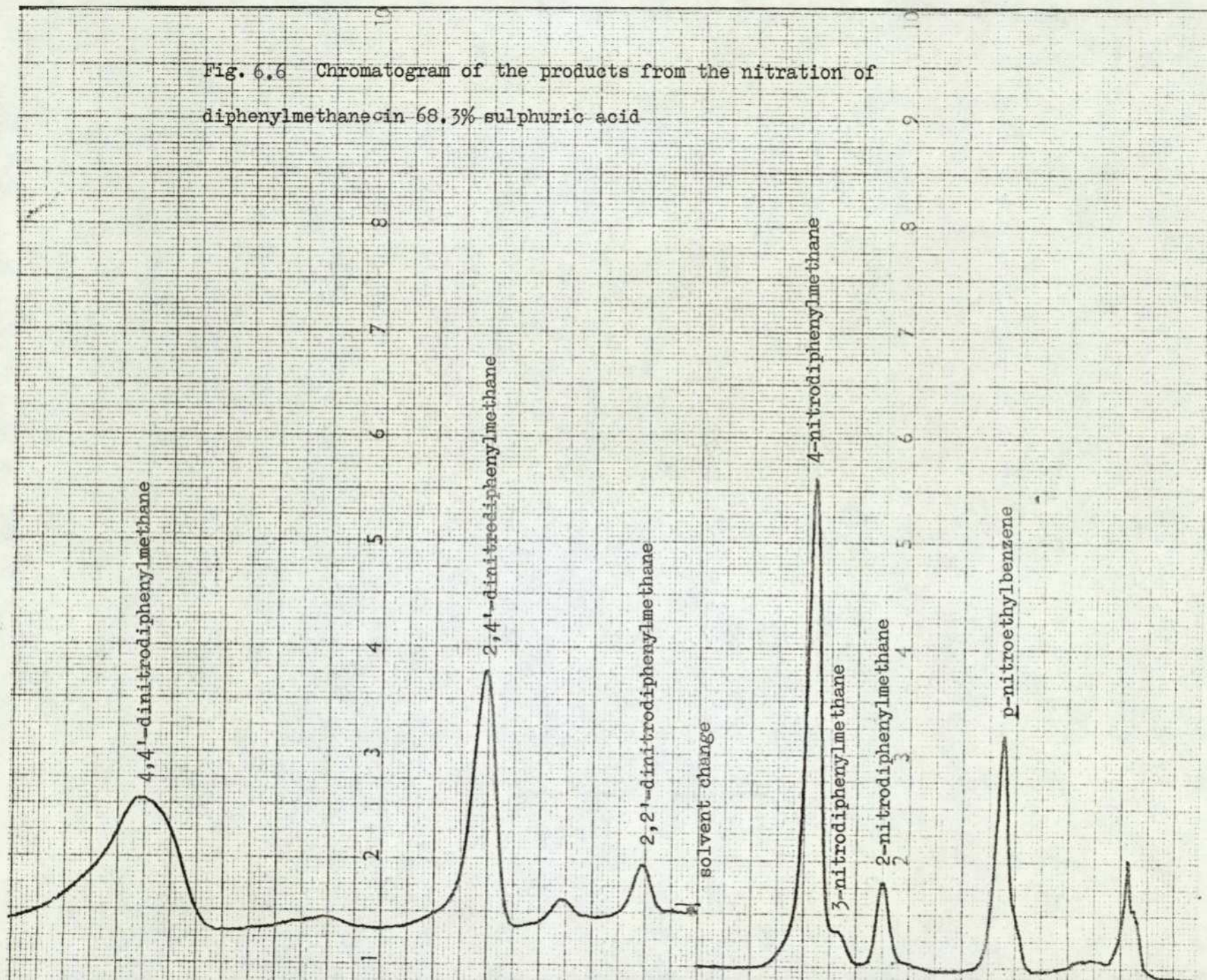
Compound	Weight/g
2-nitrodiphenylmethane	0.0065
3-nitrodiphenylmethane	0.0035
4-nitrodiphenylmethane	0.0302
2,2'-dinitrodiphenylmethane	0.0027
4,4'-dinitrodiphenylmethane	0.0374
2,4'-dinitrodiphenylmethane	0.0128
<u>p</u> -nitroethylbenzene (reference standard)	0.0145

The method of relative response factors as described in Section 7.5 was used.

$$c_x/c_s = A_x/A_s \times f$$

Factor f for 2-nitrodiphenylmethane	: 0.96
Factor f for 3-nitrodiphenylmethane	: 0.85
Factor f for 4-nitrodiphenylmethane	: 0.42

Fig. 6.6 Chromatogram of the products from the nitration of diphenylmethane in 68.3% sulphuric acid



Factor f for 2,2'-dinitrodiphenylmethane : 0.31

Factor f for 2,4'-dinitrodiphenylmethane : 0.41

Factor f for 4,4'-dinitrodiphenylmethane : 0.20

Amount of 2-nitrodiphenylmethane =

$$= \frac{0.0065}{0.0145} \times 1.15 \times 10^{-5} \times 0.96 \text{ moles}$$

$$= 4.97 \times 10^{-6} \text{ moles}$$

$$\% \text{ of 2-nitrodiphenylmethane} = \frac{4.97 \times 10^{-6}}{3.12 \times 10^{-5}} \times 100$$

$$= 16.2\%$$

Similarly:

$$\% \text{ of 3-nitrodiphenylmethane} = 7.7$$

$$\% \text{ of 4-nitrodiphenylmethane} = 32.9$$

$$\% \text{ of 2,2'-dinitrodiphenylmethane} = 2.1$$

$$\% \text{ of 2,4'-dinitrodiphenylmethane} = 13.6$$

$$\% \text{ of 4,4'-dinitrodiphenylmethane} = 9.0$$

Table 6.10 gives the yields of nitrocompounds from the nitration of diphenylmethane in various concentrations of sulphuric acid.

6.322 DIPHENYLETHER

A typical determination of the yields:-

Concentration of sulphuric acid : 62.2% w/w

Amount of diphenylether : 5.66×10^{-5} moles

Amount of nitric acid : 5.82×10^{-3} moles

Concentration of sulphamic acid ca $0.05 \text{ mole dm}^{-3}$

Amount of reference standard

p-nitroanisole : 2.75×10^{-5} moles

Fig. 6.7 shows the chromatogram obtained (h.p.l.c. conditions as in Table 6.4).

Table 6.10

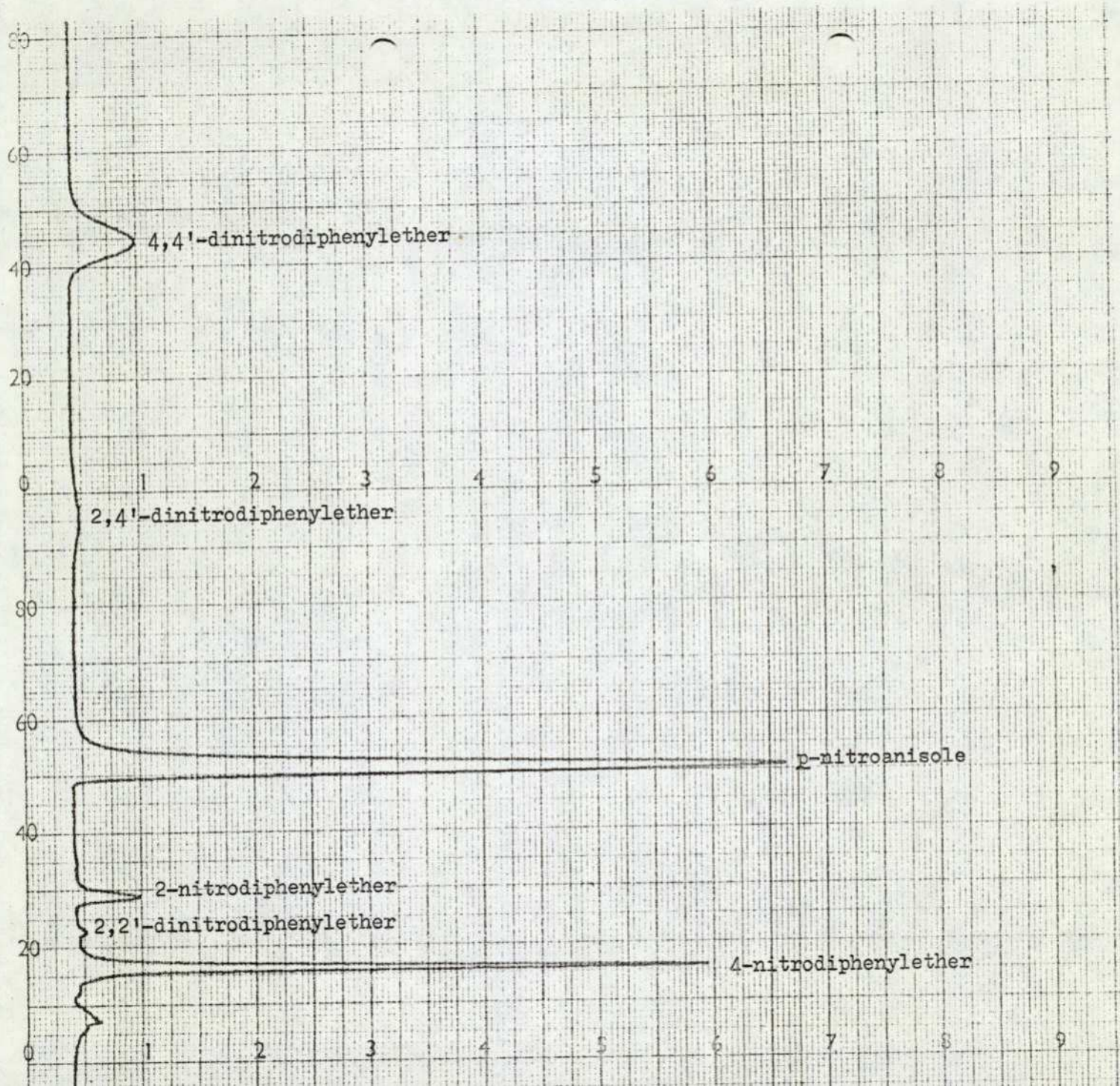
Yields of nitrocompounds from the nitration of diphenylmethane ^{b,c,d} in sulphuric acid

H ₂ SO ₄ (%) ^a	2-Nitro- diphenyl- methane	3-Nitro- diphenyl- methane	4-Nitro- diphenyl- methane	2,2'-Dinitro- diphenyl- methane	2,4'-Dinitro- diphenyl- methane	4,4'-Dinitro- diphenyl- methane	Σ of rings containing nitro groups (%) ^e
68.4	16.2	7.7	32.9	2.1	13.6	9.0	105
70.6	10.3	4.8	18.1	3.8	16.1	9.8	93
70.6	12.8	5.2	21.7	3.1	10.5	9.8	87
72.7	8.2	4.2	16.3	5.6	19.2	12.2	103
74.3 ^f	5.1	2.2	9.9	5.7	23.4	12.2	100
77.8	4.0	1.9	7.6	6.0	25.2	13.0	102
80.7	3.3	1.5	5.2	6.0	25.8	13.0	97

a) $\pm 0.1\%$ w/w; b) $[\text{ArH}] = 1.23 \times 10^{-4} \text{ mole dm}^{-3}$; c) $[\text{Sulphamic acid}] = 0.05 \text{ mole dm}^{-3}$;

d) $[\text{HNO}_3] = 1.28 \times 10^{-4} \text{ mole dm}^{-3}$; e) $\pm 2\%$; f) Kinetic measurements carried out in this solution.

Fig. 6.7 Chromatogram of the products from the nitration of diphenylether in 62.2% sulphuric acid



Peak weights from chromatogram

Compound	Weight/g
2-nitrodiphenylether	0.0034
4-nitrodiphenylether	0.0185
p-nitroanisole (reference standard)	0.0358

The method of relative response factors as described in Section 7.5 was used.

$$c_x/c_s = A_x/A_s \times f$$

Factor f for 2-nitrodiphenylether : 5.88

Factor f for 4-nitrodiphenylether : 0.80

Amount of 4-nitrodiphenylether =

$$= \frac{0.0185}{0.0358} \times 2.75 \times 10^{-5} \times 0.80 \text{ moles}$$

$$= 1.13 \times 10^{-5} \text{ moles}$$

$$\% \text{ of 4-nitrodiphenylether} = \frac{1.13 \times 10^{-5}}{5.66 \times 10^{-5}} \times 100$$

$$= 20 \%$$

Similarly:

$$\% \text{ of 2-nitrodiphenylether} = 27 \%$$

Table 6.11 gives the yields of mono-nitro compounds from the nitration of diphenylether in various concentrations of aqueous sulphuric acid.

Table 6.11

Yields of mono-nitro compounds from the nitration
of diphenylether^{b,c,d} in sulphuric acid at 25^o

H ₂ SO ₄ (%) ^a	2-Nitro- diphenyl- ether	4-Nitro- diphenyl- ether	Mass balance (%) ^e	2-/4- ratio
59.6	21.8	15.6	37	1.39
62.2	27.1	20.0	47	1.36
63.8	29.0	21.9	50	1.32
66.3	19.6	14.8	34	1.32

a) $\pm 0.1\%$ w/w

b) $[\text{ArH}] = 2.26 \times 10^{-4} \text{ mole dm}^{-3}$

c) $[\text{HNO}_3] = 2.33 \times 10^{-2} \text{ mole dm}^{-3}$

d) $[\text{Sulphamic acid}] \text{ ca } 0.05 \text{ mole dm}^{-3}$

e) $\pm 2\%$

6.4 DISCUSSION

6.41 DIPHENYLMETHANE

Good first-order kinetic plots were obtained for the nitration of diphenylmethane over a range of acidity. This is at first sight at variance with the observation of considerable amounts of dinitration.

Dr R.B. Moodie has provided an analysis of the $X \xrightarrow{k_1} Y \xrightarrow{k_2} Z$ situation¹²⁴ and shown that good first-order kinetics will be observed, when a wavelength is used at which Y and Z (but not X) absorb, if either $\epsilon_Y = \epsilon_Z$ (any k_2/k_1) or $\epsilon_Y/\epsilon_Z = k_2/k_1$ (ϵ is the molar absorptivity). From the values of ϵ_Z/ϵ_Y obtained from the nitration of 2-, 3- and 4-nitrodiphenylmethane at 273 nm (see Section 6.311) it follows that a value of $k_1/k_2 \sim 2$ allows an explanation of the results and such a value is very reasonable.

The rate profile obtained⁶⁶ ($k_2(\text{obs})$ is k_2 above) is slightly above and almost parallel to that of benzene which suggests that the observed rate is not much affected by encounter control in this region of acidity. The relative rate $k_2(\text{obs})$ diphenylmethane/ $k_2(\text{obs})$ benzene is 4 which is at variance with that observed²³, for the nitration of diphenylmethane in acetic anhydride, which has been found to be 19.5.

On the assumption of independent substitution in the two aromatic rings of diphenylmethane and complete mixing of the reactant solutions, the fraction of unsubstituted (x), monosubstituted (y) and disubstituted (z) products should accord with random pairing of substituted and unsubstituted rings¹²⁵. Let the total number of initial aromatic rings be (a) and the total number of substituted rings be (b), where (b) is also the number of nitronium ions in solution. Therefore the number of unsubstituted rings is (a-b) and the fraction of substituted rings is (b/a) and the fraction of unsubstituted rings

is $(a-b/a)$. It follows that the probabilities of removing a di-substituted, a monosubstituted or an unsubstituted molecule from the solution are $(b/a)^2$, $2b/a(a-b/a)$ and $(a-b/a)^2$ respectively. Now let R be (a/b) . Therefore:

$$z = 1/R^2, \quad y = (2/R)(1 - 1/R), \quad x = (1 - 1/R)^2$$

For equimolar nitration of diphenylmethane ($R = 2$):

$$z = 1/4, \quad y = 1/2, \quad x = 1/4$$

This applies if the rate ratio $k_1/k_2 = 1$, but if as is proposed for the nitration of diphenylmethane the rate ratio $k_1/k_2 = 2$, then

$$z = 1/8, \quad y = 3/4, \quad x = 1/8$$

For the nitration of diphenylmethane in 68 - 80% sulphuric acid, good consistent results and complete recovery of the products were obtained (Table 6.10), but dinitration seems to be anomalously high in all cases and gradually increases from 25% in 68% sulphuric acid to 45% in 80% sulphuric acid. Reaction during mixing could be a possible explanation for this but is unlikely in up to at least 77% sulphuric acid where the reaction is still fairly slow ($t_{1/2} > 36$ s). Also, in 74% sulphuric acid, normal spectral changes starting at zero absorbance were obtained during a product run (see Section 6.311), which suggests that mixing is not a problem. Another possible explanation involves solubility effects. It is probable that the mononitrodiphenylmethanes are more soluble than diphenylmethane itself and if the latter were not all in solution fast nitration of the mononitro products would result in anomalously high dinitration. However, kinetic runs under the conditions and concentrations of product studies gave the same results as those obtained for lower concentrations of diphenylmethane, confirming that the product studies were carried out under homogenous conditions. Therefore, the anomalous behaviour of

this substrate remains unaccounted for. The anomalous nitration of diphenylmethane in sulphuric acid is of interest as some important conclusions concerning the role of mixing in the nitration of bibenzyl by nitronium salts rely on arguments about the ratio of di- to mononitration¹²⁵.

6.42 DIPHENYLETHER

The kinetic studies of the nitration of diphenylether below 66% sulphuric acid indicate that two distinct changes occur, the first one being about 8 times faster than the second one in 62% sulphuric acid and about 3 times in 66% sulphuric acid. Above 66% sulphuric acid, good first-order kinetics were obtained and the rate profile for this change had zero slope. Rate profiles for both changes were constructed (Fig. 6.5) and the slow change observed below 66% sulphuric acid was shown to be due to dinitration from the second-order rate coefficients determined from the nitration of 2- and 4-nitrodiphenylethers. The rate profile for dinitration constructed from the second change (where possible) and the nitration of 2- and 4-nitrodiphenylethers (Fig. 6.5) is slightly above and parallel to that of benzene which suggests that the rate of dinitration is not affected by encounter control in this region of acidity. The rate profile for mononitration (first change) is very close to that of anisole⁵⁰ below 60% sulphuric acid, but above 60% sulphuric acid the slope gradually decreases and finally becomes zero above 67% sulphuric acid. This type of behaviour suggests that diphenylether is protonated above 60% sulphuric acid and that in above 67% sulphuric acid, the fall in rate due to increasing extent of protonation cancels the increase in rate due to the increasing concentration of the nitronium ion with acidity. If we assume that the rate profile for the unprotonated diphenylether

is parallel and approximately 0.15 units of $\log_{10} k_2(\text{obs})$ below that of anisole (Fig. 6.5) then, the observed rate of nitration of diphenylether and the estimated rate of nitration of the unprotonated species can be used to calculate the degree of protonation of diphenylether in aqueous sulphuric acid from the equation below:-

$$k_2(\text{B}) = \frac{100}{\% \text{ B}} \times k_2(\text{BH}^+) \dots\dots\dots 6.1$$

where:

$k_2(\text{B})$: estimated rate of nitration of the unprotonated diphenylether

$k_2(\text{BH}^+)$: observed rate of nitration of diphenylether

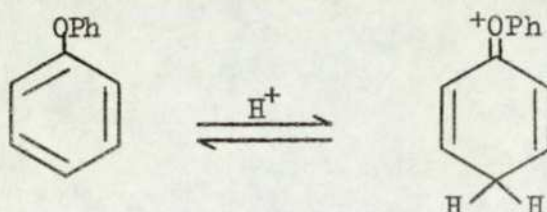
% B : percentage of free diphenylether

$$\% \text{ B} = \frac{k_2(\text{BH}^+)}{k_2(\text{B})} \times 100 \dots\dots\dots 6.2$$

For $k_2(\text{BH}^+)/k_2(\text{B}) = \frac{1}{2}$ or $\log_{10} k_2(\text{B}) - \log_{10} k_2(\text{BH}^+) = 0.3$ diphenylether is 50% protonated. In 64.5% sulphuric acid $\log_{10} k_2(\text{B}) - \log_{10} k_2(\text{BH}^+) = 0.3$ (Fig. 6.5). Therefore in 64.5% sulphuric acid, diphenylether is 50% protonated.

The difference between the slopes of the rate profiles for nitration of the unprotonated and protonated diphenylether in the region of 67 - 74% sulphuric acid, measures the variation of the acidity function that applies to the protonation of diphenylether (Hx), with the percentage of sulphuric acid (i.e. $-d\text{Hx}/d(\% \text{H}_2\text{SO}_4)$), and the value calculated from the data is 0.32. The variations of the acidity functions Ho (for primary amine protonation) and Hc (for C-protonation) with acidity, i.e. $-d\text{Ho}/d(\% \text{H}_2\text{SO}_4)$ and $-d\text{Hc}/d(\% \text{H}_2\text{SO}_4)$, in the same region of acidity, are 0.21 and 0.33 respectively. This indicates that the acidity function Hc is applicable to the above

protonation, suggesting that diphenylether is C-protonated in above 62% sulphuric acid. Evidence for C-protonation also comes from the initial extinction curves from the kinetic runs in 59.6 and in over 67% sulphuric acid. In 59.6% sulphuric acid the initial extinction curve had zero absorbance at 320 nm and in 70.5% sulphuric acid the initial extinction curve had absorbance of 0.5 which is consistent with the equilibrium shown below if the protonated form absorbs at 320 nm.



From Table 6.9 it can be seen that 2- and 4-nitrodiphenylether react at very similar rates and therefore, the product study of the nitration of diphenylether was carried out to determine the change of isomer ratio of 2- to 4-nitrodiphenylether with the acidity of the medium. The results of this study are summarised in Table 6.11 and the ratio of 2- to 4-nitrodiphenylether changes from 1.39 in 59.6% sulphuric acid to 1.32 in 66.3% sulphuric acid. These data do not enable any comment to be made on the operation of the general medium effect (Section 1.344) in the nitration of this compound.

From this study it appears that diphenylether and substituted diphenylethers are not appropriate for the projected study of two ring systems with the aim of obtaining information about the detailed structure of encounter pairs due to the problems caused by protonation.

An explanation of the anomalous dinitration observed with diphenylmethane should precede any study of substituted compounds of this type.

CHAPTER 7

GENERAL EXPERIMENTAL DETAILS

7.1 INTRODUCTION

In this section a general description will be given of the materials used and the experimental methods employed in this study. Where changes were carried out, reference has been made in the appropriate sections in each chapter.

7.2 MATERIALS

98% Sulphuric acid (Fison's AR), 70% nitric acid (Fison's AR), glacial acetic (Fison's AR), perchloric acid and sulphanilic acid were AnalaR grade reagents. The concentrations of diluted sulphuric acid solutions were determined from density measurements carried out using a Stanton specific gravity balance. The determined density at known temperature, was compared with values given in International Critical Tables of Numerical Data, Physics, Chemistry and Technology. A similar method was used to determine the concentration of stock AnalaR nitric acid solution (nominally 70%) which was found to be 70.2%. Chloroform, dichloromethane, diethyl ether, sulphamic acid, ethyl acetate, cyclohexane, acetonitrile and dichloroethane were of G.P.R. grade.

7.3 KINETIC MEASUREMENTS

A solution of the substrate in acetic acid was prepared and an aliquot (typically 0.10 ml of solution containing ca 4×10^{-4} g of substrate) was added to the appropriate concentration of aqueous sulphuric acid (25 ml) containing 0.05 molar nitrous acid inhibitor (sulphanilic acid or sulphamic acid). This solution was thermostatted at the appropriate temperature for 30 minutes. The thermometer used was calibrated against a thermometer standardised by the B.S.I. A solution of nitric acid, of the appropriate concentration, was prepared by dilution of the stock (70%) nitric acid, sometimes with water and then with the appropriate concentration of sulphuric acid. 1.0 ml of this nitric acid solution was then added to the substrate solution (to give a

concentration of nitric acid of $5.5 \times 10^{-2} - 8.98 \times 10^{-4}$ mole dm^{-3}).

The addition of the substrate in acetic acid and the nitric acid solution diluted the sulphuric acid and calculations show that a correction of -0.05% should be applied for the latter. When pipetting viscous solutions the correct volume was found to be delivered by blowing out the final drop of liquid from the pipette. After mixing, the solution was rapidly transferred to a silica cell in the thermostatted cell compartment ($\pm 0.2^\circ$ at 25.0, 40.0, 60.0 and 0.5° at 80.0) of a Perkin Elmer PE402 spectrophotometer. The change in absorbance with time was measured ($t = 0$ at time of mixing) either over a range of wavelength, or at one predetermined wavelength. The course of the reaction was followed until the absorbance reached a constant value recorded as the "infinity" reading (A_∞), usually taken after 7 - 10 half-lives.

From these measurements plots of $\log_{10}(A_\infty - A_t)$ vs time at a selected wavelength were constructed. From these, values of $k_2(\text{obs})$ were obtained using the following expression:-

$$k_2(\text{obs}) = -2.303 \times \text{slope} / [\text{HNO}_3]$$

7.4 PRODUCT ANALYSIS

(i) From reactions in less than 70% sulphuric acid.

A solution of the substrate in acetic acid was prepared and an aliquot (typically 1.0 ml of solution containing ca 4×10^{-3} g of substrate) was added to sulphuric acid (25 ml) of the required concentration, containing 5×10^{-2} g of nitrous acid inhibitor (sulphanilic acid or sulphamic acid). This solution was equilibrated at $25.0^\circ \pm 0.2^\circ$ in a thermostatically controlled water bath.

A nitric acid solution of the appropriate concentration was prepared by the dilution of the stock 70% nitric acid and 1.0 ml of this solution was then added to the substrate solution to give a concentration of nitric acid of $5.5 \times 10^{-2} - 5.5 \times 10^{-3}$ mole dm^{-3} . The solutions were initially shaken to ensure mixing (the dead space in the reaction was negligible). The reactions were allowed to proceed for ten half-lives and then quenched in 200g of crushed ice. The mixture was extracted 10 times with either chloroform or dichloromethane and dried with anhydrous magnesium sulphate. A known amount of reference standard was added and the solvent was removed on a water-bath by fractional distillation through a 12" glass column. The column was then washed down with 1 - 2 ml of the extracting solvent to yield a solution of the nitration products suitable for h.p.l.c. analysis.

(ii) From reactions greater than 70% sulphuric acid.

Reactions were of the scale described above 7.4 (i). The substrate in acetic acid was added to a vigorously stirred solution of nitric acid and nitrous acid inhibitor (sulphuric acid. The nitric acid and the substrate were in equimolar amounts in an attempt to avoid complications due to dinitration. The substrate was added to the nitric acid solution to avoid problems due to sulphonation, Termination of the reaction and the extraction of the reaction products were as described in 7.4 (i).

All nitro-products (except where specific references are made) were identified by comparison of their retention times on h.p.l.c. analysis with those of independently identified authentic samples of the compounds.

7.5 H.P.L.C.

All h.p.l.c. analyses were performed using a Waters Associates model 6000A pump, fitted with a UV detector (Cecil 272). The solvent systems, flow rates, wavelengths of detection, columns, retention times and reference standards used for analysis are given in the sections dealing with particular substrates.

The yields of nitro-products were calculated by a method based on relative response factors. The relative response factors of the nitro-products were measured with respect to a given reference standard which was added to the sample prior to analysis. The area (A_p) of a given peak is proportional to the amount of (c_p) of the respective solute, i.e:-

$$A_p = f_p \cdot c_p$$

Where f_p is a constant and depends on the chemical characteristics of component p. Therefore, using this relationship it is possible to obtain an expression for two peaks, of components s and x, where s is a standard and the amount x is required.

$$A_s = f_s \cdot c_s$$

$$\text{and } A_x = f_x \cdot c_x$$

$$\therefore \frac{c_x}{c_s} = \frac{A_x}{A_s} \times \frac{f_s}{f_x}$$

The constant ratio $f_s/f_x = f$ can be obtained from a standard solution of both reference standard and the unknown.

$$\therefore c_x = c_s \times \frac{A_x}{A_s} \times f$$

Relative peak areas were determined by cutting out peaks from photocopied traces and weighing them and in some cases comparison of height x width at half height gave the same results.

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