ISOTOPE EFFECTS IN NUCLEOPHILIC AROMATIC SUBSTITUTION

KINETIC ISOTOPE EFFECTS IN NUCLEOPHILIC AROMATIC SUBSTITUTION

By

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SCOPE AND CONTENTS:

The activation parameters and the sulphur-34 isotope effect associated with the reaction of piperidine with 2,4-dinitrodiphenylsulphone have been measured in three different solvents, after carrying out extensive tests to establish that the reaction is uncomplicated by equilibrium processes and that the experimental procedures used to measure the isotope effect do not themselves introduce any isotopic fractionation. The rate constant ratios, k^{32}/k^{34}, have been found to be 1.013 in benzene, 1.016 in acetonitrile and 1.006 in methanol. These results establish that, for reaction in benzene and acetonitrile, carbon-sulphur bond rupture occurs in a rate-determining step, while in methanol, the rupture of this bond is only partially rate-determining. The observed variation in magnitude of the isotope effect with change in solvent has been shown to provide strong evidence for a two-step mechanism involving a metastable intermediate.

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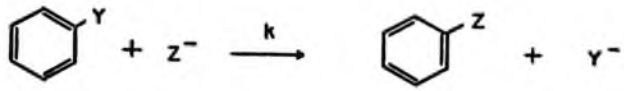
GENERAL INTRODUCTION

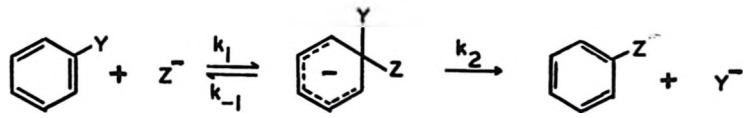
The mechanisms by which aromatic compounds undergo nucleophilic substitution have been the subject of much experimental investigation during the past decade. In this time, sufficient evidence has been obtained to demonstrate that nucleophilic aromatic substitutions may proceed by three different reaction pathways. These are (a) a bimolecular mechanism, which is followed by the great majority of such substitutions, (b) an elimination-addition mechanism, which is the normal pathway for the reaction of unactivated compounds with powerful bases and (c) a unimolecular mechanism, which has been established for only one reaction, that of the decomposition of diazonium salts.

It has been with respect to the detailed mechanism of the bimolecular process that there has been considerable controversy, at least until very recently. Two possible pathways for this reaction have been postulated. The first is a one-step (concerted) process analogous to S_N2 displacements of aliphatic compounds,



...(1)

The second is a two-step process involving a metastable intermediate,



...(2).

Bunnett (1, 2, 3) has been a strong advocate of the stepwise process and has amassed considerable evidence to support his views, while Chapman (4, 5, 6, 7, 8, 9), also an active worker in the field, has presented arguments in favour of the concerted mechanism.

Strong support for the stepwise mechanism is furnished by the fact that certain bimolecular nucleophilic aromatic substitutions involving very highly activated substrates have been shown to yield intermediates which are sufficiently stable to allow isolation and characterization (10, 11, 12). Further support has been obtained from the recent studies of the related reaction, electrophilic aromatic substitution, for which it has been shown that a two-step mechanism involving a metastable intermediate frequently, if not invariably, is followed (13, 14, 15, 16, 17). In this latter reaction, a key role has been played by kinetic isotope effect studies, which have furnished results which are incompatible with a concerted process.

This mechanistic tool, which has proved so fruitful in elucidating the mechanism of electrophilic aromatic

substitutions, has not been used previously to investigate the mechanism of bimolecular nucleophilic aromatic substitutions. The present study is, therefore, the first application of kinetic isotope effect measurements to an investigation of a representative reaction of this latter type.

There follows in this section of the thesis, first, a brief discussion of the role of kinetic isotope effect measurements in the elucidation of the mechanism of electrophilic aromatic substitution, and, second, a development of the basis upon which it was proposed in the present investigation to apply this tool to the study of the detailed mechanism of a nucleophilic aromatic substitution process.

When a bond associated with a particular atom is broken in the slow step of a reaction, the rate of the overall reaction, in general, will be slower the heavier the isotopic mass of this atom. This rate difference, resulting from the presence of the heavier isotope, is referred to as the kinetic isotope effect and has been used widely in attempting to establish whether or not a bond to the isotopic atom is ruptured in a rate-determining step (18, 19). For example, the observation by Melander (20) in 1950 of almost identical rates of nitration of toluene and tritium-labelled toluene was interpreted in terms of a two-step process with the rate-determining step being the formation of an intermediate in which the bond to hydrogen or tritium is still

intact:

$$ArH + NO_2^+ \xrightarrow{\text{slow}} \left[Ar\begin{matrix}H\\NO_2\end{matrix}\right]^+ \longrightarrow ArNO_2 + H^+ \quad \ldots(3).$$

A one-step process was considered to be excluded since the bond to isotopic hydrogen is necessarily ruptured in this single step.

It was later pointed out by Hammond (21) that the only conclusion one is justified in drawing, on the basis of the observation of a zero or very small isotope effect, is that the zero-point energies associated with the stretching and bending vibrations of the bond to the isotopic atom are not changed appreciably in the transition state. This, of course, would be the case for the mechanism involving rate-determining formation of an intermediate. Not excluded, however, is a one-step process in which the transition state is reached before the carbon-hydrogen bond has undergone any significant change in its zero-point energy. Similarly, the observation of an effect, $k^H/k^T = 1.45$, in the sulphonation of bromobenzene and bromobenzene-4-T (22) can be interpreted either in terms of a two-step mechanism in which proton-elimination is partially rate-determining, or in terms of a single-step process involving a transition state in which the carbon-hydrogen bond is weakened appreciably. The magnitude of the isotope effect under any given set of

reaction conditions, then, cannot distinguish unambiguously between a concerted and a stepwise mechanism. This point has not always been appreciated in past applications of isotope effect studies to reaction mechanism problems.

Although the observation of a zero, small, or large isotope effect in a reaction is of little value in establishing the detailed pathway of the reaction, the observation of a variation in the magnitude of the isotope effect under changing reaction conditions can. If, for example, the electrophilic aromatic substitution is subject to base catalysis, the relative rates with which the intermediate formed in a two-step process reverts to reactants and decomposes to products will depend upon the concentration of the base, B:

$$ArH + Z^{+} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \left[Ar\begin{matrix} H \\ Z \end{matrix} \right]^{+} + B: \xrightarrow{k_2} ArZ + H{:}B^{+} \qquad \ldots(4).$$

At high concentrations, such that $k_2\,[B:] \gg k_{-1}$, the rate-determining step is the formation of the intermediate and the isotope effect associated with the displaced hydrogen will be very small or zero. At very low base concentrations, such that $k_2\,[B:] \ll k_{-1}$, decomposition of the intermediate to products is the slow step. This involves the rupture of the carbon-hydrogen bond and might be expected to

give rise to a significant rate difference for hydrogen- and deuterium-containing substrates. Variation in base concentration, therefore, can give rise to a variation in magnitude of the isotope effect as the second step becomes more fully rate-determining. A concerted mechanism, on the other hand, gives rise to an isotope effect, either large or small, which is independent of base concentration. The first, and only, application of this "variable isotope effect" criterion was by Zollinger (13, 23, 24) in 1955 in a study of the mechanism of the diazo-coupling reaction.

A similar criterion of mechanism is possible, in principle, in aromatic halogenation reactions in which the relative rates of return and decomposition of an intermediate formed in a two-step process will be determined by the concentration of halide ion,

$$ArH + X_2 \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \left[Ar\begin{matrix}H\\X\end{matrix}\right]^+ + X^- \qquad \left[Ar\begin{matrix}H\\X\end{matrix}\right]^+ \xrightarrow{k_2} ArX + H^+ \qquad \ldots(5).$$

Only the two-step mechanism would be expected to give rise to an isotope effect whose magnitude would be dependent upon halide ion concentration. This test of mechanism has been

applied to a bromodecarboxylation reaction by Grovenstein and Ropp (14) and to a bromodesulphonation reaction in this laboratory (17). To date, no successful application to ordinary halogenation (halodeprotonation) has been reported.

In nucleophilic aromatic substitution, there is no obvious reagent whose concentration might be expected to influence the relative rates with which an intermediate, if formed, would revert to reactants or decompose to products[1]. It is well established, however, that the energies of activation of reactions involving the creation or destruction of charge are strongly solvent dependent. In a nucleophilic aromatic substitution reaction producing charged species from neutral molecules by a two-step mechanism,

$$ArX + Y: \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \left[\bar{A}r\begin{matrix}\diagup \overset{+}{Y} \\ \diagdown X\end{matrix}\right]$$

$$\left[\bar{A}r\begin{matrix}\diagup \overset{+}{Y} \\ \diagdown X\end{matrix}\right] \xrightarrow{k_2} ArY^+ + X^- \qquad \ldots(6).$$

---

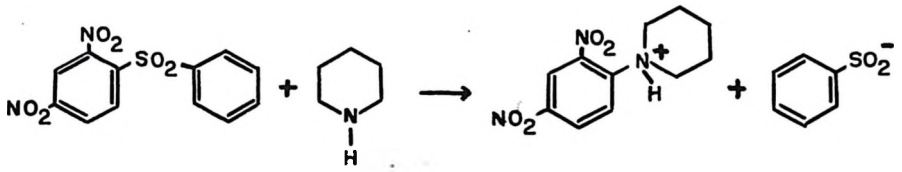
1. When the work reported in this thesis was nearing completion, base catalysis in the reaction of primary and secondary amines with 2,4-dinitrohalobenzenes was reported (25). A study of the halogen isotope effect as a function of base concentration might prove fruitful in these systems, provided that carbon-halogen bond rupture is concurrent with the departure of the proton from nitrogen.

the transition states for the formation and decomposition of the intermediate will differ considerably in both magnitude and distribution of charge. In the transition state corresponding to the second step, there will be a full formal charge on Y; in the transition state for formation of the intermediate, there will be only a partial unit charge. An increase in the polarity of the solvent, therefore, would be expected to stabilize, through solvation, the second transition state more than the first, and hence increase the k_2/k_{-1} ratio. Provided that the energies of the two transition states are not too greatly different, it might be possible by changing solvent to bring about a sufficient variation in the relative magnitudes of the two rates as to cause a major change in magnitude of the isotope effect associated with the leaving group, X. If the nucleophilic aromatic substitution proceeds by a one-step mechanism, a change in solvent can be expected to bring about only a small change in the extent of C-X bond rupture in the transition state and, hence, will have relatively little influence upon the magnitude of the isotope effect. Indeed, it has been amply demonstrated for reactions known to proceed in one step, for example, decarboxylation, that variations in the magnitude of an isotope effect with changing solvent are minor.

A large variation in magnitude of the isotope

effect with change in solvent, then, would provide strong evidence in support of the two-step mechanism. Conversely, a small change could be interpreted either in terms of a one-step process or in terms of a two-step process in which there is a large difference in the magnitude of the two rate constants, k_{-1} and k_2, under all solvent conditions. Although such a result would shed no light on the question as to whether or not the reaction mechanism involves an intermediate, it certainly would not be without significance since the magnitude of the isotope effect would give an insight into the extent to which the C-X bond is weakened in the highest energy state of the overall reaction. Indeed, as Hammond (21) has pointed out, the most important objective of an isotope effect study is to obtain information concerning the configuration of the transition state in the slow step, regardless of precisely what that step might be.

The reaction chosen for this study was that of 2,4-dinitrodiphenylsulphone with the nucleophilic reagent piperidine:



...(7).

This reaction is particularly suitable for an isotope effect investigation for several reasons. Firstly, the bond broken during reaction is to sulphur, a very convenient element for precise isotope abundance ratio measurements. Although sulphur has a relatively high mass, isotope effects are appreciable, approximately one to two per cent for S^{32}/S^{34}. Secondly, sulphur-34 is present in appreciable quantities in material containing a normal isotope abundance ratio. This natural label then obviates the time-consuming synthesis of isotopically enriched reactant. Thirdly, the reaction is quantitative. Fourthly, the product, benzenesulphinic acid, has markedly different chemical properties from the original sulphone. Since heavy element isotope effect studies are carried out by comparing the isotope abundance ratio of the reactant with that of the product formed during a very small extent of reaction, it is necessary to achieve a separation of the product from the large excess of reactant. The different chemical properties of these two sulphur-bearing materials facilitates their separation for measurement of isotope abundance ratios.

The solvents chosen were a non-polar solvent, benzene, a polar solvent, acetonitrile, and a polar hydroxylic solvent, methanol. These solvents differ considerably in their solvating properties and might be expected

to bring about quite large changes in the k_{-1}/k_2 ratio for the reaction under investigation.

The sulphur isotope effect investigation was preceded by a careful kinetic study of the reaction at several temperatures in each of the three solvents. On the basis of the results obtained, a temperature of $10^{\circ}C.$ was chosen for the isotope effect measurements. The rate constants also were used to evaluate the activation heats and entropies for reaction in these solvents. These quantities proved helpful in interpreting the isotope effect results in terms of solvation phenomona.

HISTORICAL INTRODUCTION

General

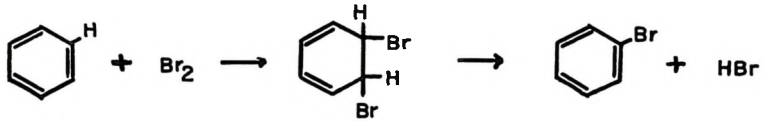
When the investigation reported in this thesis was initiated, the mechanism of both electrophilic and nucleophilic aromatic substitutions were unknown. Since that time, kinetic and isotope effect studies have gone far in resolving the detailed mechanism of electrophilic aromatic substitution reactions and the role of an intermediate in such processes has been placed on a firm basis. Considerable progress also has been made towards the understanding of the mechanism of nucleophilic aromatic substitution reactions, particularly in the past two or three years, although the complete lack of kinetic isotope effect data has made much more difficult the distinction between a concerted and stepwise reaction pathway. The weight of the evidence, however, supports a mechanism which is analogous to that now generally accepted for electrophilic substitution. For this reason, and because the kinetic isotope effect criterion applied in the present study has played such a key role in the elucidation of the mechanism of the latter class of reactions, the first section of this introduction is devoted to a review of the major studies relating to the role of intermediates in electrophilic

processes. This is followed by a review of the literature relating to the mechanism of nucleophilic aromatic substitution reactions.

Electrophilic Aromatic Substitution

In an electrophilic substitution, an electron-deficient reagent attacks a carbon atom of the aromatic ring system, expelling the previously present atom or molecular grouping and forming a new bond between the ring carbon and the attacking reagent. While this reagent may be either neutral or positively charged, it is always electron deficient and the electron pair forming the new bond originates in the aromatic ring. Such familiar reactions as nitration, sulphonation, halogenation, and the Friedel-Crafts are all examples of this type of substitution.

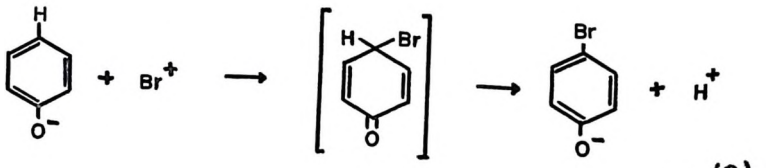
The earlier theories regarding the mechanism of these reactions were based upon analogies to addition reactions of aliphatic double bonds. Bromination of benzene, for example, was regarded as an addition of bromine to one of the Kekule double bonds followed by elimination of hydrogen bromide (27).



...(8).

This was a plausible mechanism and considerable evidence was amassed in its support. While the adduct from benzene would be expected to be much too unstable to permit isolation, definite well-characterized halogen adducts were indeed obtained in the bromination of other aromatic hydrocarbons. For example, phenanthrene and anthracene both add bromine in the cold to form 9,10-dibromo adducts which lose hydrogen bromide on warming to yield 9-bromophenanthrene and 9-bromoanthracene, respectively. Analogous behaviour was observed for a number of other polynuclear aromatic hydrocarbons and, in light of this, it was thought likely that the majority of electrophilic substitution reactions proceeded by such an addition-elimination mechanism.

As early as 1901, however, a second mechanism for electrophilic aromatic substitutions had been proposed by Lapworth (28). He postulated that in the bromination of phenols, molecular bromine dissociated to a very small extent into the ions Br^+ and Br^-. The Br^+ ion was considered to react with a phenolate ion to yield an intermediate, I, which then decomposes in a subsequent step forming the reaction products, viz:

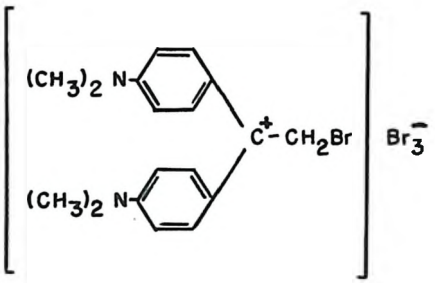


I

...(9).

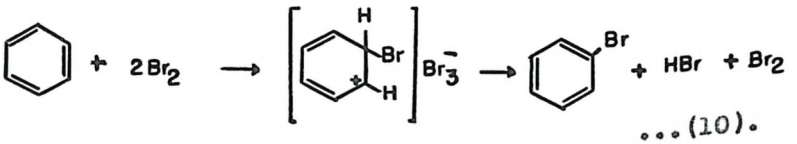
Modern investigations have shown Lapworth's postulate to be substantially correct, except that the actual brominating species is frequently more complex than the simple Br^+ ion.

Lapworth's postulate was generally overlooked until, in 1928, an ionic mechanism for electrophilic substitution was once again proposed. Pfeiffer and Wizinger (29) had shown that 1,1-di-(p-dimethylaminophenyl)-ethylene does not add bromine in the normal manner but instead gives an ionic salt which was shown to have the structure, II.



II

They then suggested that, by analogy, electrophilic aromatic substitutions might follow a pathway involving a similar salt-like intermediate, III;



...(10).

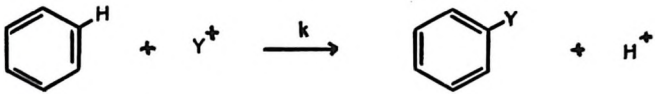
III

In 1936, Price and co-workers (30, 31) undertook a detailed investigation of the reaction of bromine with phenanthrene and showed definitely that the 9,10-dibromo adduct is not the precursor of the 9-bromo substitution product which is formed under catalytic conditions. The addition-elimination mechanism, therefore, had to be excluded as a possible mechanism for electrophilic aromatic substitutions. An alternative formulation of a mechanism was not suggested and, for several years, the exact nature of the course of these substitution reactions remained an open question.

About this time, great progress was being made in the field of instrumentation and accurate, reliable instruments, such as ultra-violet and infra-red spectrophotometers, mass spectrometers, polarographs, and others, became generally available. Accurate kinetic studies using these new tools frequently shed important light on the nature of the reactive species in electrophilic aromatic substitution reactions but were less successful in elucidating the detailed reaction pathways which these species follow.

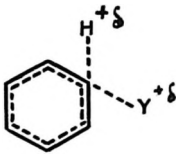
It is possible to postulate two pathways by which aromatic electrophilic substitutions can occur. These are:

(i) The one-step (concerted) mechanism leading directly to products:



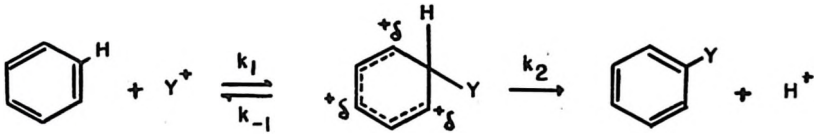
...(11).

and passing through a transition state, IV,



IV

and (ii) the two-step (stepwise) mechanism involving a metastable intermediate, V,



V

...(12).

The important difference between these two mechanisms is that only one transition state is involved in the first, while two transition states, one for formation and one for decomposition of the intermediate, are involved in the second. This distinction is conveniently illustrated by means of energy, reaction coordinate diagrams where maxima represent transition states and minima represent intermediates. Fig. 1 shows two members of the family of curves (chosen to represent extreme situations) for a one-step reaction pathway. The two transition states, B and B', represent quite different configurations: B resembling the reactants, A, very closely, and B' being very similar to the products, C. Fig. 2 shows two alternate pathways for the two-step mechanism (again, chosen to represent extremes). Formation of the intermediate, I, is shown as the rate-controlling step in 2(a) and its decomposition to products, C, is rate-controlling in 2(b). The transition state of the rate-controlling step then may be either B or B'.

While all four transition states of Fig. 1 and 2 represent different configurations, they may be placed in two categories. Those marked B are similar in that the carbon-hydrogen bond broken during reaction is essentially intact, while in those marked B', this bond is very nearly completely ruptured. This similarity of transition states

has made it difficult to establish criteria for distinguishing the two reaction pathways.

Rate studies normally cannot be used as a criterion of mechanism. For a one-step mechanism, from equation 11,

$$\text{rate} = k_{obs} [ArH] [Y^+] \quad \ldots(12).$$

while the steady state treatment of the two-step process yields an identical expression, the observed rate constant now being a function of k_1, k_{-1}, and k_2, viz.,

$$k_{obs} = \frac{k_1 \times k_2}{k_{-1} + k_2} \quad \ldots(13).$$

Under certain circumstances, however, kinetic studies may differentiate between these two mechanisms. These exceptions to the general rule arise when the reaction is subject to catalysis or inhibition. The rate expressions then will differ in respect to dependence upon concentration of the catalysing or inhibiting species. The following section presents a detailed description of the use, limitations, and complications of these kinetic criteria.

If, in addition to the substitution product, there is produced in the reaction some stable molecule or ion, for example, halide ion in a halogenation reaction, the two reaction pathways lead to quite different rate laws.

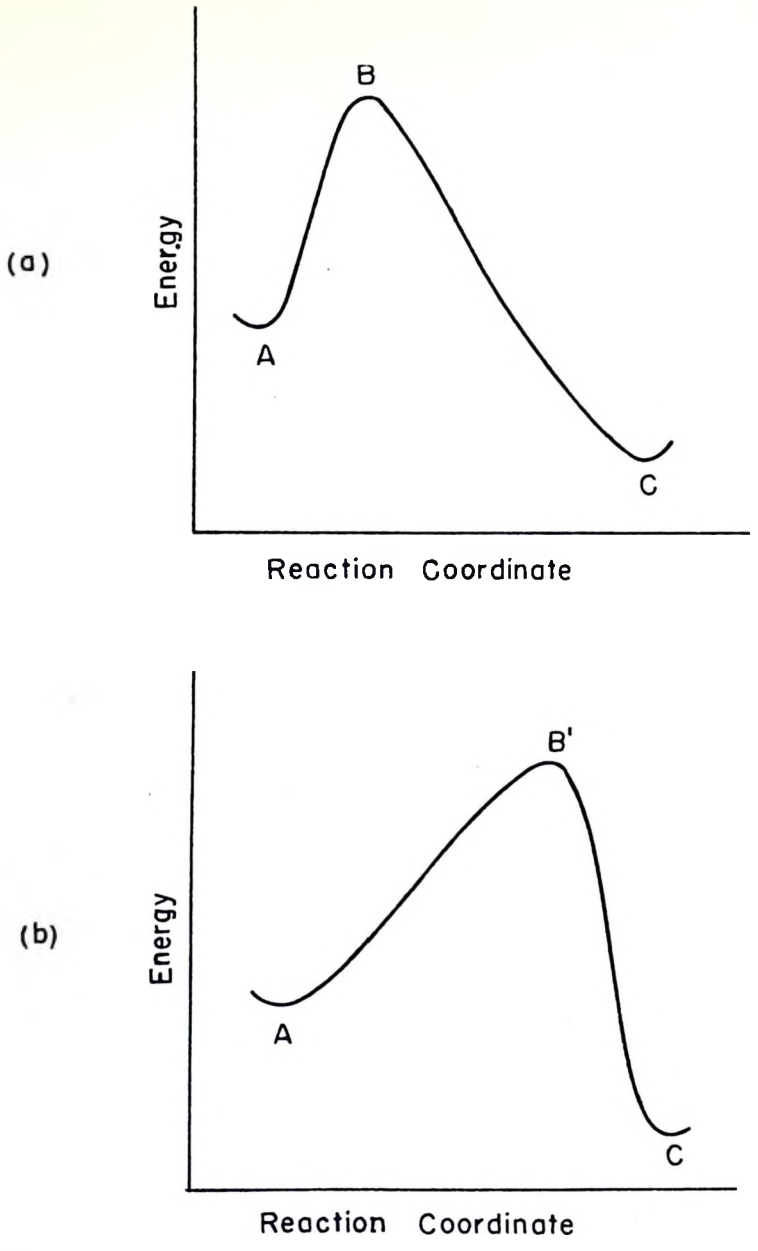


Fig. I. Energy profiles for a reaction proceeding by a concerted mechanism.

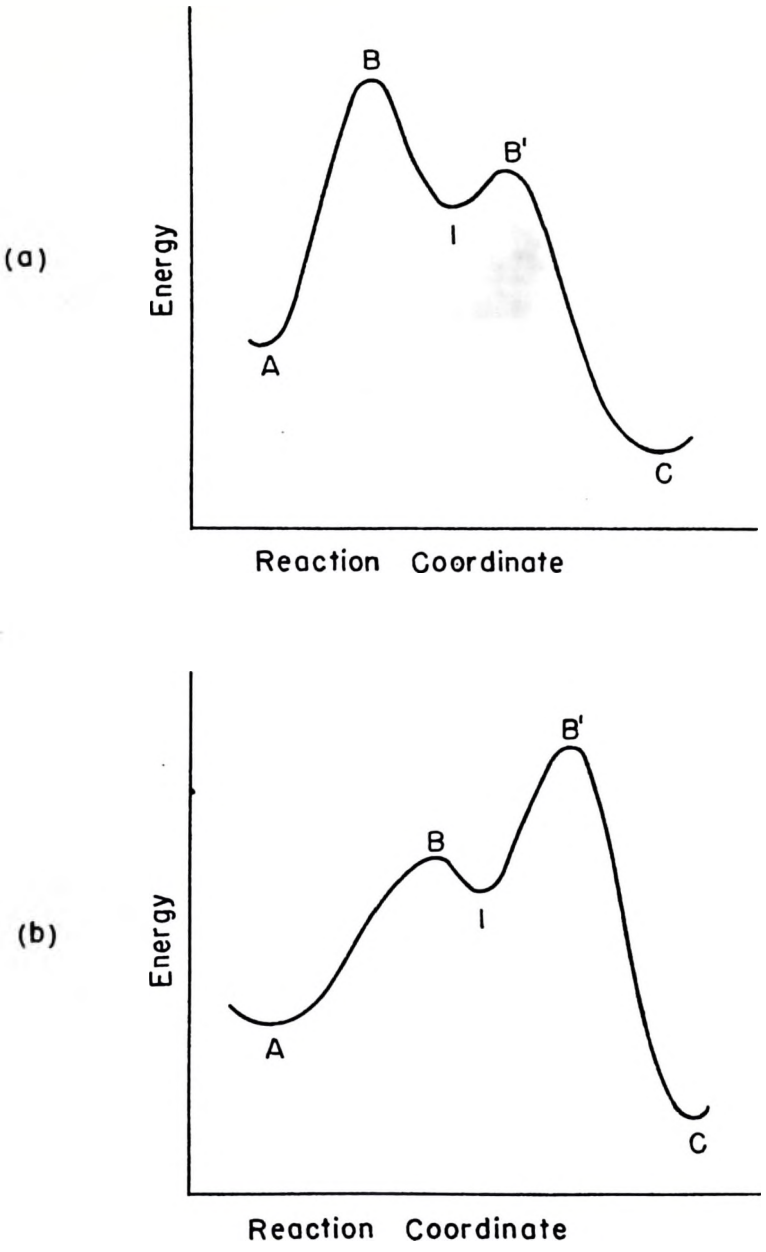


Fig. 2. Energy profiles for a reaction proceeding by a stepwise mechanism.

The reaction rate for the one-step mechanism:

$$ArH + X_2 \xrightarrow{k} ArX + H^+ + X^- \qquad ...(14).$$

will follow the expression

$$\text{rate} = k\,[ArH][X_2] \qquad ...(15).$$

while for the two-step mechanism:

$$ArH + X_2 \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \left[Ar\begin{smallmatrix}H\\X\end{smallmatrix}\right]^+ + X^-$$

$$\left[Ar\begin{smallmatrix}H\\X\end{smallmatrix}\right]^+ \xrightarrow{k_2} ArX + H^+ \qquad ...(16).$$

the rate expression is

$$\text{rate} = \frac{k_1 k_2}{k_{-1}[X^-] + k_2}\,[ArH][X_2] \qquad ...(17).$$

It follows that only halogenations proceeding by the two-step pathway will be subject to rate inhibition by halide ion. In practice, it is not possible to measure the true molecular halogen concentration, $[X_2]$, in the reacting system. What is measured is the sum of the concentrations of molecular halogen and trihalide ion, the latter resulting from the equilibrium

$$X_2 + X^- \underset{}{\overset{K_e}{\rightleftharpoons}} X_3^- \qquad ...(18).$$

The relationship between the true molecular halogen concentration and that actually measured, $[X_2]_m$, is given by the expression,

$$[X_2] = \frac{[X_2]_m}{1 + K_e [X^-]} \qquad \ldots(19).$$

Equations 15 and 17 then become, respectively,

$$\text{rate} = \frac{k}{1 + K_e [X^-]} [ArH] [X_2]_m \qquad \ldots(20).$$

$$\text{rate} = \frac{k_1 k_2}{[1 + K_e [X^-]][k_{-1} [X^-] + k_2]} [ArH][X_2]_m \qquad \ldots(21).$$

In a given kinetic experiment, the halide ion concentration will be essentially constant, and, therefore, a second order rate constant, k_{obs}, can be evaluated. It can be seen from equations 20 and 21 that k_{obs} is a different function of halide ion concentration for the two mechanisms. For the concerted process, the expression is

$$k_{obs} = \frac{k}{1 + K_e [X^-]} \qquad \ldots(22).$$

and for the stepwise process,

$$k_{obs} = \frac{k_1 k_2}{[1 + K_e [X^-]][k_{-1} [X^-] + k_2]} \qquad \ldots(23).$$

These two equations provide a means of distinguishing the two mechanisms. By rearranging 22 and 23 one obtains

$$k_{obs}\left[1 + K_e\ [X^-]\right] = k \qquad \ldots(24).$$

and

$$k_{obs}\left[1 + K_e\ [X^-]\right] = \frac{k_1\ k_2}{k_{-1}\ [X^-] + k_2} \qquad \ldots(25).$$

It can be seen that the one-step mechanism requires that $k_{obs}\left[1 + K_e\ [X^-]\right]$ remain constant with increasing concentration of halide ion, while the two-step process predicts a decrease in this quantity. It is important to note, however, that the relationship between $k_{obs}\left[1 + K_e\ [X^-]\right]$ and $[X^-]$ for reaction by this latter mechanism is non-linear.

There is a possibility that molecular halogen is not the active halogenating species, but rather that it is some entity arising from interaction of halogen with the solvent. In aqueous solution, the equilibrium

$$X_2 + H_2O \underset{}{\overset{K_1}{\rightleftharpoons}} H_2OX^+ + X^- \qquad \ldots(26).$$

can give rise to hypohalous acidium ion which is known to be a powerful halogenating agent (32).

This species then may bring about halogenation by either a concerted mechanism,

$$H_2O\,X^+ + ArH \xrightarrow{k} ArX + H_2O + H^+ \quad ...(27).$$

or by a stepwise mechanism,

$$H_2O\,X^+ + ArH \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \left[Ar\begin{matrix}H\\X\end{matrix}\right]^+ + H_2O$$

$$\left[Ar\begin{matrix}H\\X\end{matrix}\right]^+ \xrightarrow{k_2} ArX + H^+ \quad ...(28).$$

The kinetic expressions for these are:

$$\text{rate} = \frac{k\ K_1}{[1 + K_e[X^-]][X^-]}[ArH][X_2]_m \quad ...(29).$$

for the one-step mechanism, and

$$\text{rate} = \frac{K_1\ k_1\ k_2}{[1 + K_e[X^-]][k_{-1} + k_2][X^-]}[ArH][X_2]_m \quad ...(30).$$

for the stepwise. Equations 29 and 30 are kinetically indistinguishable, the rate constants observed being given by the one expression,

$$k_{obs} = \frac{K_1\ k'}{[1 + K_e[X^-]][X^-]} \quad ...(31).$$

which, on rearrangement, gives

$$k_{obs}\left[1 + K_e\ [X^-]\right] = \frac{K_1\ k'}{[X^-]} \qquad \ldots(32).$$

As in the two-step mechanism with molecular halogen as the halogenating species, the quantity $k_{obs}\left[1 + K_e\ [X^-]\right]$ decreases with increasing concentration of halide ion. Unlike this mechanism, however, the one or two-step process involving hypohalous acidium ion predicts a linear relationship between $k_{obs}\left[1 + K_e\ [X^-]\right]$ and $[X^-]$.

One is able, in theory then, to distinguish reactions where molecular halogen is the active halogenating species from those where hypohalous acidium ion fills this role and, in addition, to distinguish the concerted from the stepwise mechanisms for those reactions involving molecular halogen, on the basis of the relationships between $k_{obs}\left[1 + K_e\ [X^-]\right]$ and halide ion concentration. Unfortunately, in practice, such distinctions cannot always be made.

Considering the two-step process with molecular halogen as the electrophilic reagent, it can be seen that under the circumstance, $k_2 \gg k_{-1}[X^-]$, equation 25 (page 23) reduces to

$$k_{obs}\left[1 + K_e\,[X^-]\right] = k_1 \qquad \ldots(33).$$

Which is identical to the expression for a one-step process. The observation of a constancy of the quantity $k_{obs}\left[1 + K_e[X^-]\right]$, therefore, cannot distinguish between the concerted mechanism and the two-step mechanism in which formation of the intermediate is rate determining. This is the situation which is frequently encountered in bromination studies.

When the converse situation holds, namely, $k_2 << k_{-1}[X^-]$, equation 25 becomes

$$k_{obs}\left[1 + K_e\ [X^-]\right] = \frac{k_1\ k_2}{k_{-1}[X^-]} \qquad \ldots(34).$$

which is kinetically indistinguishable from the expression (equation 32) for a one- or two-step process with hypohalous acidium ion as the electrophilic reagent. In other words, the observation of a linear relationship between $k_{obs}\left[1 + K_e\ [X^-]\right]$ and $[X^-]$ does not unambiguously establish H_2OX^+ as the halogenating species. It is this complication which has prevented the elucidation of the mechanism of aromatic iodination.

In summary, kinetic studies of halide ion inhibition of halogenation reactions only partially elucidate the mechanism of reaction. Observation of a constant value for $k_{obs}\left[1 + K_e\ [X^-]\right]$ at different concentrations of halide ion excludes halogenation by

hypohalous acidium ion but does not distinguish between a one-step or a two-step mechanism involving molecular halogen. Observation of a linear decrease in $k_{obs}\left[1 + K_e[X^-]\right]$ with increasing halide ion concentration, on the other hand, excludes a concerted process involving molecular halogen but fails to differentiate between a stepwise mechanism with molecular halogen as the electrophile and a mechanism, either stepwise or concerted, involving hypohalous acidium ion. It is only when a plot of $k_{obs}\left[1 + K_e[X^-]\right]$ versus $[X^-]$ is non-linear that one can, with reasonable certainty, exclude all mechanisms except a stepwise process involving molecular halogen as the electrophile.

A further complication arises when the decrease in the quantity $k_{obs}\left[1 + K_e[X^-]\right]$ with increasing halide ion is quite small. This result excludes halogenation by hypohalous acidium ion but does not necessarily establish the two-step mechanism involving molecular halogen. This small depression rather may arise from a second-order kinetic salt effect resulting from the replacement by sodium halide of the salt used to maintain constant ionic strength. Such a second order effect was noted by Bell and Rawlinson in brominations of anisoles (33).

A further kinetic criterion for distinguishing between the concerted and stepwise mechanisms is based upon

the supposition that, if carbon-hydrogen bond rupture is involved in a rate determining step, the reaction may be subject to base catalysis and, if so, the kinetic dependence of rate on base concentration would be different for the two mechanisms. For a one-step process involving base catalysis,

$$\text{rate} = k[\text{ArH}][\text{Y}^+][\text{B:}] \qquad \ldots(35).$$

and for the two-step mechanism

$$\text{rate} = \frac{k_1 k_2}{k_{-1} + k_2[\text{B:}]}[\text{ArH}][\text{Y}^+][\text{B:}] \qquad \ldots(36).$$

A concerted mechanism, therefore, clearly requires a linear dependence of rate upon catalyst concentration, while a stepwise mechanism requires a complex, non-linear rate dependence. The form of this non-linear dependence is evident from the following considerations.

At very low base concentrations, k_{-1} will be very much larger than $k_2[\text{B:}]$ and equation 36 becomes

$$\text{rate} = \frac{k_1 k_2}{k_{-1}}[\text{ArH}][\text{Y}^+][\text{B:}] \qquad \ldots(37).$$

This is kinetically indistinguishable from equation 35 and catalysis will be linear. As the base concentration increases, however, the term $k_2[\text{B:}]$ in the denominator of

equation 36 begins to make a significant contribution and the rate becomes increasingly less than that predicted by equation 37. Eventually, at very high base concentrations, k_{-1} becomes negligible compared to $k_2[B:]$ and equation 36 becomes

$$\text{rate} = k_1 [ArH][Y^+] \qquad \ldots(38).$$

that is, the rate is now independent of base concentration.

The curvature of the relationship between rate and base concentration is, of course, dependent upon the relative magnitudes of k_2 and k_{-1}. When k_2 is very much smaller than k_{-1}, equation 36 will approximate quite closely to equation 37 over the available range of base concentrations and the relationship between rate and base concentration will be essentially linear. The observation of this linear relationship is, therefore, compatible with either the concerted or stepwise mechanisms. A complex, non-linear dependence of rate on base concentration, on the other hand, is strong evidence for the two-step mechanism.

During the past fifteen years, a new criterion of mechanism, namely, the kinetic hydrogen isotope effect has played an important role in the study of electrophilic aromatic substitution reactions. These isotope effects show which bonds are broken and which remain intact in the

rate-controlling step of a reaction and, thus, are able to shed light upon the detailed pathway of the substitution process itself.

The potential energy curves (Morse curves) for bonds of hydrogen, deuterium and tritium are considered to be essentially identical, while the zero-point energies of the bonds are lower the heavier the isotopic mass of the atom. A greater amount of energy, therefore, must be expended to rupture a deuterium or tritium bond than would be required for a bond to hydrogen. As a consequence, any reaction involving in the rate-determining step the rupture of a bond associated with a particular hydrogen atom can be expected to proceed more slowly with a reactant in which this hydrogen has been replaced by one of its isotopes.

This decrease in rate is called the kinetic isotope effect, and its magnitude[1] is related to the extent of bond rupture (stretching) in the transition state.

An electrophilic aromatic substitution which proceeds by the concerted mechanism will, of course, involve carbon-hydrogen bond rupture in the rate-determining step and, therefore, would be expected to exhibit an isotope effect. The isotope effect observed, however, may have any magnitude up to the maximum for carbon-hydrogen bond rupture. This is because the transition state may lie anywhere along the reaction coordinate (see Fig. 1) and, therefore, may involve any extent of stretching of the carbon-hydrogen bond up to a nearly complete bond rupture.

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1. Three different ways of indicating magnitudes of isotope effects are used extensively in the literature. The first, and simplest, gives the ratio of rate constants for reaction of species containing light and heavy isotopes, for example, k^H / k^D for species containing hydrogen and deuterium. The second expresses the difference in rates of the two species, relative to that of the heavier isotope:

$$\frac{k^H - k^D}{k^D} \quad \text{or} \quad \frac{k^H}{k^D} - 1$$

The third, used with the heavier elements whose isotope effects are small, expresses the isotope effect as a percentage rate difference,

$$100 \left[\frac{k^H}{k^D} - 1 \right] .$$

Normally, one would expect an appreciable extent of carbon-hydrogen bond stretching in the transition state, and an isotope effect of moderate to large magnitudes, but there is no reason to suppose that a very limited extent of carbon-hydrogen bond stretching cannot occur. A very small isotope effect, then, is not incompatible with a one-step mechanism but, in all likelihood, arises because the reaction follows some other mechanism.

For an electrophilic aromatic substitution proceeding by a two-step mechanism, the observed rate constant is given by

$$k_{obs} = \frac{k_1 \quad k_2}{k_{-1} + k_2} \qquad \ldots(13).$$

The corresponding expressions for isotopically labelled reactants, for instance, of species containing hydrogen or deuterium, are 39 and 40,

$$k^H_{obs} = \frac{k^H_1 \quad k^H_2}{k^H_{-1} + k^H_2} \qquad \ldots(39).$$

$$k^D_{obs} = \frac{k^D_1 \quad k^D_2}{k^D_{-1} + k^D_2} \qquad \ldots(40).$$

and the observed isotope effect will be given by the ratio of these two equations, viz.:

$$\left[\frac{k^H}{k^D}\right]_{obs} = \frac{k_1^H \; k_2^H \; (k_{-1}^D + k_2^D)}{k_1^D \; k_2^D \; (k_{-1}^H + k_2^H)} \qquad \ldots(41).$$

The magnitude of the isotope effect observed in any particular reaction following the two-step mechanism will depend upon the relative magnitudes of k_2 and k_{-1}. When the intermediate proceeds to products much more frequently than it reverts to reactants, that is, when k_2 is very much larger than k_{-1}, equation 41 reduces to

$$\left[\frac{k^H}{k^D}\right]_{obs} = \frac{k_1^H}{k_1^D} \qquad \ldots(42).$$

Since k_1 is the rate constant for the bond-formation step and does not involve the hydrogen isotope, k_1^H / k_1^D is very close to unity[1], and the observed isotope effect $(k^H/k^D)_{obs}$ also is very nearly unit. When the converse relationship

---

1. There may be a small secondary isotope effect associated with this step but it will be almost two orders of magnitude smaller than the primary effects considered here (34, 35).

holds, the intermediate reverting to reactants much more frequently than proceeding to products, equation 41 becomes

$$\left[\frac{k^H}{k^D}\right]_{obs} = \frac{k_1^H \; k_2^H \; k_{-1}^D}{k_1^D \; k_2^D \; k_{-1}^H} \qquad \ldots(43).$$

This expression now includes k_2, the rate constant for the bond rupture step, which is strongly dependent upon the isotopic mass of the leaving group. The ratio k_2^H/k_2^D is not unity and $\left[k^H/k^D\right]_{obs}$ will be larger than one. When k_2 and k_{-1} are of comparable magnitudes, the isotope effect will lie between the limits given by equations 42 and 43. The two-step mechanism then may give rise to no isotope effect, or a large isotope effect, or, indeed, an isotope effect of any intermediate magnitude.

From the foregoing, it can be seen that both the concerted and stepwise mechanisms are compatible with a wide range of isotope effect values and the fact that a reaction exhibits an isotope effect, or alternatively, shows no isotope effect, is not sufficient to establish the reaction mechanism. This point has not always been appreciated in the past and observation of a zero isotope effect frequently has been considered to be unequivocal evidence for the two-step mechanism.

There are, however, certain reactions in which a study of isotope effects may serve to elucidate the particular mechanism. For example, those reactions previously discussed which are subject to catalysis or inhibition, under certain circumstances, may show a variation in the magnitude of the isotope effect with variation in concentration of the catalyst or inhibition.

The application of this "variable kinetic isotope effect" criterion to halogenations, for example, sometimes permits one to establish the reaction mechanism or the nature of the electrophilic reagent in cases where ordinary kinetic studies are unfruitful.

Kinetic studies in which it is found that $k_{obs}\,[1 + K_e[X^-]]$ varies linearly with halide ion concentration, (as discussed on pages 22 to 27), do not distinguish between halogenations proceeding by a stepwise mechanism with molecular halogen as the electrophile and those involving hypohalous acidium ion and following either the one-step or two-step mechanism. The rate constant for the reaction involving hypohalous acidium ion is

$$k_{obs} = \frac{K_1 \; k'}{[1 + K_e[X^-][X^-]}$$

and the isotope effect observed, therefore, is given by

$$\left[\frac{k^H}{k^D}\right]_{obs} = \frac{k'^H}{k'^D} \qquad \ldots(44).$$

This expression does not involve halide ion and the isotope effect is constant with variation in halide ion concentration. For a reaction following the two-step mechanism and involving molecular halogen as the electrophile, the rate constant is

$$k_{obs} = \frac{k_1 \; k_2}{\left[1 + K_e [X^-]\right]\left[k_{-1} [X^-] + k_2\right]}$$

which leads to the following expression for the rate constant ratio, $\left[k^H/k^D\right]_{obs}$

$$\left[\frac{k^H}{k^D}\right]_{obs} = \frac{k_1^H \; k_2^H \left[k_{-1}^D [X^-] + k_2^D\right]}{k_1^D \; k_2^D \left[k_{-1}^H [X^-] + k_2^H\right]} \qquad \ldots(45).$$

Since this expression includes terms in $[X^-]$, the magnitude of the observed isotope effect clearly will be dependent upon halide ion concentration. At very low halide ion concentrations, $k_2 >> k_{-1} [X^-]$, and equation 45 becomes

$$\left[\frac{k^H}{k^D}\right]_{obs} = \frac{k_1^H}{k_1^D}$$

The ratio k_1^H/k_1^D is very close to unity and the isotope effect observed then will be very small. At high halide ion concentrations, on the other hand, equation 45 becomes

$$\left[\frac{k^H}{k^D}\right]_{obs} = \frac{k_1^H \; k_2^H \; k_{-1}^D}{k_1^D \; k_2^D \; k_{-1}^H}$$

This expression contains the term k_2^H/k_2^D, the ratio of the rate constants for the step involving the rupture of the bond to isotopic hydrogen, and hence predicts a large isotope effect. An increase in the magnitude of the observed isotope effect with increasing halide ion concentration, therefore, is strong evidence in favour of the stepwise mechanism involving molecular halogen and is incompatible with a mechanism involving hypohalous acidium ion.

A second case in which ordinary rate studies do not distinguish between two halogenation mechanisms, but where kinetic isotope effect studies may, arises when the quantity $k_{obs}\left[1 + K_e\left[X^-\right]\right]$ is found to decrease only slightly with increasing halide ion concentration (see pages 25, 26). This result clearly eliminates hypohalous acidium ion as the halogenating species but does not distinguish between the concerted and the stepwise

mechanisms involving molecular halogen. The rate constant for the concerted process is given by

$$k_{obs} = \frac{k}{1 + K_e [X^-]}$$

which leads to the following expression for the isotope effect:

$$\left[\frac{k^H}{k^D}\right]_{obs} = \frac{k^H}{k^D}$$

This, in contrast to equation 45 for the stepwise mechanism, requires that the observed isotope effect be unaffected by halide ion. The observation then of a variation in magnitude of the isotope effect with increasing halide ion concentration is clearly incompatible with a one-step mechanism and the reaction mechanism must, therefore, be stepwise. It is important to note, however, that the converse result, namely, an isotope effect whose magnitude is independent of halide ion concentration does not distinguish between the two mechanisms since both the stepwise process in which $k_2 \gg k_{-1} [X^-]$ and the concerted process lead to kinetic expressions in which there is no halide ion term.

This "variable kinetic isotope effect" criterion also can be applied to elucidation of mechanisms of

electrophilic aromatic substitutions which are subject to base catalysis. In these reactions, the relationships between the magnitude of the isotope effect and the base concentration is different for the one-step and the two-step mechanisms. For a reaction following a concerted pathway, it follows from equation 35 (page 28) that the observed rate constant is

$$k_{obs} = k\,[B:] \qquad \ldots(46).$$

and the isotope effect observed in the reaction, therefore, will be

$$\left[\frac{k^H}{k^D}\right]_{obs} = \frac{k^H}{k^D}$$

The magnitude of the isotope effect then depends only upon the degree of carbon-hydrogen bond rupture in the transition state and is independent of the base concentration. An entirely different relationship results if the reaction follows a stepwise mechanism. Under these circumstances, the observed rate constant, from equation 36 (page 28), is

$$k_{obs} = \frac{k_1\, k_2\,[B:]}{k_{-1} + k_2\,[B:]} \qquad \ldots(47).$$

and the observed isotope effect will be

$$\left[\frac{k^H}{k^D}\right]_{obs} = \frac{k_1^H k_2^H\left[k_{-1}^D + k_2^D[B:]\right]}{k_1^D k_2^D\left[k_{-1}^H + k_2^H[B:]\right]} \qquad \ldots(48).$$

This expression shows clearly that the magnitude of the isotope effect is not independent of, but varies with, base concentration. The form of the dependence of isotope effect magnitude and base concentration may be obtained from a consideration of the limiting cases. At very low base concentration, the relationship $k_{-1} \gg k_2[B:]$ holds and equation 48 reduces to

$$\left[\frac{k^H}{k^D}\right]_{obs} = \frac{k_1^H\ k_2^H\ k_{-1}^D}{k_1^D\ k_2^D\ k_{-1}^H}$$

This expression involves k_2, the rate constant for the rupture of the carbon-hydrogen bond step and an isotope effect will be observed, the exact magnitude of which will depend upon the reaction under study. At high base concentrations, the reverse relationship, $k_2[B:] \gg k_{-1}$ holds, equation 48 becomes

$$\left[\frac{k^H}{k^D}\right]_{obs} = \frac{k_1^H}{k_1^D}$$

and the isotope effect is essentially zero since k_2 does not appear in this expression.

The observation of a variation in isotope effect with changing base concentration is not compatible with a concerted process and, therefore, is very strong evidence in favour of the two-step mechanism. The converse observation, that the isotope effect does not vary with base concentration, however, is not proof for a one-step reaction pathway. If k_{-1} of the two-step process is very much larger than k_2, then k_{-1} may well be much larger than $k_2[B:]$ over the entire range of experimentally attainable base concentrations. The isotope effect then will always be given by

$$\left[\frac{k^H}{k^D}\right]_{obs} = \frac{k_1^H\, k_2^H\, k_{-1}^D}{k_1^D\, k_2^D\, k_{-1}^H}$$

and will be essentially constant. The observation of such behaviour, being compatible with either a one- or two-step mechanism, therefore, fails to distinguish these two possible reaction pathways.

In summary then, it can be said that neither rate studies or kinetic isotope effect measurements can establish unequivocally the concerted mechanism. Any result which is compatible with this mechanism is also compatible with a two-step process in which the formation of an intermediate is rate-determining. The observation of a non-linear variation in rate or of a variation in a

kinetic isotope effect with changing concentration of a catalyst or an inhibitor, however, excludes the one-step process. Such observations, therefore, are strong evidence for the stepwise mechanism.

The remainder of this section will discuss individual reactions on which ordinary kinetic studies and isotope effect measurements have been carried out.

Nitrations

The first reported kinetic isotope effect study in an aromatic substitution process was that of Melander (20, 36, 37) who showed that in the nitration of benzene, toluene, bromobenzene, and naphthalene, tritium is replaced by the nitro group at the same rate (within experimental error) as is hydrogen. Similar results were reported soon after by other workers (38, 39) in deuterium isotope effect studies on nitration of nitrobenzene and benzene.

Melander interpreted his results in terms of a two-step mechanism with formation of the intermediate rate-controlling:

$$ArH + NO_2^+ \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} [ArHNO_2]^+$$

$$B: + [ArHNO_2]^+ \xrightarrow{k_2} ArNO_2 + H:B^+ \quad \ldots(49).$$

Since the carbon-hydrogen bond in this intermediate is still intact, no isotope effect would be expected. The alternative one-step mechanism,

$$ArH + NO_2^+ \xrightarrow{k} ArNO_2 + H^+ \qquad ...(50).$$

would be expected to give rise to an isotope effect since the carbon-hydrogen bond is now being ruptured in the rate determining step. It was not until 1955 that Hammond (21) pointed out that Melander had overlooked the reaction pathway shown in Fig. 1(a) and that a zero isotope effect is also compatible with a concerted mechanism.

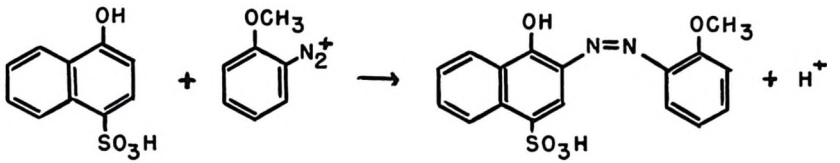
Hammond argued that the absence of an isotope effect does not necessarily require that the carbon-hydrogen bond remain unaltered in the rate-determining step. What really is shown is that the zero point energies of the bending and stretching modes of this bond are not changed significantly on going from reactants to the transition state. If formation of an intermediate is the rate-determining step, this condition, obviously, is met. For a concerted process, however, this condition also is met if the transition state is reached before the carbon-hydrogen bond loses any appreciable part of its zero point energy. What Melander had shown then was that carbon-hydrogen bond rupture has not made appreciable progress in the transition state of the rate-determining step.

Sulphonations

Melander, in his original papers (36, 37) also reported that sulphonation, in contrast to nitration (and also bromination) of toluene gives rise to an appreciable isotope effect. Later, in a more complete study Larsson and Melander (22) observed that sulphonation of bromobenzene isotopically labelled in the para-position shows a deuterium isotope effect, k^H / k^D of 1.4 and a tritium effect, k^H / k^T of 2.0. A somewhat higher deuterium effect has recently been reported for sulphonation of nitrobenzene and some substituted trimethylanilinium ions (40). Since these observed isotope effects are considerably less than normally observed in reactions where carbon-hydrogen bond rupture is rate determining (38), Melander interpreted these results in terms of a step-wise mechanism in which the rate constants k_{-1} and k_2 are of comparable magnitudes. These small but appreciable isotope effects are, however, equally compatible with a one-step mechanism in which carbon-hydrogen bond rupture is only slightly advanced in the transition state.

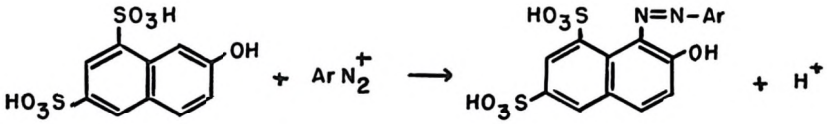
Diazo - Coupling Reactions

The first conclusive proof of the mechanism of an electrophilic aromatic substitution reaction was obtained by Zollinger (13) from studies on diazo-coupling reactions. In certain systems (23), typically those exhibiting no steric hindrance at the site of substitution, such as:



...(51).

no base catalysis is shown nor is there any isotope effect. In others, such as:



...(52).

isotope effects of magnitudes approximately equal to the

maximum predicted theoretically for carbon-hydrogen bond rupture are observed. Furthermore, these reactions are subject to catalysis by base. Their rates, however, are not linearly dependent upon the base concentration, as would be required by a one-step mechanism, but rather follow the relationship:

$$\text{rate} = \frac{k_1 \; k_2}{k_{-1} + k_2[B:]}[ArH][Ar'N_2][B:] \qquad \ldots(53).$$

As discussed earlier, this result is readily accommodated by the two-step mechanism.

If the very reasonable assumption is made that the specific rate constants for formation and return to reactants of the intermediate are essentially unaffected by isotopic substitution, then it follows, from equation 47 (page 39), that

$$k^H_{obs} = \frac{\frac{k_1 \; k_2^H}{k_{-1}}[B:]}{1 + \frac{k_2^H}{k_{-1}}[B:]} \qquad \ldots(54).$$

and

$$k^D_{obs} = \frac{\frac{k_1 k_2^D}{k_{-1}}[B:]}{1 + \frac{k_2^D}{k_{-1}}[B:]} \qquad \ldots(55).$$

By determining separately the variation in rate with base concentration for deuterated and undeuterated reactants, the ratios k_2^H / k_{-1} and k_2^D / k_{-1} can be evaluated, and from these, k_2^H / k_2^D can be calculated. The results of such an investigation for the coupling reaction of 2-naphthol-6,8-disulphonic acid with p-chlorobenzenediazonium ion (24) is shown in Table I.

TABLE I

KINETIC ISOTOPE EFFECTS IN THE COUPLING OF 2-NAPHTHOL-6,8-DISULPHONIC ACID WITH p-CHLOROBENZENEDIAZONIUM ION IN THE PRESENCE OF DIFFERENT BASES

Base	Base Concentration (m./l.)	$[k^H / k^D]_{obs}$	k_2^H / k_2^D
Water	55.6	6.66	6.58
Pyridine	0.0232	6.01	6.16
Pyridine	0.905	3.62	6.67

mean 6.4 ± 0.3

These results are in accordance with the predictions of the stepwise mechanism. In the presence of water, a weak base, the term k_{-1} is very much larger than $k_2[B:]$. The intermediate is essentially in equilibrium with reactants and a large isotope effect is observed. Pyridine, a much stronger base, causes an increase in k_2 and, therefore, an increase in $k_2[B:]$. A smaller isotope effect then results. At higher pyridine concentration, the $k_2[B:]$ term becomes much larger than k_{-1} and the observed isotope effect is quite small. That the quantity, k_2^H / k_2^D remains relatively constant in spite of the large variation in $[k^H / k^D]_{obs}$ provides further strong support for the two-step mechanism.

Halogenations

A large body of experimental work has been reported on the mechanism of halogenation reactions, particularly relating to the nature of the electrophilic reagent. The following discussion of chlorinations, brominations, and iodinations, however, will be restricted to those studies where molecular halogen has been used as the reagent.

Iodination. This reaction was one of the first of the aromatic halogenation reactions to be investigated kinetically. Painter and Soper (41) and later

Berliner (42, 43) studied the kinetics of iodination of phenols and amines by iodine in hydroxylic solvents. Berliner (44, 45) also studied kinetics of iodination of these substrates by iodine monochloride. The results obtained are consistent with I_2 (ICl) acting as the halogenating species in a two-step mechanism involving an intermediate in equilibrium with the reagents, that is:

$$ArH + I_2 \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} [ArHI]^+ + I^- \qquad [ArHI]^+ \xrightarrow{k_2} ArI + H^+ \qquad \ldots(56).$$

with $k_{-1}\,[I^-] \gg k_2$.

The results, however, are equally consistent with H_2OI^+ (or I^+) as the attacking reagent in either a one- or two-step iodination:

$$I_2 + H_2O \underset{}{\overset{K}{\rightleftharpoons}} H_2OI^+ + I^- \qquad ArH + H_2OI^+ \xrightarrow{k'} ArI + H^+ + H_2O \qquad \ldots(57).$$

since, as shown in the earlier discussion of kinetic criteria, the rate expressions for these two mechanisms are indistinguishable.

Isotope effect studies have been carried out on iodinations of phenol (46) and of anisole (47). These

reactions exhibited isotope effects, k^H / k^D , of approximately four. In a similar study, iodinations of amines showed isotope effects varying from one to four, depending upon the particular amine (48, 49). These results, as emphasized earlier, show that carbon-hydrogen bond rupture occurs in the rate-determining step but do not provide evidence favouring one mechanism or the other. The application of the "variable kinetic isotope effect" criterion should, however, distinguish between these two possibilities since, as discussed on pages 35 to 38, only when molecular halogen acts as the halogenating species may a hydrogen isotope effect be halide ion dependent. Grimson and Ridd (50) applied such a test to the iodination of glyoxaline (imidazole). They observed an isotope effect, k^H /k^D , of 4.4 which remained constant as iodide ion concentration was lowered from 0.01 molar to approximately 0.0005 molar. Similarly, Berliner (51) observed a constant isotope effect, k^H /k^D , of 3.8 in iodination of anisole by iodine monochloride over the chloride ion concentration range, 0.3 to 0.9 molar.

These results, while certainly supporting an iodination by H_2OI^+ , may still be accommodated by a two-step mechanism with molecular halogen as the electrophile.

This is because it is at least possible that in these reaction systems, k_{-1} is so much larger than k_2 that the term $k_{-1}[X^-]$ in the expression for the isotope effect (equation 45)

$$\left[\frac{k^H}{k^D}\right]_{obs} = \frac{k_1^H k_2^H\left[k_{-1}^D [X^-] + k_2^D\right]}{k_1^D k_2^D\left[k_{-1}^H [X^-] + k_2^D\right]}$$

always is very much greater than k_2, even at the lowest halide ion concentrations studied. Under these circumstances, the observed isotope effect is given by

$$\left[\frac{k^H}{k^D}\right]_{obs} = \frac{k_1^H k_2^H k_{-1}^D}{k_1^D k_2^D k_{-1}^H}$$

and remains at its maximum over the whole range of halide ion concentrations studied. Thus, at this time, an unambiguous decision between iodination by hypohalous acidium ion or by molecular halogen cannot be made.

Brominations. The kinetics of brominations are frequently complicated by higher order terms with respect to bromine, the rates appearing to be governed by expressions of the form:

$$\text{rate} = \left[k_1 + k_2[Br_2] + k_3[Br_2]^2 + \ldots\right][ArH][Br_2] \quad \ldots(58).$$

The extent of participation of these higher order terms is strongly dependent upon solvent, temperature, etc. In certain cases, however, brominations may be made to exhibit second order kinetics. Wilson and Soper (52) studied bromination of o-nitroanisole in water, and Berliner and Beckett (53) studied bromination of naphthalene in aqueous acetic acid. In both of these studies, second order kinetics was observed and the quantity $k_{obs}\left[1+K_e\left[Br^-\right]\right]$ was found to be constant with changing bromide ion concentration. As discussed previously, this latter result completely eliminates hypobromous acidium ion as the bromination species, but it is compatible with bromine acting as the electrophile in either a concerted process or a two-step process in which formation of an intermediate is rate-determining.

Isotope effect studies have not, unfortunately, resolved this question of mechanism. In contrast to iodinations, brominations normally do not exhibit isotope effects. For instance, Melander (20) and de la Mare (54) both observed a zero isotope effect, k^H / k^D equalling unity, in the bromination of benzene. Berliner (47) has suggested that this difference between bromination and iodination may be due to a less rapid proton loss from the intermediate containing the less electronegative iodine, or to a more rapid return of the much more sterically

crowded iodine-containing intermediate to reactants. This latter explanation is supported by the observation of an isotope effect, k^H / k^D, of two in the bromination of bromodurene (55) and of 2-naphthol-6, 8-disulphonic acid (13) and an effect, k^H / k^T of approximately ten in bromination of 1,3,5-tri-tertiarybutylbenzene (56). Bromination isotope effects also have been found where the aromatic substrate is quite reactive (57).

As discussed earlier in this section, the observation of a constant value for $k_{obs}\left[1 + K_e\,[Br^-]\right]$ and a zero isotope effect may be interpreted in terms of either a concerted or stepwise mechanism with molecular bromine as the electrophile. An appreciable isotope effect, on the other hand, may be interpreted in terms of either a concerted or stepwise mechanism with Br_2 or H_2OBr^+ as the halogenating agent. The only possible way to resolve these difficulties is through isotope effect measurements conducted at different bromide ion concentrations. If the isotope effect is found to vary with changing concentration of halide ion, then the two-step mechanism involving molecular bromine is very strongly indicated.

The only study of this kind to be reported to date is that of Berliner and Schueller (34). They found exactly the same isotope effect, $k^H / k^D = 1.15$, at 0.1 and 0.2 molar bromide ion concentrations. This result is

consistent with either a two-step mechanism with formation of the intermediate being rate determining (the observed isotope effect then must be a secondary, rather than a primary, one) or a concerted mechanism with only a slight weakening of the carbon-hydrogen bond in the transition state.

Thus, the question of mechanism of brominations cannot be answered unequivocally since the available evidence fails to distinguish the two-step and the concerted mechanisms.

Chlorinations. In non-aqueous solvent systems, chlorinations normally proceed with molecular chlorine as the electrophilic reagent (58, 59, 60). The only reported isotope effect study is that of Baciocchi et al who found that chlorination of 3-bromodurene in acetic acid exhibits a very small isotope effect, k^H / k^D being nearly unity. The isotope effect for bromination of this compound, in comparison, was $k^H / k^D = 1.4$. It would appear from these two results, and from iodinations ($k^H / k^D = 4$ for most reactions studied) that isotope effects generally follow the order, iodination > bromination > chlorination. This trend reflects the degree of steric crowding in the intermediate which, in turn, influences the relative rates of its return to reactants and decomposition to products, and

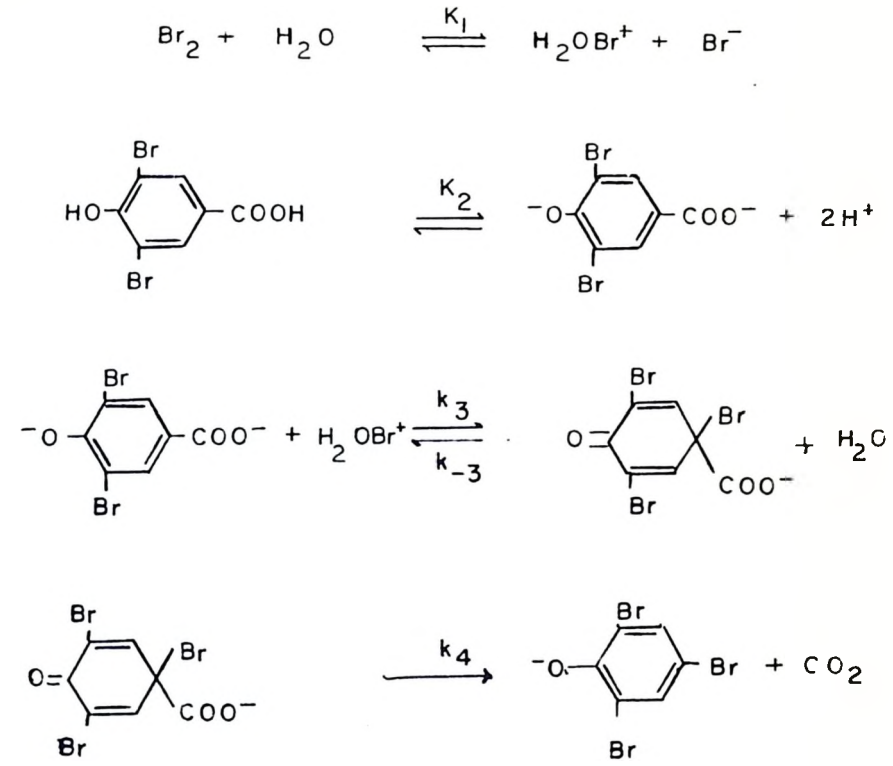
thus tends to support Berliners postulate.

Bromodecarboxylation

Although the question of a concerted versus a stepwise mechanism is still open as far as ordinary aromatic brominations are concerned, there is a bromination reaction in which kinetic isotope effects have provided conclusive evidence in support of the latter mechanism. This is the bromodecarboxylation reaction in which a carboxyl group attached to an activated aromatic ring is displaced by bromine.

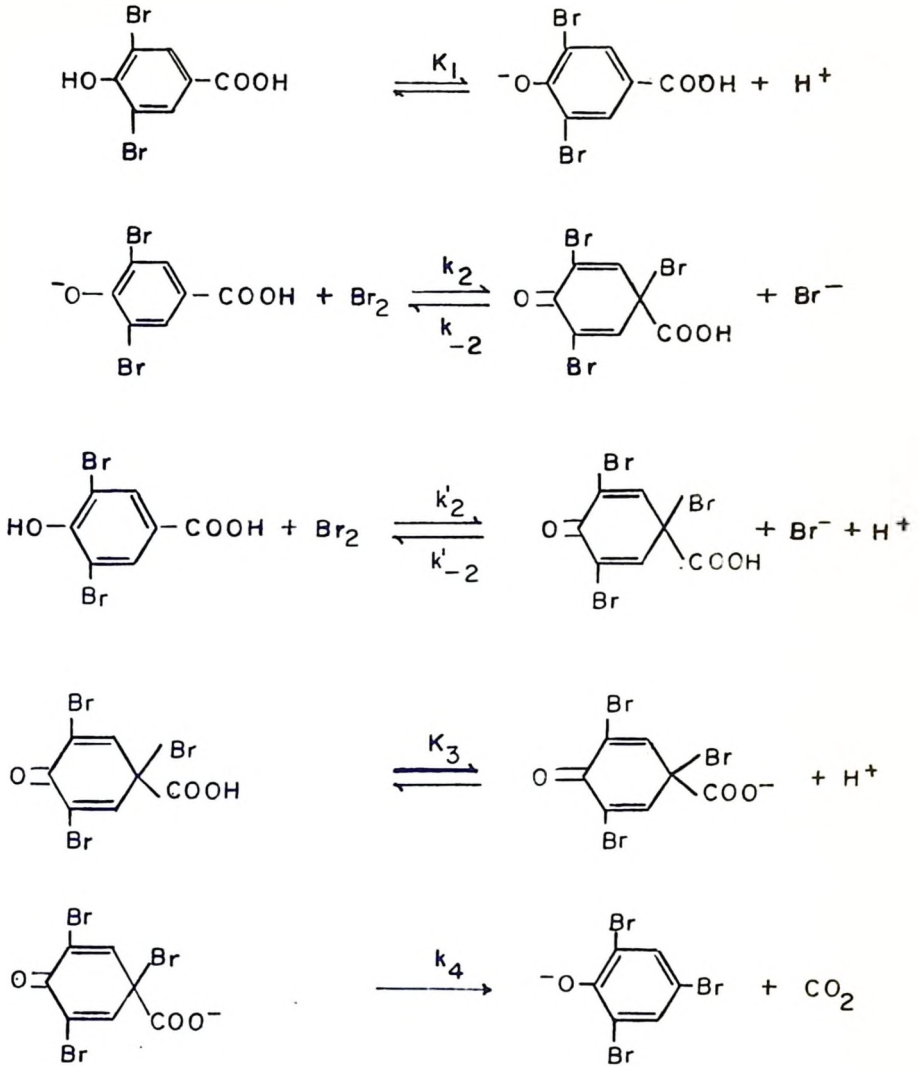
For the reaction of bromine with 3,5 - dibromo -4- hydroxybenzoic acid, Grovenstein and Henderson (61) were unable to distinguish by ordinary kinetic means between the following mechanisms:

Mechanism A



...(59).

Mechanism B



...(60).

Grovenstein and Ropp (14) have been successful in distinguishing between these two possibilities by measuring, at different bromide ion concentrations, the carbon isotope effect associated with the carboxyl carbon. Although carbon isotope effects are very small compared to those of hydrogen ($100\left[\frac{k^{12}}{k^{13}} - 1\right]$ is of the order of one to five per cent) isotopic analysis by high-precision mass spectrometry permits their measurement to the nearest 0.1 per cent. For mechanism A, an appreciable isotope effect would be expected if k_4 is rate-controlling but a very small, or zero, isotope effect if k_3 is rate-controlling. In either case, however, halide ion is not involved and the isotope effect would, therefore, be independent of bromide ion concentration. For mechanism B, on the other hand, ordinary kinetics showed that, in the absence of bromide ion, the rate controlling steps must be k_2 and k_2'. The isotope effect, therefore, would be very small. At high bromide ion concentrations, the reversal of the intermediate is forced and k_4 becomes rate controlling. An isotope effect of a normal magnitude (about five per cent) then should be observed. It was found that at very low bromide ion concentration (no added bromide ion) the isotope effect was 0.0 - 0.2 per cent, but as the bromide ion concentration was raised to 0.3 molar the isotope effect was 4.5 per cent. This latter isotope effect compares closely

with the theoretical value of 4.4 per cent calculated for a rate-determining bond rupture.

These results, therefore, eliminate hypobromous acidium ion as the electrophilic reagent, and demonstrate unambiguously the present of an intermediate in the bromination reaction.

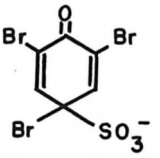
Bromodesulphonation

A very thorough kinetic study by Cannell (15) has provided strong evidence in support of a two-step mechanism for the bromodesulphonation reaction. This reaction, which is closely related to bromodecarboxylation, is the direct replacement by bromine of a sulphonate group attached to an activated aromatic ring.

$$ArSO_3H + Br_2 \longrightarrow ArBr + SO_3 + H^+ + Br^- \quad \ldots(61).$$

Spectroscopic measurements demonstrated that when sodium 3,5 - dibromo - 4 - hydroxybenzenesulphonate, VI, is treated with bromine water, the reactants combine immediately to form the 2,4,6 - tribromo -2,5 - cyclohexadien - 1-one-4 sulphonate ion, VII.

VI

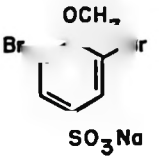


VII

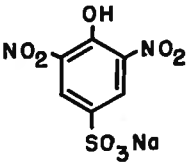
The spectral absorption of this compound is then slowly replaced by that of 2,4,6-tribromophenol, the product of the reaction. Kinetically, the reaction is zero order in whichever reactant, sulphonate or bromine, is in excess and is first order in the other. These results would appear to establish definitely the formation of an intermediate in the reaction but do not, of course, distinguish between molecular bromine and H_2OBr^+ (or Br^+) as the actual brominating species.

With less reactive compounds, VIII, IX, and X, Cannell (16) could not obtain spectroscopic evidence for the formation of an intermediate. The rate variation

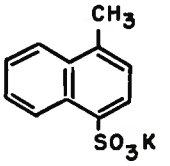
VIII



IX



X



XI

with change in bromide ion concentration, however, was found to be in accordance with the two-step mechanism.

$$ArSO_3^- + Br_2 \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \left[Ar\begin{smallmatrix}^{+}\\ \diagup \\ \diagdown \\ {}^{-}\end{smallmatrix}\begin{smallmatrix}Br\\ \\ SO_3^-\end{smallmatrix}\right] + Br^-$$

$$\left[Ar\begin{smallmatrix}^{+}\\ \diagup \\ \diagdown \\ {}^{-}\end{smallmatrix}\begin{smallmatrix}Br\\ \\ SO_3^-\end{smallmatrix}\right] \xrightarrow{k_2} ArBr + SO_3^- \qquad \ldots(62).$$

with

$$k_{obs} = \frac{k_1 \; k_2}{\left[1 + K_e \; [Br^-]\right]\left[k_{-1}\,[Br^-] + k_2\right]} \qquad \ldots(63).$$

As pointed out in the earlier discussion of mechanistic criteria, (page 26), when $k_{-1}\,[Br^-]$ is very large relative to k_2, expression 63 reduces to

$$k_{obs} = \frac{k'}{\left[1 + K_e \; [Br^-]\right][Br^-]}$$

which is also the kinetic expression for either a concerted or a stepwise mechanism involving H_2OBr^+ as the brominating species.

For two of the reactants studied, sodium 3,5 -dibromo -4 - aminobenzenesulphonate, VIII, and sodium 3,5 - dinitro- 4 - hydroxybenzenesulphonate, X, the kinetic data, in fact,

are accommodated fully as well by equation 54 as by 53. For example, k_{-1}/k_2 for VIII works out to 2,200 $l.mole^{-1}$. For sodium methoxybenzenesulphonate, IX, the kinetic data are unreliable since Cannell had overlooked the competing reaction of bromodeprotonation which yields sodium 3-bromo-4-methoxybenzenesulphonate and, under the conditions used, can account for as much as fifty per cent of the bromine consumed (17). It would appear then that no conclusions can be reached concerning the role of an intermediate or the nature of the brominating species from Cannell's work on compounds VIII, IX, and X.

Finally, for compound XI, potassium 1-methylnaphthalene -4-sulphonate, the rate data obeyed the expression,

$$k_{obs} \left[1 + K_e [Br^-] \right] = \text{constant} \qquad \ldots(64).$$

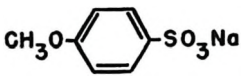
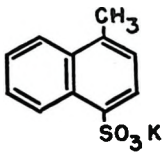
This observation is indicative of the concerted mechanism with molecular bromine as the electrophile, but it can also be accommodated by the two-step mechanism involving this electrophile provided that the bond formation step in this mechanism is rate-determining.

In a very recent study, Baliga, in the McMaster University Laboratories, was able to demonstrate the presence of an intermediate in the bromodesulphonation of sodium p-methoxybenzenesulphonate, IX, and potassium

4-methylnaphthalene-1-sulphonate, XI, by showing that the magnitude of the sulphur isotope effect is dependent upon bromide ion concentration. His results are shown in Table II.

TABLE II

EFFECT OF BROMIDE ION CONCENTRATION UPON SULPHUR ISOTOPE EFFECTS IN BROMODESULPHONATION REACTIONS

Sulphonate	$[Br^-]$ m./l.	k^{32} / k^{34}
 IX	0.0	1.0032 ± 0.0012
	0.03	1.0127 ± 0.0009
	0.50	1.0173 ± 0.0008
 XI	0.0	1.0023 ± 0.0008
	2.0	1.0075 ± 0.0007

It is seen that with both IX and XI, the isotope effect at zero bromide ion is very small, 0.02 to 0.03 per cent, which is the magnitude of a secondary isotope effect. With the methoxy compound, IX, the isotope effect is very sensitive to bromide ion concentration, increasing to 1.7 per cent at 0.50 molar bromide. This is about the maximum value to be expected for a reaction in which a bond to the

sulphur atom is ruptured in the rate-determining step. These results then firmly establish the intermediate complex mechanism for reaction of compound IX with molecular bromine. In the case of the naphthalene-sulphonate, the isotope effect, although very much less sensitive to bromide ion changes, nevertheless, does vary significantly. It was clearly demonstrated by Baliga that this change was not due simply to a salt effect. It would appear, therefore, that this compound also undergoes bromodesulphonation by the two-step mechanism. The relative insensitivity of its rate and isotope effect to bromide ion concentration can be accounted for on the basis of a very small k_{-1}/k_2 ratio.

The preceding discussion has shown that the role of an intermediate in electrophilic aromatic substitutions has been demonstrated unambiguously only in specific cases of the diazo-coupling reaction, bromodecarboxylation, and bromodesulphonation. In addition, both rate and isotope effect data obtained in other types of aromatic substitutions are entirely compatible with the two-step mechanism. It is probable then, that most, if not all, electrophilic aromatic substitution reactions follow this stepwise pathway. There is always the possibility, however, that certain reactions, particularly those in which the quinoid configuration corresponding to an intermediate might be expected to possess a high energy, might proceed by the one-step mechanism.

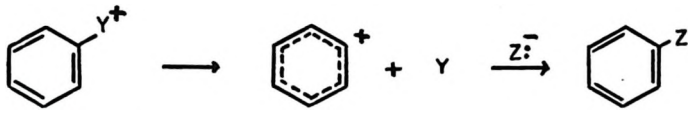
Nucleophilic Aromatic Substitution

The essential difference between electrophilic and nucleophilic aromatic substitutions is that, in the former, the aromatic substrate furnishes the electron pair forming the new bond while, in the latter, these electrons arise in the nucleophile. The nucleophilic reagent then is an entity carrying an unshared electron pair and may be charged on neutral. This reagent attacks a centre of low electron density on the aromatic ring and expels some atom or group as an anion or neutral molecule.

During the last ten years, it has been found that, unlike electrophilic aromatic substitutions, three distinct mechanisms are available for nucleophilic substitution reactions of aromatic compounds. These are (a) an unimolecular mechanism, (b) an elimination-addition mechanism, and (c) a bimolecular mechanism. Of the reviews (1, 2, 3, 62, 63, 64, 65) which have appeared on this subject of mechanism in the last decade, the most recent are by Bunnett (3, 65) and by Huisgen and Sauer (63, 64). It is proposed to give in this section of the thesis, a brief outline of the most significant work relating to the unimolecular and the elimination-addition

mechanism and, because of the nature of the present investigation, to attempt a full and critical discussion of the present status of our knowledge concerning the bimolecular pathway.

The unimolecular mechanism is a two-step sequence analogous to the S_N1 mechanism for nucleophilic aliphatic substitutions. The aromatic substrate first ionizes to an aryl cation, XII, and either an anion or a neutral molecule, and the former then reacts rapidly with any nucleophilic reagent present in the system, viz:



XII

...(65).

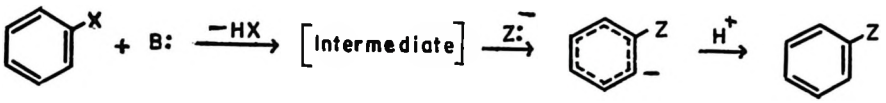
Only one reaction is known which definitely follows this pathway. This is the thermal decomposition of aryl diazonium salts in solution (66). These decompositions exhibit first order kinetics, but more importantly, their rates are unaffected by the kind or concentration of nucleophilic reagents present (67, 68), thus excluding the possibility of a bimolecular pseudo-first order reaction. The effect of substituents on rate supports

an S_N1 type of mechanism, rates being accelerated by electron-releasing and retarded by electron-withdrawing substituents in the meta position while being retarded by both electron-releasing and withdrawing groups in the para position (69). Hughes (70) explains this rather surprising effect of electron-releasing para substituents on the basis of a resonance interaction of the substituent with the diazonium group leading to an increased extent of double-bond character of the carbon-nitrogen bond. This lowers the energy of this bond in the gound state and leads to a higher activation energy for the ionization step.

Not all thermal decompositions of diazonium salts proceed by the unimolecular mechanism. For example, Lewis and Hinds (71) showed that p-nitrobenzenediazonium bromide, when heated in aqueous solution, yields p-nitrophenol and p-nitrobromobenzene by both the unimolecular and bimolecular mechanisms.

The elimination -addition ("aryne")mechanism is a process in which a strong base brings about the elimination of the elements of an acid ^{H}X from an aromatic ring.

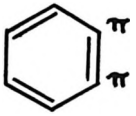
The resulting intermediate then adds any nucleophilic reagents present in the reaction mixture.



...(66).

The intermediate possesses an unusual bond and is variously represented as XIIIa or XIIIb. The name "aryne" arises from the obvious analogy to alkynes in the very common representation, XIIIa.

XIIIa

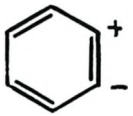


XIIIb

The exact nature of the bond represented by the triple line or by the double π is not known, but it has been suggested (82) that it is analogous to the cis -bent excited state of acetylenes (72).

The elimination-addition mechanism was reviewed comprehensively very recently (64, 65) so only a brief

outline will be presented in this thesis. The mechanism was first proposed by Wittig (73, 74, 75). He considered the reaction to involve the unusual intermediate, XIIIc,



XIII c

which was permanently polarized in the manner shown, and specifically rejected the formula XIIIa. Ten years later, this mechanism was placed on a firm basis by Roberts (76) who showed that nearly equal quantities of aniline-1-C^{14} and aniline-2-C^{14} result when chlorobenzene+C^{14} is treated with sodamide.

Other evidence in support of the elimination-addition mechanism include:

(a). the formation of 2-phenyl-1-naphthoic and 1-phenyl-2-naphthoic acids in the same ratio, 2:1, from the action of phenyllithium on 1-and 2-fluoronaphthalene (77);

(b). the formation of the same mixture of naphthylpiperidines on treatment of 1-chloro-, 1-bromo-, and 1-iodonaphthalene with piperidine and sodamide (78);

(c). the formation of a Diels-Alder adduct when o-bromofluorobenzene is treated with lithium or magnesium in the presence of furan (79) or anthracene (80);

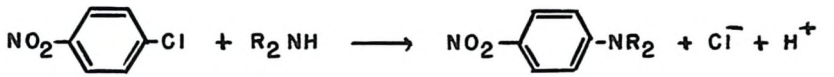
(d). the absence of reaction of halobenzenes lacking ortho hydrogens (81);

(e). the existence of a normal isotope effect, $k^H/k^D = 5.5$, in the reaction of bromobenzene and bromobenzene-2-D with potassium amide (82, 83);

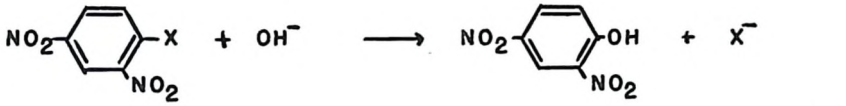
(f). the observation that iodobenzene-1-C^{14} and iodobenzene-1-C^{14}-2,4,6-D_3 give, on treatment with sodamide, exactly the same ratio of aniline-1-C^{14} to aniline-2-C^{14} (84); and finally,

(g). the recently reported spectroscopic evidence for the existence of gaseous "benzyne" (85).

The bimolecular mechanism is by far the most common pathway for nucleophilic aromatic substitution reactions. Some typical reactions known to follow this mechanism are as follows:



...(67)



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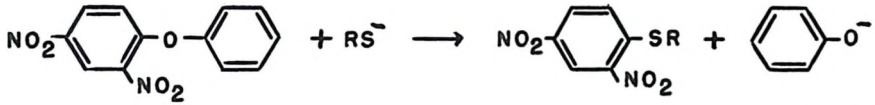
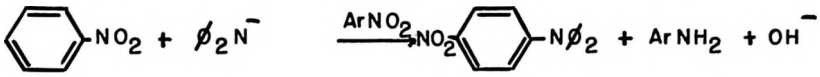


...(69)

These examples illustrate one of the major differences between electrophilic and nucleophilic aromatic substitutions. In the former, the group displaced is usually hydrogen while in the latter it is much more frequently some atom or grouping which can form a stable anion. It is not impossible to displace hydrogen by a nucleophilic reagent but this displacement is brought about only under very severe reaction conditions because of the

high energy required to form a hydride ion. Often, this difficulty can be overcome by carrying out the displacement in the presence of an oxidizing agent which converts the incipient hydride ion to the much more stable hydroxide ion (86, 87). Examples of such hydride eliminations are:



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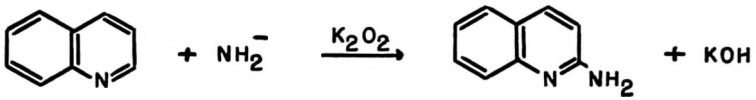


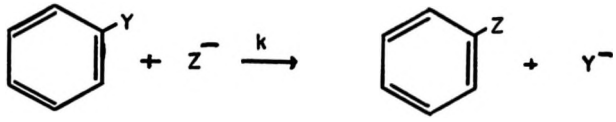
...(71)

Bimolecular nucleophilic aromatic substitutions conform to the criteria for bimolecular reactions listed by Hughes (88). The kinetics are second order, first order in each component, and rates increase with increasing nucleophilicity of the reagent. Rates are enhanced by electron-withdrawing substituents ortho or para to the reaction centre and are retarded by electron-releasing groups in these positions. The effects of these electron-withdrawing substituents upon rates correlate well with the Hammett σ^- constants for para substituents (89) showing

that these substituents are very strongly conjugated with the reaction centre.

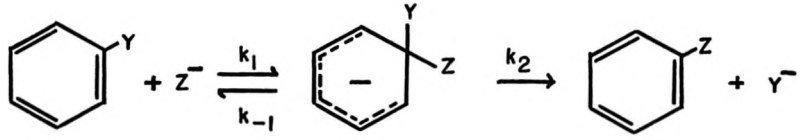
Nucleophilic aromatic substitutions do not proceed readily unless at least one electron-withdrawing substituent is present ortho or para to the reaction centre. Addition of a second or third activating group to the remaining ortho or para positions usually results in a rate increase (90) but, occasionally, the rate may be retarded (91, 92). The steric requirements for nucleophilic aromatic substitutions are not large because the approach of the nucleophile to the reaction centre is lateral to the plane of the ring but when very bulky substituents are present in both ortho positions, their steric effects may outweigh their electronic effects and, by hindering the approach of the nucleophile, they may increase, rather than decrease, the activation energy. Electron-withdrawing groups in the meta positions also may provide sufficient activation for reaction to take place (93), but if both ortho (or para) and meta substituents are present, rates generally are reduced from that of the substrate carrying only the ortho substituent. The meta substituent in the disubstituted compound prevents coplanarity of the ortho substituent with the ring and thereby reduces the extent of conjugation of this ortho substituent in the transition state (4).

The same question regarding the mechanism of bimolecular nucleophile aromatic substitution arises as in the case of electrophilic substitution. Does the reaction proceed by a one step process involving a single transition state:



...(72).

or does it proceed in two steps through an actual intermediate, XV?



XV

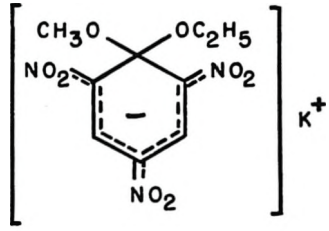
...(73).

This question has been the subject of some considerable controversy during the past ten years but at the time the work reported in this thesis was initiated, no evidence had been presented which favoured either mechanism. In 1952, Bunnett, in his Chemical Reviews article (1), strongly advocated the stepwise mechanism and, since that

time, has sought evidence in support of this point of view. Others, prominently Chapman, have upheld with equal fervor the concerted process, at least until very recently. The evidence which has been presented to date tends to favour a two-step mechanism involving a metastable intermediate very similar to that known to exist in some electrophilic substitutions. The remainder of this section will be devoted to a critical review of the work directed toward the solution of this problem of mechanism.

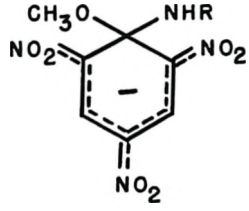
It has been known since the late eighteen hundreds that in certain nucleophilic aromatic substitutions stable intermediates may be isolated. The earliest of these stable intermediates were reported by Jackson (10). Upon mixing polynitrobenzenes with alcoholates, intensely coloured crystalline precipitates were obtained which had the composition of a 1:1 adduct of the two reagents. In a similar study, Meisenheimer (11) isolated from the reaction of methoxide ion with 2,4,6-trinitrophenetol, an intermediate which was shown to be identical to that obtained from ethoxide ion and 2,4,6-trinitroanisole.

The structure, XVI, was given to this adduct:



XVI

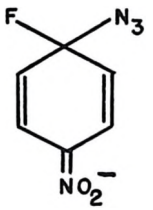
and this assignment has been confirmed recently by Forster from spectral measurements (94, 95). Other examples of stable adducts resulting from the reaction of strong nucleophiles with highly activated substrates have been reported, the most recent being a series of quinoid nitronates, XVII, which may be



XVII

formed either by the action of methoxide ion on trinitrophenylamines or by the action of amines on 2,4,6-trinitromethoxybenzene (12).

A particularly interesting study with a less highly activated system was reported in 1960 by Miller (96), who observed that, in the reaction of p-fluoronitrobenzene with sodium azide in dry dimethylformamide, azide ion is consumed in a first order process, yet no fluoride ion is formed and a spectral absorption characteristic of a quinoid structure makes its appearance at the same rate. The addition of water to the system brings about the formation of fluoride ion and p-azidonitrobenzene with the disappearance of the spectral absorption. These results constitute strong evidence for the formation of an intermediate, XVIII,



XVIII

which cannot proceed to products in the absence of a suitable solvating medium for fluoride ion. Other reactions yielding stable intermediates have been listed elsewhere (97).

The isolation and characterization of intermediates in nucleophilic aromatic substitutions is strong evidence in favour of the two-step mechanism, just as Cannell's proof of a stable quinoid intermediate in bromodesulphonation of sodium 3,5-dibromo-4-hydroxybenzenesulphonate, VI, is strong evidence for the corresponding mechanism in electrophilic aromatic substitution. One is not justified, however, in generalizing from those reactions in which stable intermediates have been obtained, to all nucleophilic aromatic substitutions. With the exception of the recent work of Miller, referred to above, all cases in which stable intermediates have been isolated have been with highly activated aromatic substrates and it is conceivable that these substrates utilize a reaction pathway not generally available to reactions of less highly activated compounds.

Proponents of both the stepwise and concerted mechanisms have cited, as support for their views, the relative reactivities in nucleophilic substitution of the various aryl halides. The normal order of reactivity observed is Ar-F > Ar-Cl > Ar-Br > Ar-I (98, 99) which is the reverse of the order of carbon-halogen bond strengths. This would suggest a transition state in which the carbon-halogen bond is still intact and has been considered by some to be evidence for the two-step mechanism in which formation of the intermediate is rate-determining.

It can be interpreted, alternatively, as a single step process in which bond rupture has been made little progress in the transition state. This latter interpretation assumes a potential energy curve of the type shown in Fig. 1(a)(page 20), while the former assumes a curve of the type shown in Fig. 2(a). The reverse order of halogen mobility, $I > Br \sim Cl \gg F$, also has been observed (100, 101) and this result may be interpreted in terms of either a concerted or two-step mechanism in which carbon hydrogen bond rupture is well developed in the transition state. The potential energy curves corresponding to this situation are shown in Fig. 1(b) and 2(b).

Chapman (4, 5, 6, 7, 8, 9) has argued that there is no need to invoke an intermediate to explain mobilities of halogen and effects of ring substituents. His explanation of the order of halogen mobilities is as follows. The rate of reaction is governed by two factors, the electronegativity of the halogen to be displaced and the strength of the carbon bond to be broken. The more electronegative the halogen, the lower will be the electron density at the site of substitution and, therefore, the smaller the repulsion energy between the attacking nucleophile and the substrate. The activation energy also will be smaller and the expected order of the rates will be $F \gg Cl \sim Br > I$. Carbon-halogen bond strengths

are, of course, C-F $\gg$ C-Cl $\sim$ C-Br $>$ C-I and, on the basis of this factor the expected order of rates would be the reverse, namely, I $>$ Br $\sim$ Cl $\gg$ F. The order observed in any particular reaction then will depend upon which of these two factors is called more strongly into play. Chapman expressed the view, that, until such time as the presence of an intermediate can be established, it is preferable to consider that nucleophilic aromatic substitutions proceed by a simple synchronous displacement mechanism.

The most direct way of determining whether or not a particular bond is broken in the rate-determining step of a reaction is by a study of the kinetic isotope effect. The role which such studies have played in the elucidation of the mechanism of electrophilic aromatic substitution has been discussed in some detail in the preceding section of this thesis. In nucleophilic aromatic substitutions, hydrogen is only displaced under reaction conditions quite unsuitable for isotope effect studies. The isotope effects associated with the heavier elements, nitrogen, sulphur, oxygen, or halogen, which commonly form the bond to carbon which is ruptured during reaction, are two to three orders of magnitude smaller than those for hydrogen isotopes and specialized equipment is needed to measure

them with any accuracy. For this reason, no isotope effect study of nucleophilic aromatic substitution has been reported to date.

After the work in this thesis had begun, a paper by Bunnett appeared reporting the results of a so-called "element effect" study which he considered to provide the same information concerning mechanism as would be given by a kinetic isotope effect study (102). What Bunnett did was to measure the rate and activation parameters for the reaction of piperidine with a series of 1-substituted-2, 4-dinitrobenzenes differing in the nature of the displaced atom or group in the 1-position. He reasoned that if the reaction were to follow a concerted mechanism, reaction rates for the members of the series would be expected to vary widely, since there would be a partial rupture of the bond to the displaced group in the transition state. On the other hand, similar rates for the individual members would imply a stepwise mechanism with formation of the intermediate rate-determining. The results of this study are shown in Table III.

TABLE III

RELATIVE RATES AND ARRHENIUS ENERGIES FOR REACTION OF 1- SUBSTITUTED-2,4-DINITROBENZENES WITH PIPERIDINE IN METHANOL

1-Substituent	Relative Rate Constant at 0°C	$E_{exp.}$ K-cal./mole
-F	3300	-
$-NO_2$	890	-
$-SO_2-C_6H_4-CH_3$	100	-
$-SO-C_6H_5$	4.7	10.8
-Br	4.3	11.8
-Cl	4.3	11.6
$-SO_2-C_6H_5$	3.2	12.0
$-O-C_6H_5$	3.0	10.5
-I	1.0	12.0

For reactions of the last six 1-substituents in Table III, which represent five different bonds to carbon, the rate variation is only about fivefold and, if reaction of the iodo compound were to be excluded, this variation is only about sixty per cent. The absence of an "element effect" shows that bond rupture cannot have made significant progress in the rate-determining step. In a two-step

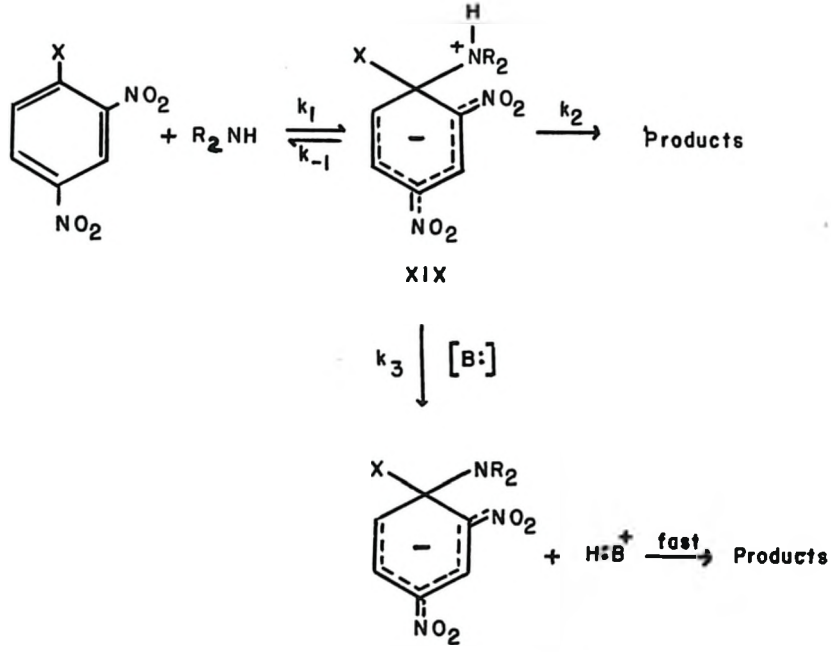
mechanism, this condition is met when formation of the intermediate is rate-controlling, and Bunnett's data, therefore, are entirely compatible with such a mechanism. It is possible, but less probable, that a one-step mechanism is operating. The electronic effects of the elements comprising the bond to carbon which is ruptured could conceivably lead to a fortuitous cancellation of energy differences from bond to bond, and thus lead to only minor rate variations. In any heterolysis of a bond of halogen, nitrogen, oxygen, or sulphur to an unsaturated carbon atom, there are two opposing factors governing the rate. One is the electro-negativity of the element, the other is the conjugation of the p electrons with the π electrons of the ring. With chlorine and bromine, for instance, the greater electronegativity of chlorine lowers the electron density at the reaction centre and would enhance the rate of the chloro compound over that of the bromo. On the other hand, the greater conjugation of the p electrons of chlorine with the π electrons of the ring in the ground state leads to a greater loss of resonance stabilization on assuming the transition state. This factor would retard the rate of the chloro compound compared to that of the bromo. Bunnett considered that a balance of these factors could account for the observed

constancy of rate for two, or possibly even three of the compounds studied but that such a cancellation of effects to occur for all five bonds was extremely improbable. He is probably correct,but it should be recalled that, even in S_N2 reactions of saturated compounds where the compensatory factor of conjugation is lacking, rates of chlorine, bromine, and iodine substitution do not vary widely (103).

There is a much more serious objection to Bunnett's argument that the lack of an element effect establishes the two-step mechanism. This is that the equivalence in rates can be interpreted just as well in terms of a concerted process in which bond rupture has made little progress in the transition state. It will be recognized that this is exactly the same objection as was raised by Hammond (21) with respect to Melanders conclusion that the absence of an isotope effect in electrophilic aromatic substitution establishes the two-step mechanism.

If, as Bunnett avers, these reactions do proceed through an intermediate, XIX, a proton must be removed from the amino nitrogen to form the products. The reaction, then, could be subject to base catalysis. A two-step

mechanism involving base catalysis may be written as:



...(74).

The rate expression for this mechanism is

$$\text{rate} = \frac{k_1\left[k_2 + k_3[B:]\right]}{k_{-1} + \left[k_2 + k_3[B:]\right]}\,[ArX][R_2NH] \qquad \ldots(75).$$

When $\left[k_2 + k_3[B:]\right] \gg k_{-1}$, this expression simplifies to

$$\text{rate} = k_1\,[ArX]\,[R_2NH] \qquad \ldots(76).$$

that is, the formation of the intermediate is the rate-controlling step. Under these circumstances, the number and modes of decomposition of the intermediate to products are of no consequence kinetically and base catalysis is not observed. When $k_2 + k_3 [B:]$ is very much smaller than k_{-1}, however, equation 75 reduces to

$$\text{rate} = \frac{k_1 [k_2 + k_3 [B:]]}{k_{-1}} [ArX] [R_2NH] \quad \ldots(77).$$

and base catalysis will be shown. The magnitude of this catalytic effect will, of course, depend upon the relative magnitudes of k_2 and k_3 for if $k_2 \gg k_3$ it is only at very high base concentrations that the term $k_3[B:]$ will contribute appreciably to the rate.

A number of studies have been carried out in recent years with the object of determining whether or not base catalysis can play a role in nucleophilic aromatic substitution. Bunnett (104) found no catalysis by hydroxide ion in the reactions of 1-chloro-, 1-iodo-, 1-benzenesulphono-, and 1-p-nitrophenoxy-2,4-dinitrobenzene with piperidine. Ross (25, 105, 106, 107, 108) on the other hand, observed base catalysis in the reactions of 1-chloro-, 1-bromo-, and 1-iodo-2,4-dinitrobenzene with butylamine. These observations are fully compatible with

the two-step mechanism outlined above; in reactions with piperidine, $k_2 + k_3 [B:] >> k_{-1}$, whereas in reactions with butylamine, the opposite relationship would hold. The results, however, also may be accommodated by a concerted mechanism. It is conceivable, in reactions with butylamine, that removal of the proton from the amine occurs concurrently with the attack of nitrogen upon the reaction centre and that the base, by assisting in proton removal, enhances the nucleophilic activity of the amine and thus increases the rate. Piperidine is a much stronger nucleophile and may not require the assistance of the base, the product of the rate-determining step being N-(2,4-dinitrophenyl)-piperidinium ion which then rapidly loses a proton to form the final product. While this concerted mechanism is less probable, Bunnett's and Ross' data do not eliminate it and these base catalysis effect studies cannot be considered unequivocal proof of a two-step mechanism.

Until this time, no single investigation directed toward distinguishing the one-step from the two-step mechanism had provided an unambiguous answer. Some of the experimental data could be explained more logically on the basis of a two-step mechanism, but other interpretations involving plausible concerted processes were not excluded. In late 1958, as the work reported in this thesis was

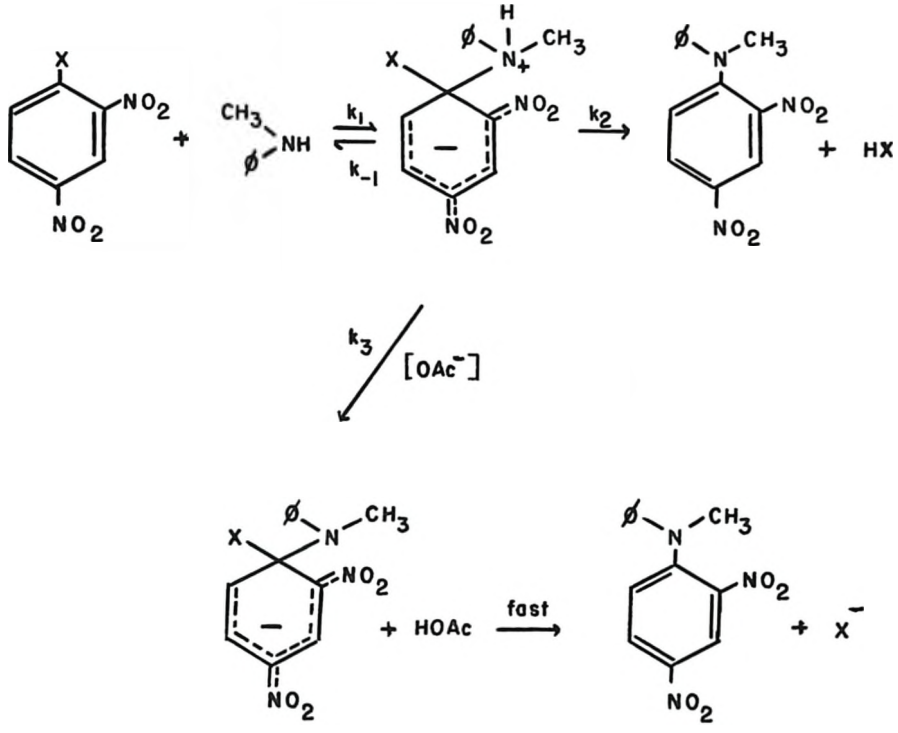
being concluded, an important paper by Bunnett and Randall appeared which can be said to have established the stepwise mechanism for some typical nucleophilic aromatic substitutions (109). Because of the importance of this paper, it will be reviewed in some detail.

The reaction of N-methylaniline with 1- fluoro-, 1-chloro-, and 1-bromo-2,4- dinitrobenzene in ethanol is second order, first in each reactant, and the relative rates of reaction are in the order, Br $\rangle$ Cl $\rangle\rangle$ F. The reaction of the fluoro compound, but not of the chloro or bromo, is subject to catalysis by acetate ion. This catalysis is of the general base type and shows a linear response of rate with base concentration up to the highest concentrations experimentally attainable. A mechanism involving the interaction of acetate ion with N-methylaniline to convert it to the much more reactive nucleophile, N-methylanilide ion,

$$CH_3COO^- + C_6H_5NHCH_3 \rightleftharpoons CH_3COOH + C_6H_5\ddot{N}CH_3^- \quad \ldots(78).$$

is ruled out because this would lead to a specific base catalysis. Consistent with these results is a two-step process identical to that postulated for reaction of piperidine or butylamine with these halodinitrobenzenes:

Mechanism I



...(79).

with an identical rate expression (equation 75) so that

$$k_{obs} = \frac{k_1 \; k_2 + k_1 \; k_3 \; [OAc^-]}{k_{-1} + k_2 + k_3 \; [OAc^-]} \qquad \ldots(80).$$

When $k_2 + k_3 [OAc^-] \gg k_{-1}$, this equation reduces to

$$k_{obs} = k_1$$

and the reaction is insensitive to acetate ion. If, however, $k_{-1} \gg k_2 + k_3 [OAc^-]$, equation 80 becomes

$$k_{obs} = \frac{k_1 k_2}{k_{-1}} + \frac{k_1 k_3}{k_{-1}} [OAc^-] \qquad \ldots(81).$$

and the rate is a linear function of the acetate ion concentration. It is entirely reasonable that k_2 would be very much greater for rupture of a carbon-chlorine or carbon-bromine bond than for rupture of a carbon-fluorine bond, and the difference in sensitivity to acetate ion for these three substrates is, therefore, readily understood.

Other interpretations, however, are not entirely excluded by the observed kinetics. The following mechanism involving the reversible displacement of halide by amine in either a concerted or stepwise process followed by removal

of a proton from nitrogen by solvent or base:

Mechanism II

$$ArX + C_6H_5NHCH_3 \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} Ar\overset{+}{N}H(CH_3)C_6H_5 + X^-$$

$$Ar\overset{+}{N}H(CH_3)C_6H_5 + Solvent \xrightarrow{k_2} ArN(CH_3)C_6H_5 + Solvent.H^+$$

$$Ar\overset{+}{N}H(CH_3)C_6H_5 + OAc^- \xrightarrow{k_3} ArN(CH_3)C_6H_5 + HOAc \qquad ...(82).$$

leads to exactly the same rate expression as does Mechanism I. For a linear response of rate to the acetate ion concentration, however, it is necessary to postulate $k_{-1}[F^-] \gg k_3[OAc^-]$. This would seem most unlikely since it is well known that acetate ion is a much more powerful nucleophile than is fluoride.

There is a third mechanism which conceivably could account for the observed catalysis of the fluoro compound. This involves the formation of a hydrogen-bonded complex between the acetate ion and the amine followed by reaction of this complex, either by a concerted or stepwise mechanism, with the aryl fluoride.

Mechanism III

$$OAc^- + NH(CH_3)C_6H_5 \overset{K}{\rightleftharpoons} AcO^- \cdots\cdots HN(CH_3)C_6H_5$$

$$AcO^- \cdots\cdots HN(CH_3)C_6H_5 + ArF \xrightarrow{k'} ArN(CH_3)C_6H_5 + HOAc + F^- \quad \ldots(83).$$

The kinetic expression for mechanism III is

$$\text{rate} = K\,k'\,[ArF]\,[C_6H_5NHCH_3]\,[OAc^-] \quad \ldots(84).$$

This mechanism should be easily distinguished from mechanism I for equations 75 and 84 predict quite different rate behaviour with respect to base concentration. In mechanism I, when acetate concentration is increased to the point where $k_3\,[OAc^-] \gg k_{-1}$, equation 75 reduces to

$$k_{obs} = k_1$$

and the rate becomes insensitive to further increases in base concentration. For reaction by mechanism III, however, equation 84 predicts a strictly linear dependence of rate with base concentration at all acetate concentrations. The catalysis by acetate ion, it will be remembered, does indeed remain linear in base concentration over the experimentally realizable range and, therefore, no distinction between mechanisms I and III is provided. When Bunnett and Randall turned to a more powerful base,

hydroxide ion in aqueous dioxane, they made the important observation that a plot of the rate constant versus hydroxide ion concentration is not linear, but rather shows a decreasing slope at higher base concentrations. This result is in accord with mechanism I and would seem to be quite incompatible with any one-step mechanism. The results of this investigation, therefore, constitute the most convincing evidence in support of an intermediate thus far presented. The only reservation of the author of this thesis relates to the precision of the hydroxide ion catalysis data. Inspection of Bunnett and Randall's plot of rate constant versus base concentration shows the deviation from linearity at the lower base concentrations, the region in which the authors consider the data to be most precise, is small, while at higher base concentrations, where departures from linearity are most marked, the data, regrettably, is not particularly reproducible. In all probability, Bunnett's and Randall's conclusions regarding mechanism are correct, but the evidence upon which these are based cannot be considered to be entirely unambiguous.

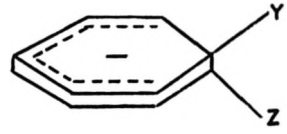
Base catalysis implies the rupture of a carbon-hydrogen bond in the rate-determining step and one would expect to observe a hydrogen isotope effect. An early

study by Hawthorne (110) of isotope effects in the reactions of o- and p-nitrochlorobenzenes with piperidine and N - deuteropiperidine showed that the aromatic substrates react with the isotopic amines at idential rates within experimental error. It was not known, however, if these reactions are subject to base catalysis and this result then does not shed any light upon the details of the mechanism. Ross (108) measured the rates of reaction of butylamine and N,N-dideuterobutylamine with 1-chloro-2,4-dinitrobenzene, a reaction known to be subject to base catalysis and, surprisingly, observed no isotope effect, $k^H/k^D = 1.0$. This might seem anomolous since the two results, base catalysis and no isotope effect, would appear to be mutually incompatible. Recently, Westheimer (111) has drawn attention to the large variations observed in the magnitude of isotope effects for reactions known to involve carbon-hydrogen bond rupture in the rate-determining step. In a detailed treatment, he has shown that a proton abstraction with an accompanying bond formation may exhibit a zero, or even a reverse isotope effect. In Ross' system, proton abstraction, indeed, is accompanied by formation of a new bond to hydrogen and the observation of a zero isotope effect then is compatible with base catalysis.

At this point, it may properly be asked: "What is the probable structure of this intermediate and of the transition state leading to its formation and decomposition?"

Bunnett (112) has discussed the structure of the symmetrical species formed along the reaction path and has come to the conclusion, on quantum mechanical grounds, that whether it corresponds to a potential energy maximum and is thus a transition state, or to a potential energy minimum and is, therefore, an intermediate, it has sp^3 hybridization of carbon at the reaction centre and does not possess benzenoid resonance. The resonance stabilization of the aromatic ring is lost, but this is partially offset by formation of a pentadienate resonance hybrid which also has an appreciable resonance stabilization (113).

The intermediate postulated for nucleophilic aromatic substitutions then may be represented as XX.



XX

with the bonds to Y and Z being directed above and below the plane of the ring. This is essentially the same as the intermediate which has been postulated in electrophilic aromatic substitutions (114, 115).

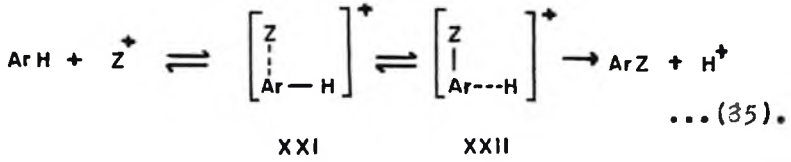
The nature of the transition state for formation of such an intermediate in electrophilic substitution has been considered by Dewar (116) and Mason (117). From their work on nitration (Dewar) and chlorination (Mason) they have concluded that, in the transition state, the attacking reagent is relatively remote from the site of substitution, and the hybridization of the carbon atom comprising this site is intermediate between sp^2 and sp^3, the amount of sp^3 hybridization depending upon both the attacking reagent and the aromatic substrate. In general, the less selective (ie., the more reactive) the attacking reagent is, the smaller will be the amount of sp^3 hybridization of the developing bond and the more the transition state will resemble the reactants. On the other hand, the more reactive the aromatic substrate undergoing substitution, the greater will be the amount of sp^3 hybridization and, therefore, the more closely the transition state will resemble the intermediate.

It would appear logical that, in nucleophilic aromatic substitutions a very reactive attacking species

would not require much interaction with the aromatic substrate to force the configuration of the reacting system into one resembling the postulated intermediate and, therefore, the transition state of this process would not involve any great change in the hybridization at the reaction centre. When the aromatic substrate is very reactive, the tendency to form sp^3 hybridized carbon atom at the substitution site is very high and only slight interaction with the attacking reagent would be necessary for assumption of the intermediate configuration. The transition state then would resemble the intermediate rather than the reactants. One would expect, then, that transition states in both nucleophilic and electrophilic aromatic substitution reactions to be rather similar.

In recent years, a theory of aromatic substitution has been developed by Fukui and his co-workers (118, 119). This theory, termed the "Frontier Electron Theory", assigns a dominant role to the lowest unoccupied and highest occupied molecular orbitals of the reagent and the substrate and, in principle, makes no distinction between nucleophilic and electrophilic substitutions. From this theory, Fukui (119) and Brown (120) have postulated two different reaction pathways for aromatic substitutions. Brown considered electrophilic

substitutions to proceed through two unsymmetrical charge-transfer complexes, XXI and XXII, as follows:



...(35).

XXI XXII

while for the same process, Fukui visualizes a mechanism which he describes as a continuous transfer of charge with electrons "oozing" from the substrate to the electrophile to form a "Wheland" intermediate.

Recently, Fukui has compared the two approaches (121) and has shown that they lead to mutually contradictory conclusions regarding the relationship between reactivity and the extent of charge transfer to the attacking reagent. Brown's treatment predicts that the less reactive the position on the aromatic ring, the greater will be the extent of charge transfer through this position to the attacking reagent. The developing bond in the transition state then would exhibit a greater degree of sp^3 hybridation for less reactive aromatic hydrocarbons. Fukui's treatment predicts the opposite, namely, that the extent of charge transfer is greater in more reactive positions and, in the transition state, the developing bond will contain more sp^3 character with more reactive aromatic

compounds. All in all, Fukui's treatment appears to be a mathematical statement of Dewar's and Mason's conclusions. Since this treatment does not distinguish between electrophilic and nucleophilic aromatic substitution processes, it would seem valid to consider transition states in nucleophilic substitutions to be essentially the same as those in electrophilic substitutions.

While there is no definite evidence as to the structure of the transition state for decomposition of the intermediate to products, it is known that in certain reactions at least the bond between carbon and the leaving group has undergone appreciable stretching in this transition state.

The earlier discussion has shown that it is not necessary to postulate a stepwise mechanism involving an intermediate for all aromatic substitution reactions; frequently a one-step process is adequate to explain the experimental data. The intermediate represents a potential energy well along the reaction coordinate, and the stability of the intermediate is indicated by the depth of this well. A gradation in depth of the potential well is to be expected and, indeed, such a gradation has been observed in both nucleophilic and electrophilic aromatic substitutions. The Meisenheimer adducts are

stable enough to be isolated, Miller's adduct could be detected spectroscopically but was not sufficiently stable to be isolated, and, finally, Bunnett's intermediate in the reaction of N-methylaniline and 2,4- dinitrohalobenzenes was not sufficiently stable to be detected spectroscopically but was known to be present from kinetic studies. With further decreases in stability, the potential well, eventually, will become equivalent to the saddle point of the transition state. Indications of such a situation are evident in Cannell's work upon bromodesulphonation. In some examples of this electrophilic substitution reaction, the intermediate had sufficient stability to be detected spectroscopically, in others, its presence was shown only by inference, while in still another, its presence could not be demonstrated. In the limit, of course, the difference between a reaction having two transition states and a very unstable intermediate and one having a single transition state with an unusually deep saddle point is negligible and the distinction between a concerted and a stepwise mechanism then disappears. Indeed, as Zollinger has pointed out (13), when the energy well for the intermediate is less than 0.6 kilocalories deep, the thermal motions of the system are such that the intermediate is largely by-passed.

No evidence has been presented which excludes a two-step mechanism for any aromatic substitution and, in certain reactions, this mechanism is strongly favoured. The balance of evidence, therefore, would indicate that most, if not all, aromatic substitutions proceed by mechanisms involving metastable intermediates. In the earlier discussion of electrophilic aromatic substitution reactions, it was shown that by far the most significant contributions to the problem of distinguishing between the concerted and intermediate-complex mechanism had been provided by kinetic isotope effect studies. In principle, such studies should be equally fruitful in the elucidation of the mechanism of nucleophilic aromatic substitutions but, as was pointed out earlier in connection with Bunnett's "element effect" work, the problem is rendered much more difficult because the displaced group is not hydrogen but rather one of much higher mass such as halogen, oxygen, nitrogen, or sulphur. The normal isotope effects associated with these elements are very small, of the order of one to four per cent, and very few laboratories are equipped to make such measurements with the accuracy necessary for meaningful results.

In undertaking the first kinetic isotope effect study of nucleophilic aromatic substitution, it was recognized that, as with electrophilic substitution, the

magnitude of the effect, by itself, does not settle the question of a reaction intermediate. It does indicate, however, in a way that is much more reliable than the so-called "element effect", the extent to which the bond to the displaced atom is broken in the rate-determining step. This, as Hammond (21) has pointed out so emphatically, is perhaps of even greater importance than the knowledge of whether or not a highly unstable intermediate is formed along the reaction pathway. Nevertheless, it was hoped that the isotope effect study would shed some light on the question of an intermediate.

It will be recalled that with electrophilic substitutions it was the variation in isotope effect with change in concentration of some species capable of reacting with the intermediate that provided unequivocal proof of the existence of this intermediate. When this work was started, there appeared to be no obvious way of doing this by means of an added reagent. (Base catalysis had not been detected at this time, and Hawthorne's zero isotope effect suggested that no such catalysis would be found). It was hoped, however, to accomplish the same thing by changing the solvent. The reasoning was as follows. For a concerted process, changes in solvent would be expected to alter only slightly the position of

the energy barrier along the reaction coordinate and, therefore, would have only a small (second order) effect upon the magnitude of the isotope effect. On the other hand, the change from a non-polar to a polar solvent would be expected to exert a very considerable effect upon the relative heights of the two energy barriers of the two-step mechanism since the magnitude and the distribution of charge in the two transition states is very different. If this were to be the case, one might go from the situation in which $k_{-1} \gg k_2$ to the reverse and, as a result, bring about a large variation in magnitude of the isotope effect.

EXPERIMENTAL METHODS AND RESULTS

Introduction

The experimental work described in this thesis consisted of two parts:

(a) a kinetic study of the reaction of 2,4-dinitrodiphenylsulphone with piperidine in the solvents, benzene, methanol, and acetonitrile;

(b) a sulphur isotope study of this reaction in the three solvents.

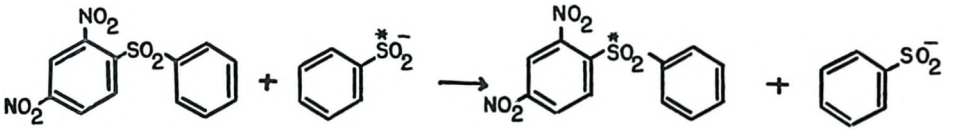
Standard methods of investigation of the kinetics were used and are described in detail later, in the following section of the thesis.

An isotope effect may be evaluated by comparing the isotopic ratio for the atom in question in the product of reaction carried out to some small known extent with the ratio for this atom in the starting compound. The latter is usually obtained from the product of complete reaction. It is necessary, therefore, to devise procedures whereby the small amount of product can be separated from the much larger amount of reactant and then degraded to a form suitable for mass-spectrometric analysis.

In the present investigation, this involved the separation of benezenesulphinic acid from 2,4-dinitrodiphenylsulphone and the conversion of sulphinate sulphur to barium sulphate and thence to sulphur dioxide.

It is, of course, essential that these separation and degradation procedures do not themselves introduce any significant isotopic fractionation which could either augment or reduce the fractionation produced by the reaction under investigation. For this reason, it was necessary to establish that the reactions employed either proceed quantitatively, or were unaccompanied by isotopic fractionation.

Since isotopic fractionation may arise from equilibrium as well as from kinetic processes, it was necessary also to establish the absence of any exchange process which could conceivably give rise to an isotopic effect not associated with the reaction under investigation. Of particular concern was a possible isotopic exchange of sulphur between the sulphone and benzenesulphinate ion:



...(86).

To test for this exchange, 2,4-dinitrodiphenylsulphone was treated with piperidine in the presence of carbon-14 labelled benzenesulphinic acid and the reaction allowed to proceed to the extent normally permitted in the kinetic isotope effect experiments. From the amount of carbon-14 incorporated into the unchanged sulphone the extent of isotopic exchange taking place under the usual reaction conditions then could be calculated. The results of this exchange test are given immediately following the description of the experiments used to evaluate the separation and degradation procedures.

A final section deals with the mass-spectrometric measurements and the calculation of isotopic effects.

Materials

Inorganic Reagents used in the kinetic and isotope effect studies were of analytical reagent grade. To ensure that contamination with extraneous sulphate was kept to a minimum, all reagents were assayed before use. If the sulphate content of the reagent was such as to yield barium sulphate in excess of three per cent of that formed from benzenesulphinic acid, the reagent was rejected. Normally, sulphate contamination from a reagent was less than one half of one per cent, and the total contamination

from all reagents was less than four per cent. Since the isotopic composition of the sulphur present in the reagents would not differ from that produced from benzenesulphinic acid by more than six per cent (122), the maximum variation in the natural abundance of sulphur isotopes, and since the products of partial and of complete reactions were treated with exactly the same quantities of the same reagents, the maximum error in the kinetic isotope effect values resulting from this contamination would be less than a tenth of one per cent.

2,4-Dinitrodiphenylsulphone was prepared by the oxidation of 2,4-dinitrodiphenylsulphide with aqueous potassium permanganate, following the general procedure of Vogel (123). The product was recrystallized from ethanol to a constant uncorrected melting point, 161-162°C.; lit. m.p. 161°C.; (124).

Piperidine. Eastman Kodak White label grade, was dried over sodium hydroxide pellets and then distilled. A middle fraction, b.p. 106-106.5°C.; obtained from a second distillation was used in the kinetic and isotope effect experiments.

Benzene, Fisher Scientific Co., Thiophene Free, A.C.S. Reagent Grade, was used without further purification.

Methanol. Carbide and Carbon Co., Anhydrous, was redistilled and a middle fraction, b.p. 62.2-62.5°C., was used in all kinetic and isotope effect experiments.

Acetonitrile. Fisher Scientific Co., A.C.S. Reagent Grade, was used without further purification.

The three solvents, benzene, methanol, and acetonitrile, were not assayed for sulphur directly, but blank runs carried out in these three solvents yielded amounts of barium sulphate which were below the limits of determination.

Benzene-C^{14}-sulphinic Acid was prepared by a zinc dust reduction of benzene-C^{14}-sulphonyl chloride obtained by the reaction of chlorosulphonic acid upon benzene-C^{14}.

Radioactive benzene, obtained from Atomic Energy of Canada Ltd., was diluted with ordinary benzene, using vacuum techniques, to give a reactant with an activity of 0.518 millicuries per mole. Chlorosulphonic acid (35.0 g., 0.30 mole) was reacted with benzene-C^{14} (7.8 g., 0.10 mole) according to the directions of Clark et al (125) to yield benzene-C^{14}-sulphonylchloride; b.p. 117-118°C. at 14 mm.; 9.9 g., 56.4 % yield. Lit. b.p. 113-114°C. at 10 mm. (125).

Benzene-C^{14}-sulphinic acid was prepared using a procedure based on the method outlined by Hickenbottom (126).

Zinc dust (10.0 g., 0.152 mole) was added cautiously in small portions to the benzene-C^{14}-sulphonyl chloride dissolved in 100 ml. of wet ether and contained in a 250 ml. round-bottomed flask fitted with a reflux condenser. When all the zinc dust had been added, the reaction mixture was refluxed for one hour, the suspension was filtered and the solids were dried at room temperature in vacuo. The dried solids were suspended in 100 ml. of a 20% aqueous sodium carbonate solution and heated at reflux temperature until no further change was noted in the appearance of the suspension. This required two and a half to three hours.

The solids were removed and benzene-C^{14}-sulphinic acid was precipitated from the filtrate by the cautious addition of hydrochloric acid. The product, recrystallized from water, yielded 4.0 g., 50.0 %; m.p. 82-83°C. (uncorrected); lit. m.p. 84°C. (127).

Additional sulphinic acid was isolated as the ferric salt from the combined aqueous solutions by the addition of ferric chloride solution. The total conversion, based upon benzene-C^{14}-sulphonylchloride, was 97.0 %.

Kinetic Studies

General

A spectroscopic method developed by Bunnett and his co-workers (102) was used to follow the rate of reaction of 2,4-dinitrodiphenylsulphone with piperidine in the three solvents. The product, N-(2,4-dinitrophenyl)-piperidine exhibits a strong absorbtion at 385 mμ., while the absorption of the other components of the reaction mixture at this wavelength is negligible.

The method, briefly, was as follows. A small aliquot of the reaction mixture was withdrawn at regular time intervals and added to a quenching solution of 0.1 N sulphuric acid in 50 per cent by volume aqueous ethanol. On completion of the experiment, these samples were diluted to a standard volume with additional quenching solution and their optical densities were determined at 385 mμ. The concentrations of these solutions were read from a previously prepared graph relating concentration of the product, N-(2,4-dinitrophenyl)-piperidine, to optical density.

Rather than synthesizing a pure sample of N-(2,4-dinitrophenyl)-piperidine for the preparation of

this concentration versus optical density plot, it was assumed that a known concentration of compound, corresponding to one hundred per cent reaction, resulted when 2,4-dinitrodiphenylsulphone had reacted with excess piperidine for many half-lives. In this way, a series of solutions of known concentration were prepared, and their optical densities were measured. That this assumption was justified was shown by the fact that the optical density measured by Bunnett (102) for a solution of known concentration of authentic N-(2,4-dinitrophenyl)-piperidine fell directly on the straight line obtained in the present work.

Rate constants for the reaction were determined at 10, 25, and 40°C. in benzene, at 0, 10, 20, 30 and 40°C. in acetonitrile, and at 0, 25, and 40°C. in methanol. These rate constants were used to evaluate the enthalpies and entropies of activation for the reaction in each of the three solvents.

Procedures

Standard solutions of 2,4-dinitrodiphenylsulphone and of piperidine were prepared. The former was stored in the dark at room temperature, while the latter was

stored in the constant-temperature bath. A 10 ml. aliquot of the sulphone solution was placed in a 100 ml. volumetric flask and enough solvent was added to fill the flask about three-quarters full. The flask was placed in a constant-temperature bath and allowed to stand for three to four hours, then a 10 ml. aliquot of the standard piperidine solution was added. The solution was made up to 100 ml. with additional solvent and vigorously shaken. These operations were carried out as rapidly as possible and normally required slightly less than one minute.

Two milliliter samples were withdrawn from the reaction vessel at regular time intervals and were added to approximately 40 ml. of quenching solution contained in 50 ml. volumetric flasks. Upon completion of the experiment, these flasks were filled to the mark with additional quenching solution. The resulting solutions were mixed thoroughly and their optical densities were determined at 385 mμ. using a Perkin-Elmer Model 4000 Spectracord Spectrophotometer. The concentrations of N-(2,4-dinitrophenyl)-piperidine were read from the previously prepared plot of optical density versus concentration.

Rate studies were carried out in benzene and methanol using pseudo-first order conditions, the piperidine component being in about thirty-fold in excess. The pseudo-first order rate constant, k', is given by the expression;

$$k' = \frac{2.303}{t} \log \frac{a}{a-x} \qquad \ldots(87).$$

where a is the initial concentration of sulphone and x is the amount of N-(2,4-dinitrophenyl)-piperidine present at time t. The constant k' was calculated by plotting $\log \frac{a}{a-x}$ against time. The best fit of the line to the points was obtained by a least squares treatment of the data. The second order rate constant, k, was calculated from the pseudo-first order constant by dividing k' by the concentration of piperidine.

The reaction in acetonitrile was too rapid to permit the measurement of rate constants under pseudo-first order conditions. These rate constants therefore were evaluated using second order conditions with the piperidine component approximately three-fold in excess. The reaction follows a second order rate law, viz;

$$k = \frac{2.303}{t(b-2a)} \log \frac{a(b-2x)}{b(a-x)} \qquad \ldots(88).$$

where a and b are the initial concentrations of sulphone and piperidine respectively, and x is the concentration of N-(2,4-dinitrophenyl)-piperidine at time t. The terms 2a and 2x appear in this expression because a second mole of piperidine reacts with the benzenesulphinic acid to form the piperidinium salt which is non-reactive.

The second order rate constant, k, was evaluated from the slope of the line obtained by plotting log $\frac{b-2x}{a-x}$ against time, the best fit to the data again being obtained by the least squares treatment.

In an earlier preliminary study, the kinetics of the reaction in benzene were measured under second order conditions. The temperature control in these experiments was not as precise as in those above but, in spite of this obvious defect, the results are in surprisingly good agreement with those obtained under pseudo-first order conditions. The rate constants, therefore, are listed with the others in Table IV.

Sample Kinetic Determinations

A representative experiment is presented in detail for each of the solvent systems. The data obtained in each experiment were used to construct a graph from which

the rate constant for the reaction was calculated. The remainder of the rate constants were obtained in a similar manner, and the results of all the rate constant determinations are summarized in Table VII.

TABLE IV

THE REACTION OF 2,4-DINITRODIPHENYLSULPHONE WITH PIPERIDINE[a] IN BENZENE AT 25°C.[b]

EXPERIMENT IV 114

Sample Number	Time min.	(x) m./l. x10^5	(a-x) m./l. x10^5	log $\frac{a}{a-x}$
I	3	7.3	93.2	0.0327
II	6	15.8	84.7	0.0741
III	9	23.3	77.2	0.1144
IV	12	28.5	71.9	0.1450
V	15	33.0	67.4	0.1730
VI	18	38.4	61.9	0.2100
VII	21	42.0	58.5	0.2352
VIII	24	46.7	53.7	0.2721
IX	27	50.0	50.4	0.2992
X	30	54.1	46.3	0.3351
XI	33	57.3	43.1	0.3660
XII	36	61.2	39.2	0.4088

(a) Initial concentration of sulphone was 1.004 x 10^{-3} m./l. and that of piperidine was 4.050 x 10^{-2} m./l.

(b) The reaction temperature was 25.05 ± 0.06°C.

Calculation of rate constant:

$$\text{Slope}_{(\text{least squares})} = 0.01029 \text{ min}^{-1}.$$

$$k' = 2.303 \times 0.01029 \text{ min.}^{-1}$$

$$k = \frac{2.303 \times 0.01029}{0.04050}$$

$$= 0.586 \text{ l. mole}^{-1}. \text{ min}^{-1}.$$

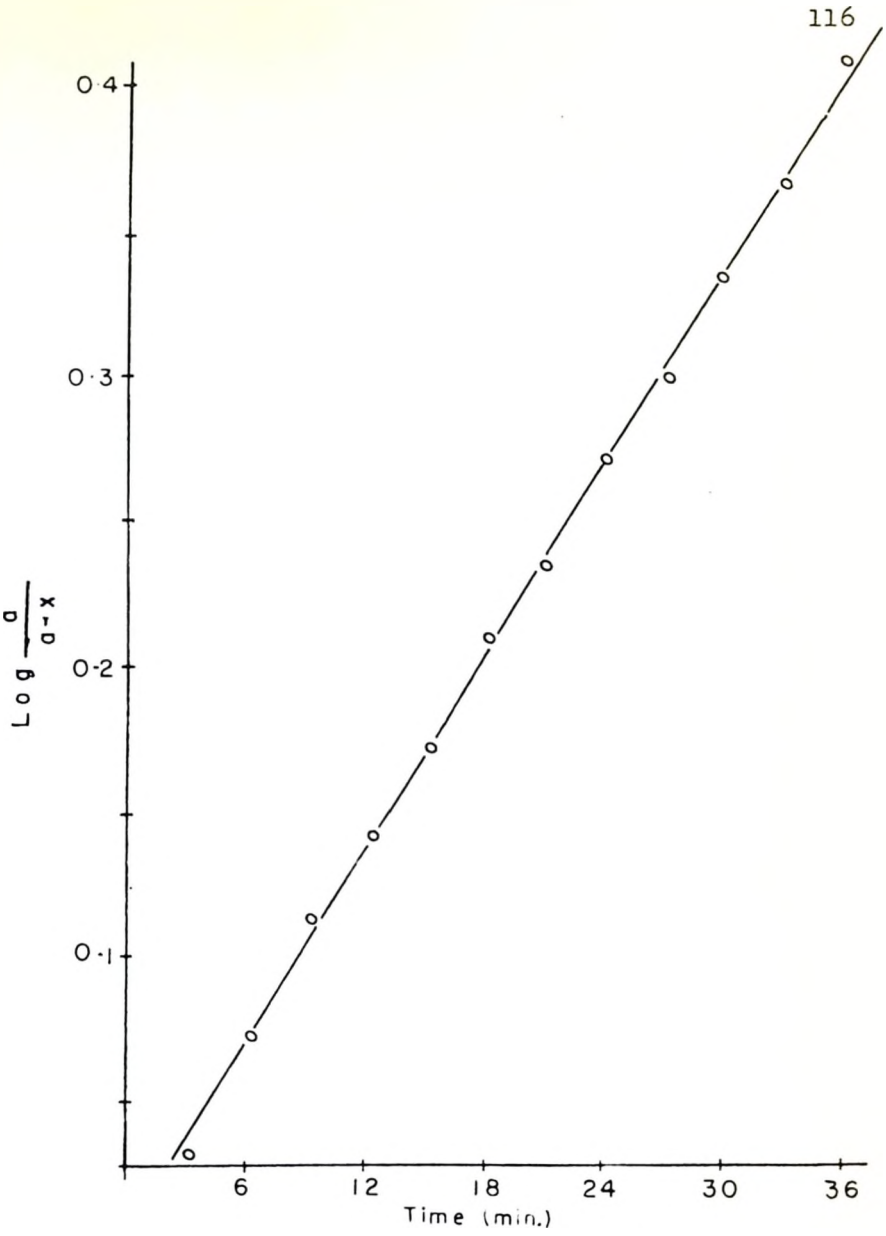


Fig. 3. Kinetic plot of a typical run in benzene for the reaction of 2,4-dinitrodiphenylsulphone and piperidine. The data were taken from Table IV.

TABLE V

THE REACTION OF 2,4-DINITRODIPHENYLSULPHONE WITH PIPERIDINE[a] IN METHANOL AT 0°C.[b]

EXPERIMENT IV 108

Sample Number	Time min.	(x) m./l. x10^5	(a-x) m./l. x10^5	$\log \frac{a}{a-x}$
I	10	3.1	84.8	0.0156
II	20	6.0	81.9	0.0307
III	30	8.6	79.3	0.0447
IV	45	12.5	75.4	0.0666
V	60	16.1	71.8	0.0879
VI	75	19.7	68.2	0.1102
VII	90	22.3	65.6	0.1271
VIII	105	25.4	62.5	0.1481
IX	120	28.6	59.3	0.1709
X	135	31.0	56.9	0.1889

(a) Initial concentration of sulphone was 3.79 x 10^{-4} m./l. and of piperidine was 4.001 x 10^{-2} m./l.

(b) The reaction temperature was 0.00°C.

Calculation of rate constant:

$$\text{Slope}_{(\text{least squares})} = 0.001452 \text{ min}^{-1}.$$

$$k' = 2.303 \times 0.001452 \text{ min}^{-1}.$$

$$k = \frac{2.303 \times 0.001452}{0.04001}$$

$$= 0.0836 \text{ l. mole}^{-1}. \text{ min}^{-1}.$$

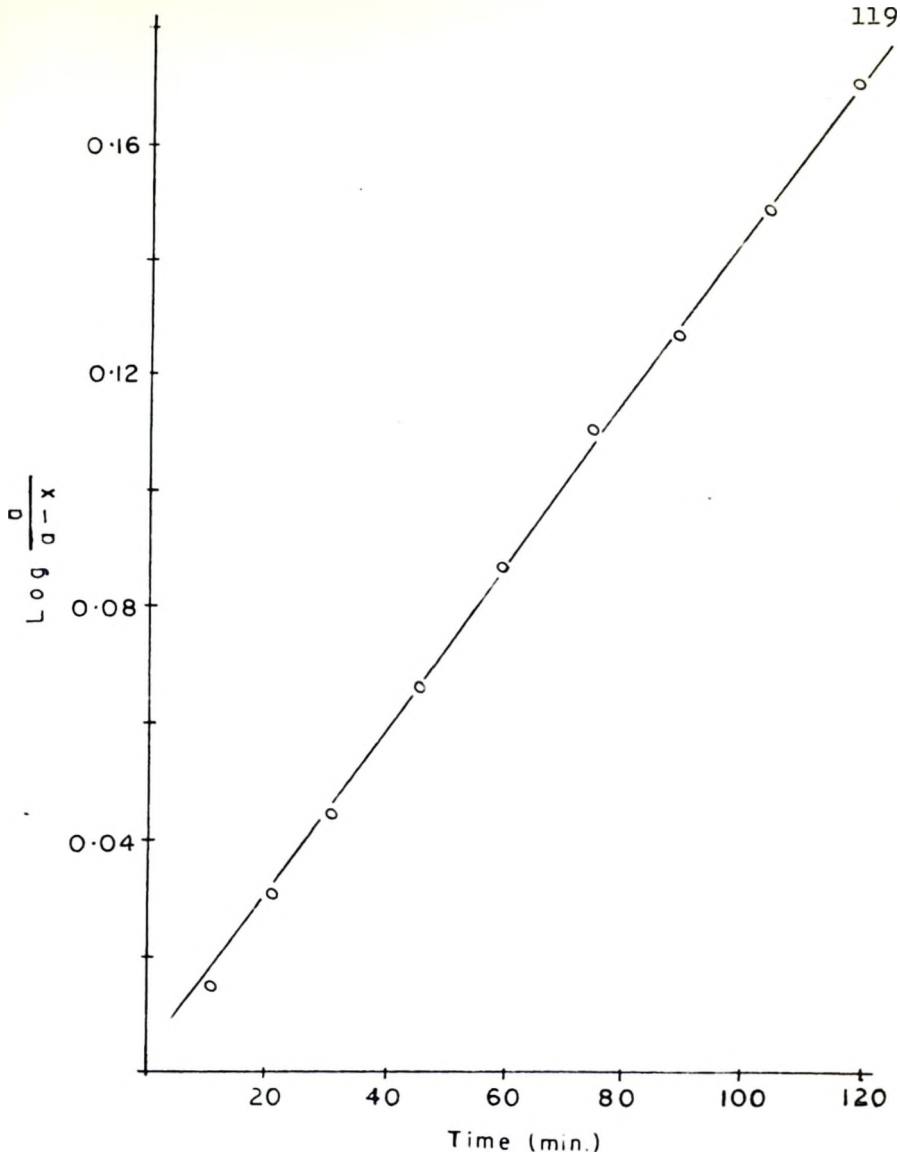


Fig. 4. Kinetic plot of a typical run in methanol for the reaction of 2,4-dinitrodiphenylsulphone and piperidine. The data were taken from Table V.

TABLE VI

THE REACTION OF 2,4-DINITRODIPHENYLSULPHONE WITH PIPERIDINE[a] IN ACETONITRILE AT 20°C.[b]

EXPERIMENT IV 138

Sample Number	Time min.	(x) m./l.x10^5	(b-2x) m./l.x10^5	(a-x) m./l.x10^5	log $\frac{b-2x}{a-x}$
I	5	8.8	185.0	57.4	0.5034
II	10	14.8	173.0	51.4	0.5272
III	15	19.4	163.7	46.8	0.5443
IV	20	23.3	156.0	42.9	0.5607
V	25	26.5	149.5	39.7	0.5754
VI	30	29.8	143.2	36.4	0.5943
VII	35	32.5	137.5	33.7	0.6101
VIII	40	35.0	132.6	31.1	0.6289
IX	45	37.2	127.0	28.9	0.6430
X	50	39.4	124.4	27.2	0.6598
XI	55	40.3	122.1	25.9	0.6733

(a) Initial concentration of sulphone(a_o) was 6.614×10^{-4} m./l., that of piperidine(b_o) was 2.025×10^{-3} m./l.

(b) The reaction temperature was 19.88 ± 0.06°C.

Calculation of rate constant:

$$\text{Slope}_{(\text{least squares})} = 0.003208 \text{ min}^{-1}.$$

$$k = \frac{2.303 \times 0.003208}{7.02 \times 10^{-4}}$$

$$= 10.52 \text{ l. mole}^{-1}. \text{ min}^{-1}.$$

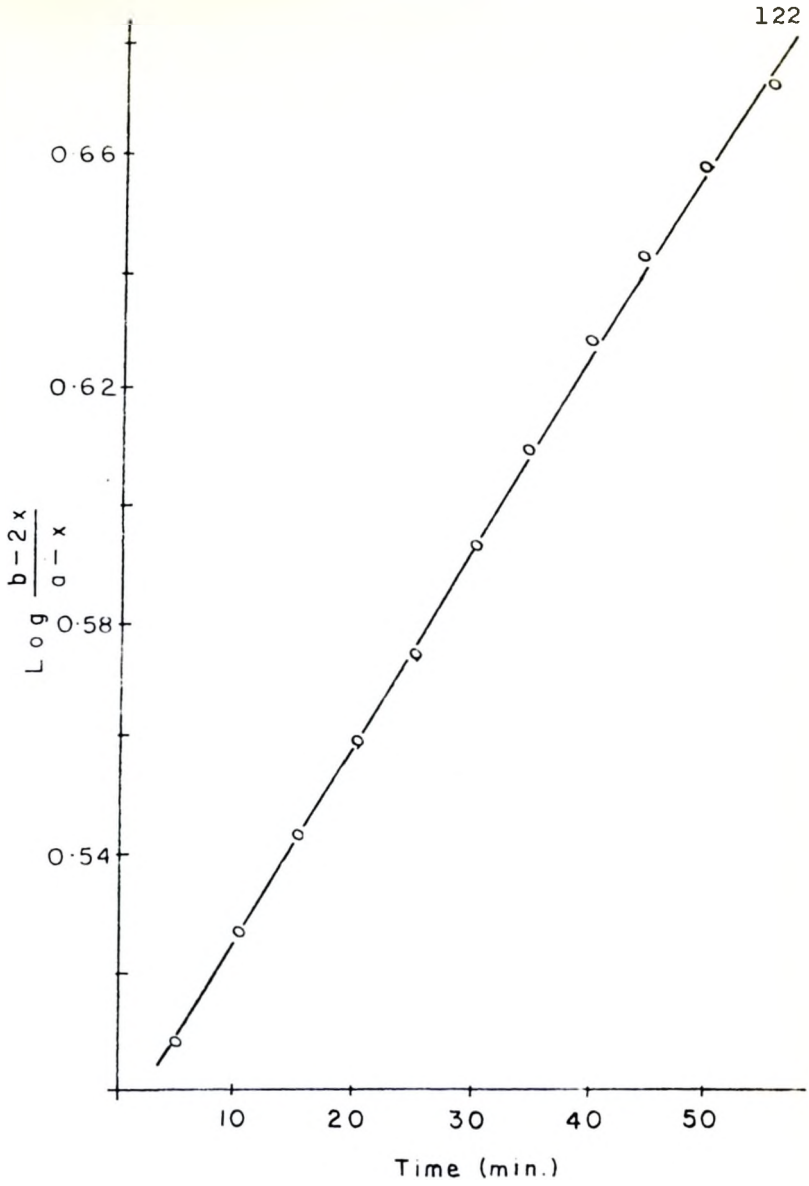


Fig 5. Kinetic plot of a typical run in acetonitrile for the reaction of 2,4-dinitrodiphenylsulphone and piperidine. The data were taken from Table VI.

TABLE VII

RATE CONSTANTS FOR THE REACTION OF 2,4-DINITRODIPHENYL-SULPHONE AND PIPERIDINE IN VARIOUS SOLVENTS

Solvent	Temp. ±0.06°C.	Initial concentrations m./l. x10³ Sulphone	Piperidine	Rate Constant k l.mole^{-1}. min^{-1}.
Benzene	9.88	1.004	40.50	0.283
		1.004	40.50	0.283
	10.0(a)	16.68	38.96	0.303
		16.81	38.96	0.330
	25.05	1.004	40.50	0.583
		1.004	40.50	0.586
	25.0(a)	16.49	10.40	0.594
		16.70	10.40	0.606
	39.86	0.6851	20.25	1.086
		0.6851	20.25	1.069
	40.0(a)	17.04	10.14	1.066
		18.63	10.14	0.997
Acetonitrile	0.00	0.6566	2.025	4.24
	9.89	0.3307	1.013	6.29
		0.3304	1.013	6.29
	19.88	0.6614	2.025	10.52
		0.6614	2.025	10.60
	29.86	0.6566	1.932	15.49
		0.6566	1.932	15.08
	39.88	0.6661	1.013	20.65
		0.6661	1.013	21.05
Methanol	0.00	1.004	40.00	0.0835
		1.000	40.04	0.0836
	25.05	1.000	40.50	0.562
		0.9728	39.84	0.554
	39.82	1.004	40.45	1.490
		1.004	40.45	1.495

(a) Temperature variation was ±0.25°C.

Calculation of Activation Heats and Entropies

The kinetic data obtained in the previous section were used to evaluate the Arrhenius activation energy, E_{exp}, for the reaction in each solvent system from the equation:

$$\log k = \frac{-2.303\ E_{exp}}{RT} + C \qquad \ldots(89).$$

The values of log k were plotted against the reciprocal of the absolute temperature, and the slope of the line was determined by a least squares treatment of the data. The error in the slope so obtained was calculated by the statistical method outlined by Dixon and Massey (128) and this error was used to calculate the 95 per cent confidence limits. In the subsequent calculations of the activation heat and entropy, these limits were used to determine the 95 per cent confidence limits for these values.

The activation heat, $\Delta H^{\ddagger}$, is related (129) to the activation energy, E_{exp}, by the equation:

$$\Delta H^{\ddagger} = E_{exp} - RT \qquad \ldots(90).$$

The values of $\Delta H^{\ddagger}$ from this calculation were substituted into the expression:

$$k = \frac{RT}{h} \cdot e^{-\frac{\Delta H^{\ddagger}}{RT}} \cdot e^{\frac{\Delta S^{\ddagger}}{R}} \qquad \ldots(91).$$

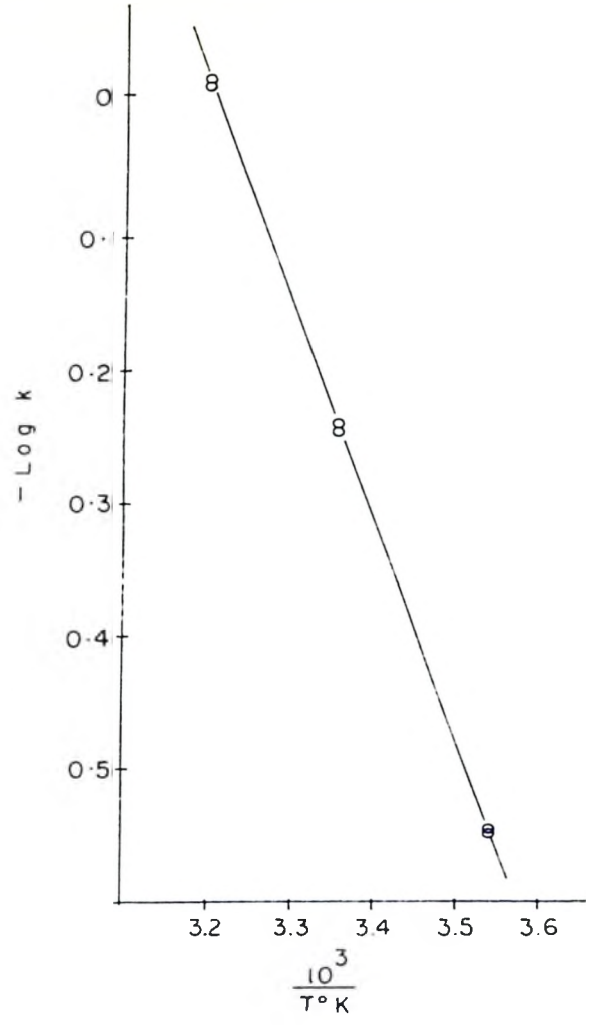


Fig. 6. Arrhenius plot of the effect of temperature upon rate of reaction in benzene. The least squares slope of the line is 1.711×10^3 with 95 per cent confidence limits of $\pm 0.060 \times 10^3$

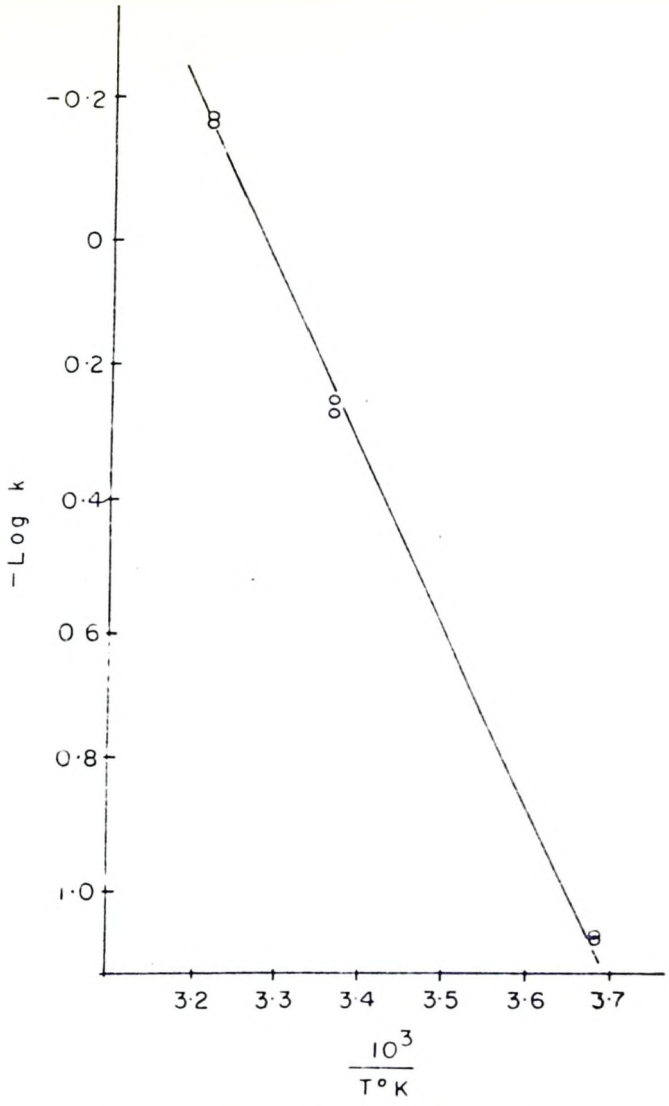


Fig. 7. Arrhenius plot of the effect of temperature upon rate of reaction in methanol. The least squares slope of the line is 2.696×10^{3} with 95 per cent confidence limits of $\pm 0.019 \times 10^{3}$.

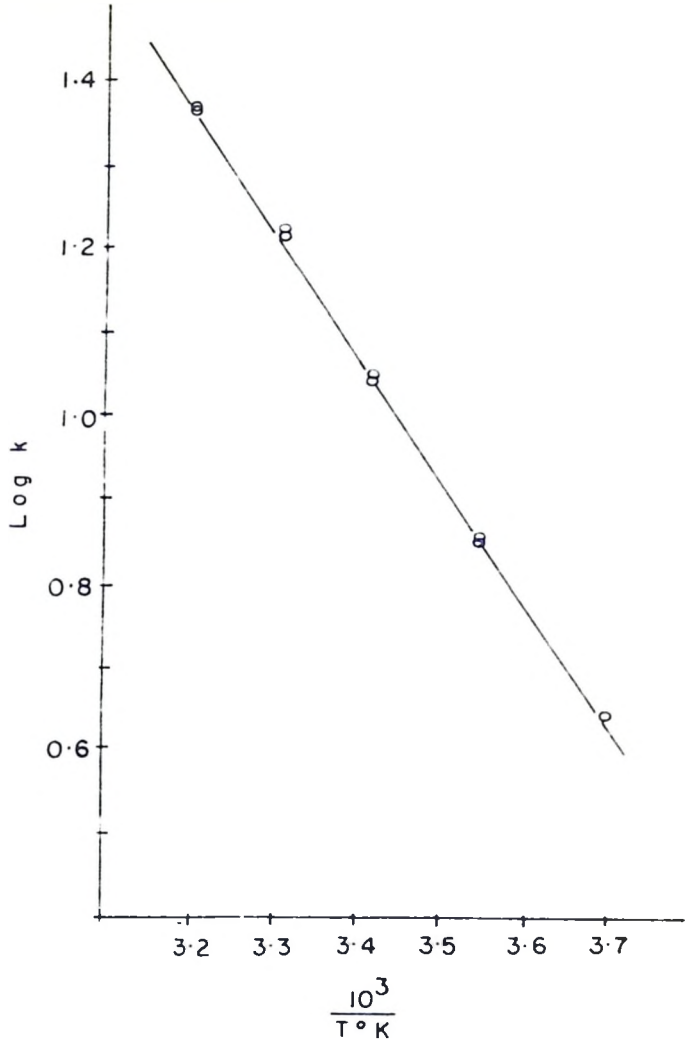


Fig. 8. Arrhenius plot of the effect of temperature upon rate of reaction in acetonitrile. The least squares slope of the line is 1.503×10^3 with 95 per cent confidence limits of $\pm 0.089 \times 10^3$.

to obtain the values of the activation entropy, $\Delta S^{\ddagger}$.

The experimental plots of log k against (1/T) for each solvent system are shown in figures 4, 5, and 6, and the values of the activation energies, heats and entropies are listed in Table VIII.

TABLE VIII

THE ARRHENIUS ENERGIES, HEATS, AND ENTROPIES OF ACTIVATION FOR THE REACTION OF 2,4-DINITRODIPHENYLSULPHONE WITH PIPERIDINE IN THREE SOLVENTS

Solvent	Eexp. K.cal./mole	$\Delta H^{\ddagger}$ K.cal./mole	$\Delta S^{\ddagger}$ e.u.
Benzene	7.8 ± 0.3	7.4 ± 0.3	-43.0 ± 0.9
Methanol	12.3 ± 0.1	11.8 ± 0.1	-28.4 ± 0.3
Acetonitrile	6.9 ± 0.4	6.5 ± 0.4	-40.5 ± 1.6

Isotope Effect Measurements

General

The ratio of the rate constants for two isotopic isomers is given directly by dividing the isotopic ratio for the atom under consideration in the reactant by the corresponding ratio for the product formed during an

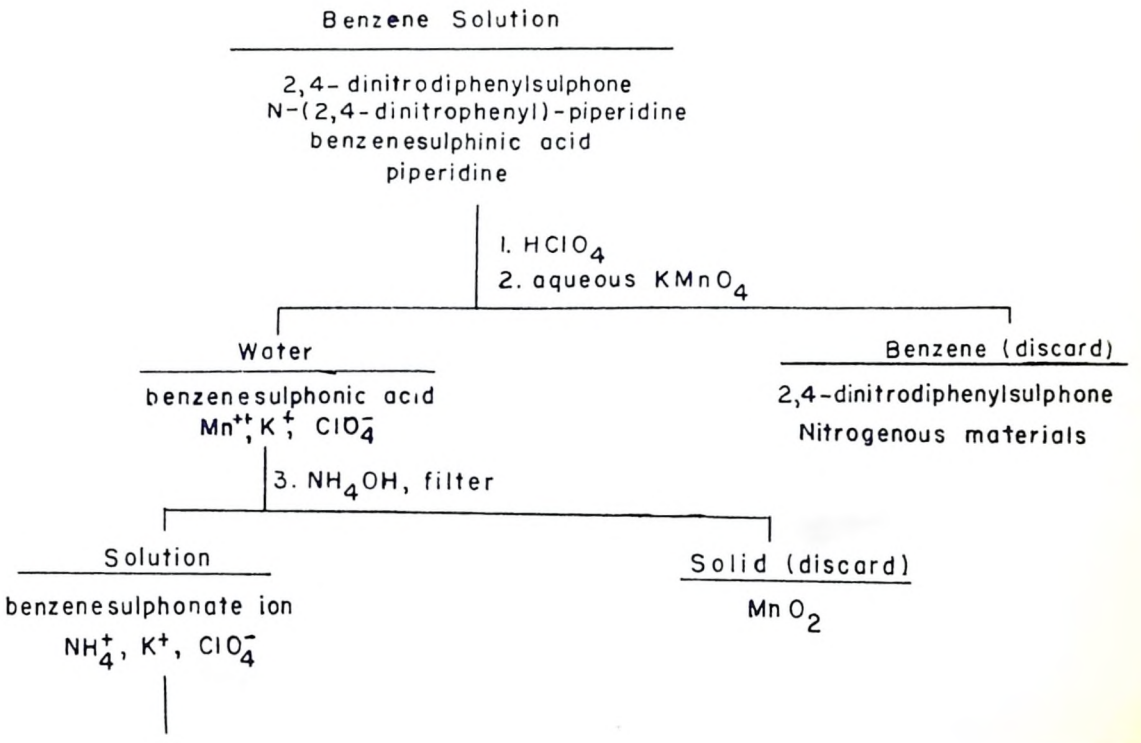
infinitesimally small extent of reaction. In practice, however, the reaction usually is allowed to proceed to some small known extent, one to ten per cent, and the isotope effect is calculated from an expression relating the ratio of the isotopic rate constants to the extent of reaction and to the isotope ratios for the atom in question in the product and in the original reactant.

The isotopic ratio for the reactant may be determined by analysis of gas samples obtained by degradation of the reactant itself. In the present study, however, a degradation procedure suitable for the reactant would be entirely different from that required for the separation and degradation of the product of partial reaction. It seemed preferable, therefore, to determine the isotopic ratio of the reactant by using the product formed in reactions which had proceeded to completion. In this way, any small isotopic fractionations which might arise in the rather involved separation and degradation procedures would be common to all samples whose isotopic ratios were being compared, and these fractionations would largely cancel in the evaluation of the isotopic effect. Fortunately, the reaction of 2,4-dinitrodiphenylsulphone with piperidine is quantitative.

The products of the reaction are N-(2,4-dinitrophenyl)-piperidine and benzenesulphinic acid. The method for the separation of the benzenesulphinic from the large excess of unreacted 2,4-dinitrodiphenylsulphone was based upon the ease of oxidation of sulphinic acids to sulphonic acids and the ready partition of sulphonic acids and sulphones between water and benzene. Reaction solutions in which benzene was the solvent were treated with aqueous permanganate until oxidation was complete and the resulting benzenesulphonic acid was separated by extraction with water. When methanol or acetonitrile was used, the solvent was first displaced by benzene using distillation procedures before addition of the permanganate.

The sulphonic acid was converted to its' ammonium salt which, after removal of water, was reductively cleaved to sulphite ion by the action of sodium in liquid ammonia. Oxidation with hydrogen peroxide gave sulphate ion, which was isolated as barium sulphate. Treatment of the latter with hydriodic acid reduced it to hydrogen sulphide which was first precipitated as cadmium sulphide and then converted to silver sulphide. The silver sulphide was burned with oxygen to sulphur dioxide using vacuum techniques and sulphur isotope ratios were determined by a mass-spectrometric analysis of this gas. Flow sheets of these procedures are shown in figures 9 and 10.

SEPARATION OF BENZENESULPHINIC ACID FROM 2,4-DINITRODIPHENYLSULPHONE



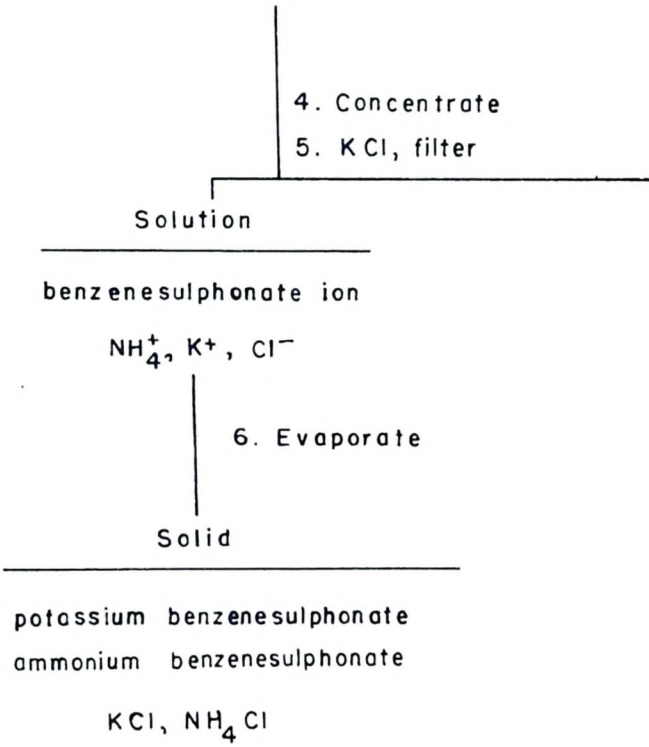
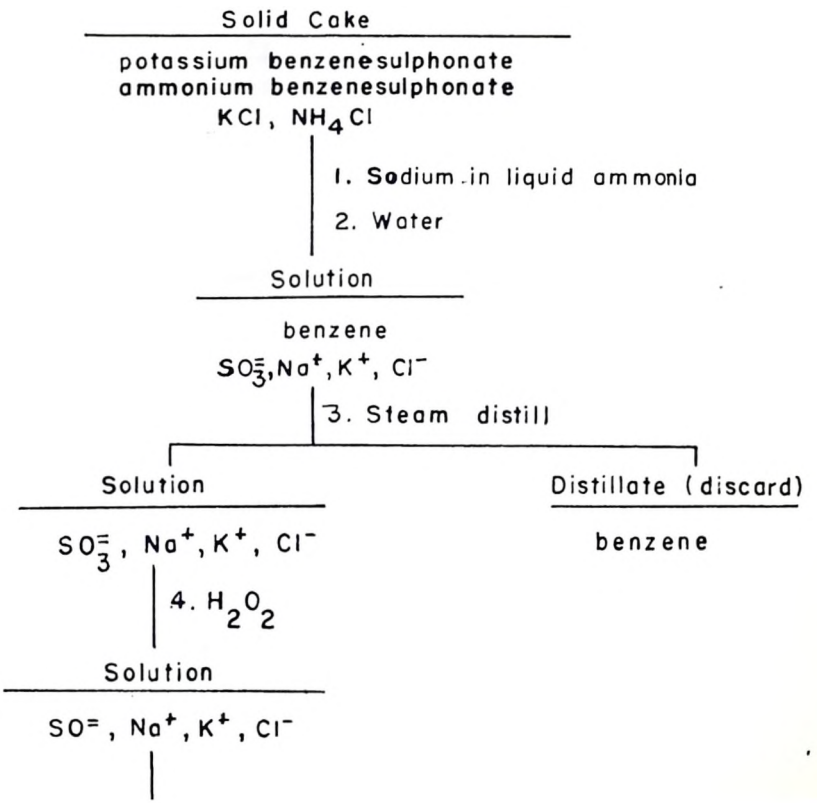


Fig. 9. Flowsheet I

Solid (discard)

$KClO_4$

REDUCTION OF BENZENESULPHONATE ION TO SULPHUR DIOXIDE



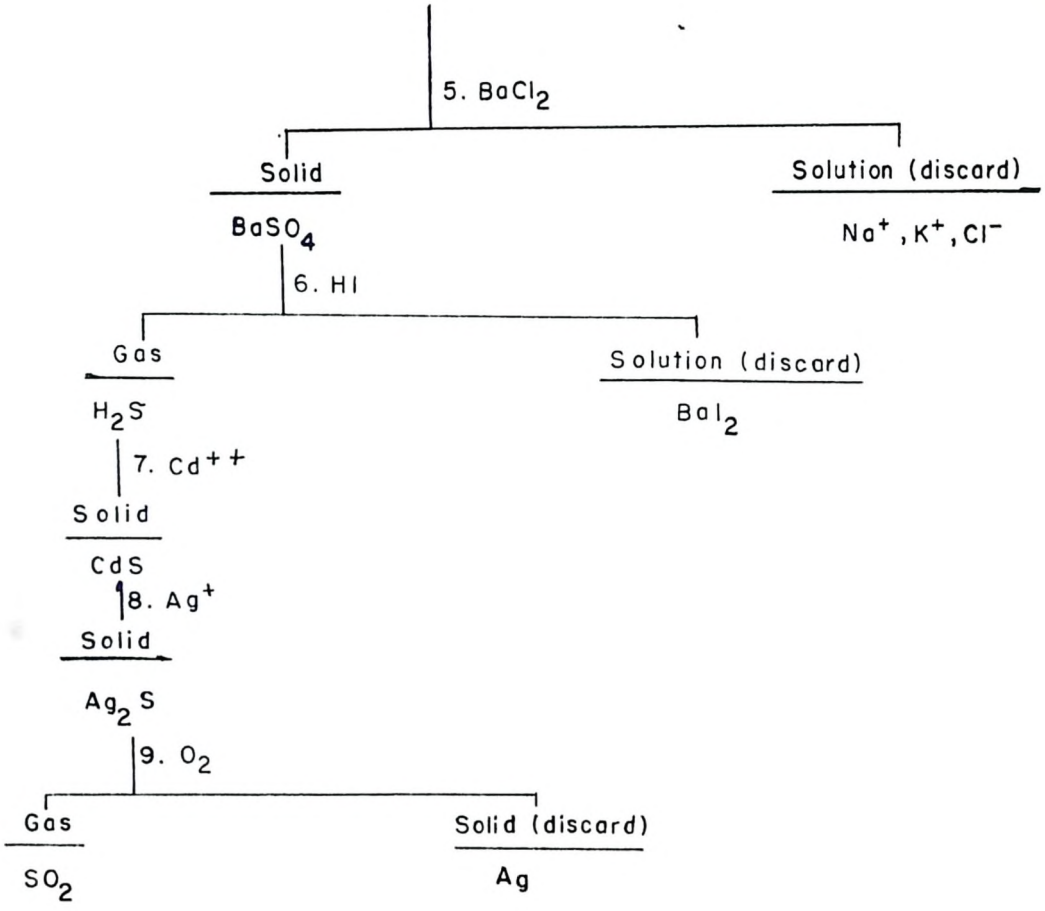


Fig. 10. Flowsheet 2.

Each of the reactions employed in this separation and degradation scheme were shown to be either quantitative or free of any significant sulphur fractionation effects. Furthermore, a sample from a complete reaction was always carried through the scheme in parallel with a sample from a partial reaction and the individual isotope effect values were calculated from the isotope ratios of the sulphur dioxide produced from the pair.

Procedures

The Preparation of Reaction Mixtures for the Determination of Sulphur Isotope Ratios

The kinetic data reported earlier in this thesis were used in determining the appropriate conditions for achieving the desired extent of reaction. For the reactions proceeding to completion (complete reactions) pseudo-first order reaction conditions were chosen and the reactions were allowed to proceed for times corresponding to more than twenty half-lives. The partial reactions were carried out under second order conditions and were allowed to proceed to approximately five per cent of completion. Quenching was accomplished by the addition of acid and the exact extent of reaction in each case was determined by optical density measurements.

For each pair of partial and complete reaction mixtures, a fresh solution of 2,4-dinitrodiphenylsulphone of accurately known concentration was prepared. With benzene or acetonitrile as solvents, solutions were approximately 0.02 molar, whereas in methanol, because of solubility limitations, the concentration was considerably lower, ca. 0.01 molar. An aliquot of each solution, 25 ml. for benzene or acetonitrile and 50 ml. for methanol was treated with one millilitre of piperidine and the reaction allowed to proceed for eight to ten hours, a time equivalent to twenty or more half-lives at these concentrations. Perchloric acid (10 ml., 72 per cent $HClO_4$) was then added.

The remainder of each solution, 475 ml. for benzene or acetonitrile and 950 ml. for methanol, was allowed to stand in a constant temperature bath for three to four hours, an accurately measured volume (0.400 ml.) of piperidine was then added and the solution was shaken vigorously and returned to the bath. At the end of the time require for five per cent reaction, perchloric acid (10 ml., 72 per cent $HClO_4$) was added and, after vigorous shaking of the two-phase system, a sample (0.508 ml.) of the organic phase was withdrawn and added to quenching solution consisting of 0.1 N sulphuric acid in 50 per cent

aqueous ethanol. The volume of this resulting solution was adjusted to 50 ml. and the concentration of the product was determined by an optical density measurement as previously described.

Separation of Benzenesulphinic Acid and 2,4-Dinitrodiphenylsulphone.

The method for separating the small amount of benzenesulphinic acid from the large excess of sulphone in the partial reaction mixtures consisted of an oxidation of benzenesulphinic acid to benzenesulphonic acid and a partitioning of this acid and the sulphone between water and benzene. For the reasons stated previously, an identical treatment was given to the reaction solutions from complete reactions.

When the reaction solvent was either methanol or acetonitrile, compounds which are miscible with water and oxidized by permanganate, it was necessary to replace the solvent with benzene before applying the oxidation procedure. This was accomplished in the following manner. The reaction solution was concentrated *in vacuo* using a rotary evaporator with a bath temperature maintained at

15-20°C. After removal of about 70 per cent of the solvent, an equivalent volume of benzene containing a few milliliters of water[1]. was added and the evaporation was continued until about 70 per cent of the new solvent mixture had been removed. Addition and evaporation of benzene and water was continued until none of the original solvent remained[2]. This normally required three liters of benzene and 100 ml. of water. The volume was finally adjusted to 500 ml. with benzene.

The benzene solution obtained in this way, or the reaction solution itself for reactions in which benzene was the solvent, was transferred to a one-liter flask fitted with a magnetic stirrer. Aqueous potassium permanganate solution (3 per cent) was added to the

---

1. Water was added to replace that removed from the perchloric acid, otherwise extensive decomposition occurred.

2. A small aliquot (1-2 ml.) of the mixture was shaken with aqueous permanganate. If there was no visible sign of reduction of the permanganate within 15 to 20 min., the solvent, methanol or acetonitrile was considered to have been almost completely removed. To ensure elimination of the last traces of the original solvent, the evaporation procedure was repeated twice following the observation of a negative test.

vigorously stirred solution in 100 ml. portions until the purple colour from the final addition persisted for three hours. The excess permanganate and manganese dioxide were destroyed by the dropwise addition of hydrogen peroxide (30 per cent). The aqueous layer then was separated, and the benzene solution was extracted six times with 50 ml. portions of water. Each water extract was washed twice with ether. The aqueous extracts were combined and made alkaline (pH 9.5-10) with concentrated ammonium hydroxide. The suspension of manganese dioxide was allowed to settle for one hour and then was removed by filtration. The filter cake was washed six times with hot water and the filtrate and washings were combined and evaporated to a volume of approximately 100 ml. Potassium chloride (20 g.) was added and brought into solution by gently heating. This solution was chilled in a refrigerator for three hours during which time essentially all the perchlorate ion separated from solution as the potassium salt. The salt was removed by filtration and washed six times with small volumes of ice cold water. The combined filtrate and washings were taken to dryness, leaving a residue of potassium and ammonium benzenesulphonate and chloride.

Cleavage of Benzenesulphonic Acid

The method for the decomposition of benzenesulphonate to inorganic sulphate was based upon a procedure developed by Sowa et. al. (130) for sulphur analysis of organic compounds.

The solid residue of potassium and ammonium benzenesulphonate and chloride was moistened with one to two milliliters of water and then dissolved in 300 ml. of liquid ammonia. Small pieces of sodium metal were added, cautiously at first until all the water had reacted and then in larger portions, until a saturated solution was obtained. The reaction volume was kept between 300 ml. and 500 ml. by the occasional addition of liquid ammonia, and additional sodium was added whenever necessary to maintain a saturated solution. After eight hours, the excess sodium was destroyed by the cautious addition of concentrated ammonium hydroxide and the ammonia was then allowed to evaporate. Water (200 ml.) was added and the mixture was boiled gently to remove traces of benzene and excess ammonia. The solids were removed from the hot solution by filtration, the filtrate was allowed to cool and hydrogen peroxide (5 ml., 30 per cent H_2O_2) was added to convert sulphite ion to sulphate. Excess peroxide was destroyed by heating the solution until there

was no further evolution of gas. The solution was acidified with concentrated hydrochloric acid (pH-2-3), brought to the boiling point and then treated with two or three drops of a saturated solution of methanolic picric acid, followed by 50 ml. of a five per cent barium chloride solution. The precipitated barium sulphate was digested, collected, washed, and ignited following standard analytical procedures. Yields of barium sulphate, based upon sulphone for complete reactions and upon benzenesulphinic acid for partial reactions, were calculated.

Conversion of Barium Sulphate to Sulphur Dioxide

The method used for the conversion of barium sulphate to sulphur dioxide for mass spectrometric analysis has been developed in the McMaster University Laboratories by Thode and his co-workers (131). Barium sulphate was reduced to hydrogen sulphide which was precipitated as cadmium sulphide. Addition of silver ion to the cadmium sulphide suspension converted it to silver sulphide which was then burned in a stream of oxygen to sulphur dioxide.

The reducing solution was prepared by adding hydriodic acid (500 g., 47 per cent HI) to a solution of concentrated hydrochloric acid (430 ml.) and hypophos-

phorous acid (144 ml., 50 per cent H_3PO_2). The resulting solution was maintained at its boiling point for three-quarters of an hour to remove sulphur impurities.

The apparatus for the reduction is shown in Figure 11. Barium sulphate (about 0.1 g.) was placed in flask A and 50 ml. of the reducing solution was added. The suspension was brought to a gentle boil and the hydrogen sulphide formed was passed in a slow stream of purified nitrogen through a gas washing flask, B, containing distilled water and then into the absorption trap, C, containing about 200 ml. of a buffered solution of cadmium acetate. This buffered solution was prepared by dissolving cadmium acetate (62.5 g.) in glacial acetic acid (500 ml.) and adding sufficient water to make a total volume of two liters. As the reduction proceeded barium sulphate slowly dissolved in A and cadmium sulphide precipitated in trap C. The reduction usually was complete in three hours.

Cadmium sulphide was converted to silver sulphide by the addition of 10 ml. of a standard solution of 0.3 N silver nitrate. The silver sulphide was collected on a small glass-wool filter plug, washed with water and acetone and dried at 110°C. The filtrate and wash liquids were combined and excess silver ion was determined

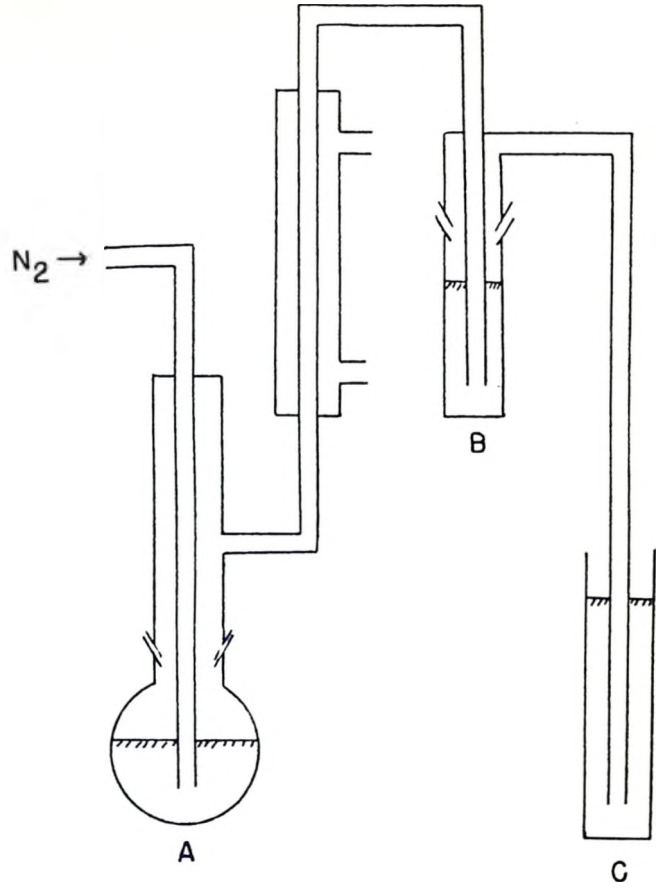


Fig.11. Apparatus for the reduction of barium sulphate

by titration with standard thiocyanate solution. The yield of silver sulphide, calculated from the amount of silver ion consumed, was found to be 98 per cent or better.

The high-vacuum system used for the conversion of silver sulphide to sulphur dioxide is shown in Fig. 12. A nichrome boat, B, containing about 0.07 g. of silver sulphide, was inserted into the quartz tube, A, which was isolated from the pumping system by closing stopcock S_3. Stopcocks S_1 and S_2 were opened and a stream of purified oxygen was passed through the quartz tube and the traps C_1 and C_2 for five minutes at the rate of half a liter per minute. The traps were immersed in liquid oxygen and the sample was slowly heated to a bright red heat with a gas-oxygen flame. The flame was removed and the oxygen flow was continued for an additional five minutes. The inlet tube, H, was replaced with a cap, J, stopcocks S_6 and S_7 were adjusted to by-pass the mercury diffusion pump, L, stopcocks S_1, S_2 and S_5 were closed and stopcocks S_3 and S_4 were slowly opened to the manifold, F, oxygen was removed from the line by the mechanical pump, P, then stopcocks S_6 and S_7 were turned to again bring the mercury diffusion pump, L, into the system. The system was evacuated to a pressure of about 10^{-5} mm. Hg., as measured on the McLoed Gauge, G, stopcock S_3 was closed

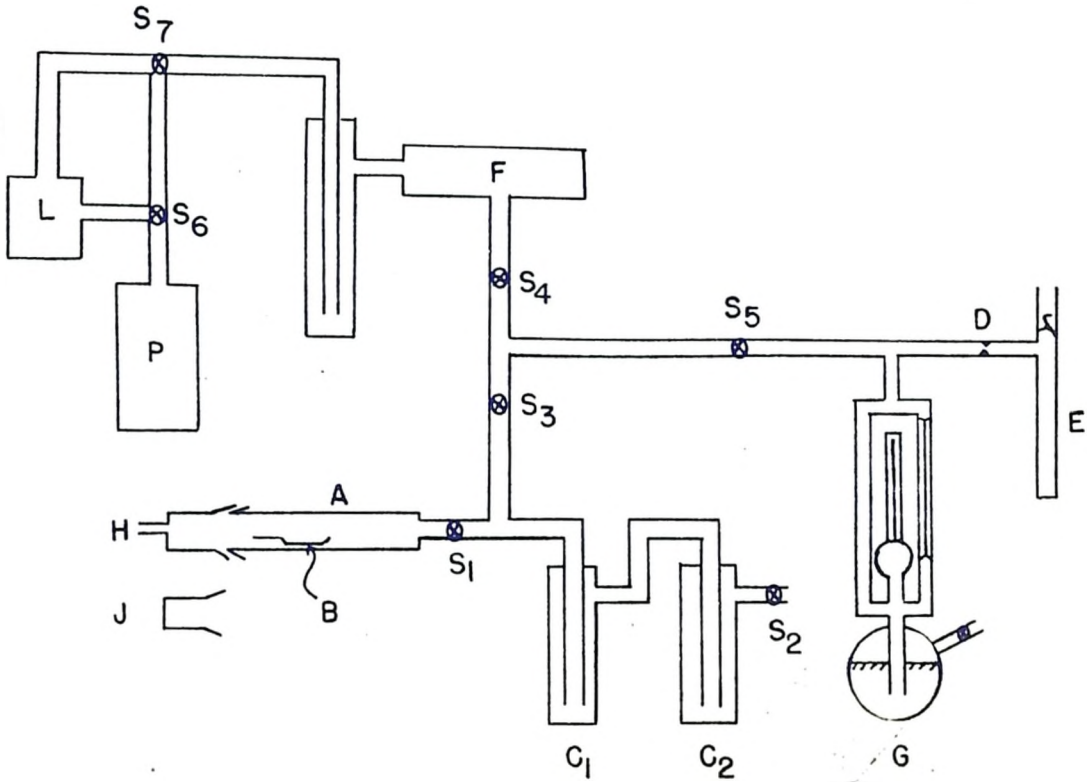


Fig.12. Apparatus for the combustion of silver sulphide to sulphur dioxide.

and the sulphur dioxide in traps C_1 and C_2 was freed of air by thawing and re-freezing. Stopcock S_3 was opened momentarily and the few milliliters of air were removed. Stopcock S_4 was closed, stopcock S_5 was opened and the liquid-air baths surrounding traps, C_1 and C_2, were replaced with dry-ice, acetone baths. Stopcock S_3 was opened and the sulphur dioxide distilled from traps C_1 and C_2 into the sample tube, E, which was immersed in liquid oxygen. When the vapour pressure in the system had fallen to 10^{-4} mm. Hg., stopcock S_4 was opened and the apparatus was evacuated to the limit of the mercury diffusion pump. Stopcock S_5 was closed, the sample tube was sealed at the constriction, D, and then removed from the system.

Tests of Separation and Degradation Procedures

It was essential to establish the absence of isotopic fractionation in each of the steps used in the separation of benzenesulphinic acid and its conversion to sulphur dioxide. A careful study therefore was made of product yields using, where applicable, synthetic mixtures of sulphone and sulphinic acid. In addition, certain direct tests for isotopic fractionation were carried out. In one series of experiments, the cleavage of benzene-sulphonic acid with sodium in liquid ammonia was

deliberately interrupted before complete conversion and the sulphur isotope ratio of the resulting product was compared with that of the product from a quantitative conversion. In a second series of experiments a mixture, containing benzenesulphinic acid and sulphone of different sulphur isotopic ratios, was separated and the isotopic ratio of the recovered acid compared with that of the initial acid.

The following sections contain a description of these tests and give the results obtained. The order of presentation is the reverse to the order in which the various procedures were applied in the actual isotope effect experiments.

Reduction of Barium Sulphate to Sulphur Dioxide

It has been shown by Harrison (131) that the isotopic effect associated with the conversion of a sulphate to hydrogen sulphide is approximately two per cent. Since, in the present investigations conversions were always better than 95 per cent, and usually between 98 and 99 per cent, it can be safely assumed that isotopic fractionation in this step of the reaction sequence is negligible.

The oxidation of silver sulphide to sulphur dioxide is somewhat less satisfactory since as much as ten per cent of the sulphur may appear as sulphur trioxide.

At the elevated temperatures used in the combustion, however, the equilibrium constant for isotopic exchange between sulphur dioxide and sulphur trioxide should be very close to unity. Furthermore, such small isotopic fractionations which might occur during this combustion should be approximately the same for all the samples and, therefore, should cancel in the calculation of the isotopic effect. In this connection, it is worthwhile noting that in this laboratory, and particularly in Dr. Thode's group, it has been observed repeatedly that sulphur dioxide samples obtained by combustion of the same sample of metal sulphide give isotopic ratios which agree consistently to better than ±0.1 per cent.

Cleavage of Benzenesulphonic Acid

The result of a number of test experiments on the conversion of benzenesulphonic acid to sulphate by the sodium-liquid ammonia method described on page 138 are given in Table IX.

TABLE IX

EFFICIENCY OF BENZENESULPHONIC ACID CLEAVAGE

Sample Number	Original Sulphinic Acid moles x10^4	Barium Sulphate Found moles x10^4	Per Cent Yield of Barium Sulphate
III 125 I	9.037	8.544	94.6
III 125 II	6.850	6.462	94.3
III 125 III	6.639	5.998	90.4
III 130 I	7.061	7.009	99.3
III 130 II	6.640	6.286	94.7

Yields of barium sulphate were somewhat variable but exceeded 90 per cent. Since yields of barium sulphate obtained from synthetic mixtures of benzenesulphinic acid and 2,4-dinitrodiphenylsulphone also were rarely less than 90 per cent, it would appear that the cleavage of the sulphinic acid is the only step of the overall separation degradation sequence in which any serious isotopic fractionation might occur (see following sections).

To test for possible fractionation in the cleavage step, a number of experiments were carried out in which the reaction was stopped before the sulphonic acid had been completely converted to sulphite ion. The isotopic ratios for the sulphur dioxide prepared from barium sulphate from

these incomplete reactions were compared with the ratio for a sulphur dioxide sample from barium sulphate which had been formed in high yield from the same sample of benzenesulphonic acid. The results of these experiments are listed in Table X.

TABLE X

ISOTOPIC FRACTIONATION DURING CLEAVAGE OF BENZENESULPHONIC ACID

Sample Number	Per Cent Yield of Barium Sulphate	S32 S34 Ratio	Fractionation (a)
III 139 II	96.6	22.346	1.0014
III 143 I	82.4	22.341	1.0009
III 143 III	82.3	22.326	1.0003
III 143 III	100 (b)	22.321	-

(a) Relative to Sample III 143 III.

(b) Yields of barium sulphate normally were 90-96 % for complete reaction, but occasionally, higher yields were obtained. A careful check of reagents showed that this higher yield (100%) did not arise from extraneous sulphur impurities and, therefore, apparently is a true percent yield.

From these results it can be seen that the conversion of sulphonic acid to sulphate in yields of at least 82 per cent causes no significant isotopic fractionation. Such small

variations as are observed can be considered indicative of the reproducibility of isotopic ratios in the present study.

Oxidation of Benzenesulphinic Acid

In test experiments, a weighed sample of benzenesulphinic acid was dissolved in benzene and oxidized with aqueous permanganate following the procedure described on page 136. The resulting benzenesulphonic acid was converted to barium sulphate using the sodium-liquid ammonia cleavage method. Table XI gives yields of barium sulphate obtained from the combined oxidation and cleavage reactions.

TABLE XI

OXIDATION AND CLEAVAGE OF BENZENESULPHINIC ACID

Sample Number	Sulphinic Acid Moles Taken x 10^4	Barium Sulphate Moles Found x 10^4	Per Cent Yield of Barium Sulphate
III 136 I	7.769	7.197	93.53
III 136 II	6.362	5.771	90.72
III 139 I	7.495	6.872	91.70
III 139 II	7.164	6.924	96.64

A comparison of the data given in this table with that in Table IX shows that the yield of barium sulphate formed from benzenesulphinic acid by oxidation followed by

cleavage is not significantly less than the yield obtained by direct cleavage of benzenesulphonic acid. It may be concluded, therefore, that the conversion of the sulphinic acid to sulphonic acid is quantitative and that no isotopic fractionation can occur in this step of the separation procedure.

Separation of Benzenesulphinic Acid and 2,4-Dinitrodiphenylsulphone

A benzene solution containing accurately known amounts of benzenesulphinic acid and 2,4-dinitrodiphenylsulphone was treated with aqueous acidified permanganate solution according to the method described on page 136 and the resulting benzenesulphonic acid was isolated and converted to barium sulphate using the standard procedure.

The benzene extract containing the sulphone was heated to a gentle boil to remove water, cooled, and made up to a standard volume. A large excess (20 - 30 fold) of piperidine was added and, after a period corresponding to twenty or more half lives for the piperidine-sulphone reaction, the optical density of the solution was measured. The amount of sulphone present in the benzene extract was calculated from the N-(2,4-dinitrophenyl)-piperidine formed in this reaction.

The efficiency of the separation procedure is given by the amount of barium sulphate formed from the benzenesulphinic acid and by the amount of N-(2,4-dinitrophenyl)-piperidine produced from the sulphone. The results of four such experiments on synthetic mixtures of sulphinic acid and sulphone are shown in Table XII.

TABLE XII

SEPARATION OF BENZENESULPHINIC ACID AND 2,4-DINITRODIPHENYLSULPHONE

Experiment Number	Sulphone			Sulphinic Acid		
	Moles Taken x 10^3	Moles Found x 10^3	Per Cent Recovery	Moles Taken x 10^3	Barium Sulphate Moles Found x 10^3	Per Cent Conversion
III 114 II	19.6	19.2	98.2	65.12	60.12	92.1
III 114 III	17.6	17.6	100.0	112.5	100.3	90.7
III 135 I	5.25	5.25	100.0	1.042	0.984	93.2
III 135 III	4.34	4.33	98.0	0.703	0.688	96.8

The data show that the recovery of sulphone is almost quantitative while the recovery, in the form of barium sulphate, of the sulphur of the benzenesulphinic acid component is 90 per cent or better. The latter corresponds closely to the yield of barium sulphate formed by oxidation and cleavage of pure benzenesulphinic acid.

It may therefore be concluded that the procedure accomplished a quantitative separation of the two components.

As a further test for the absence of contamination by sulphate arising from unreacted sulphone the separation was repeated using sulphinic acid and sulphone of differing sulphur isotope ratios. The isotopic ratio of the barium sulphate obtained from the synthetic mixtures was compared to that of the barium sulphate obtained directly from the pure benzenesulphinic acid. The results of this experiment are tabulated in Table XIII.

TABLE XIII

TEST FOR CONTAMINATION OF BARIUM SULPHATE IN SEPARATION PROCEDURES

Experiment Number	S^{32}/S^{34} Ratios		
	Sulphone	Sulphinic Acid	Barium Sulphate from Sulphinic Acid
IV 24 II	22.400	22.262	22.282
IV 24 III	22.400	22.262	22.272
IV 24 IV	22.400	22.262	22.277

The data show that there is no significant contamination of barium sulphate by sulphur from sulphone and they also provide some additional evidence for the absence of isotopic fractionation in the oxidation and cleavage procedures.

Solvent Replacement Technique

The method of solvent replacement was tested for its effect upon the efficiency of separation of the two components, benzenesulphinic acid and 2,4-dinitrodiphenyl-sulphone. Blank runs were carried out to ensure that no sulphone sulphur was obtained as barium sulphate, then artificial mixtures of sulphinic acid and sulphone were prepared in the appropriate solvent, this solvent was replaced by benzene and the solution of sulphone and sulphinic acid in benzene was treated in the manner outlined on page 150 . The per cent recoveries of sulphur from the two sources are shown in Tables XIV and XV.

TABLE XIV

SEPARATION OF SULPHONE AND SULPHINIC ACID IN METHANOL

Experiment Number	Sulphone			Sulphinic Acid		
	Moles Taken x 10^4	Moles Found x 10^4	Per Cent Recovery	Moles Taken x 10^4	Barium Sulphate Moles Found x 10^4	Per Cent Conversion
IV 85 I	97.6	94.0	96.5	none	none	-
IV 85 II	97.7	94.	97.4	none	none	-
IV 84 I	102.7	101.1	98.5	7.062	6.761	95.8
IV 84 II	97.5	96.0	98.4	7.613	7.051	92.6

TABLE XV

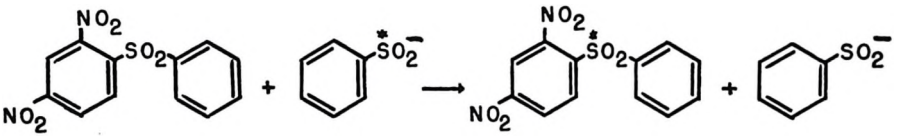
SEPARATION OF SULPHONE AND SULPHINIC ACID IN ACETONITRILE

Experiment Number	Sulphone			Sulphinic Acid		
	Moles Taken x 10^4	Moles Found x 10^4	Per Cent Recovery	Moles Taken x 10^4	Barium Sulphate Moles Found x 10^4	Per Cent Conversion
IV 89 I	98.1	95.9	97.8	none	none	-
IV 89 II	99.3	97.7	98.5	none	none	-
IV 89 III	97.7	96.9	99.1	7.026	6.681	94.6
IV 89 IV	97.5	96.5	98.9	7.761	7.221	93.0

The data show that the separations are not affected by the solvent replacement technique, and that there is no cross contamination of sulphur.

Investigation of Possible Exchange Reactions

The product, benzenesulphinic acid, is a relatively strong nucleophile and the possibility of the following exchange reaction must be excluded if the isotope effect results are to be of any significance.



...(92).

A radioactive tracer technique was used to investigate this possibility. Benzene -C^{14}-sulphinic acid was allowed to remain in contact with 2,4-dinitrodiphenylsulphone during the course of the reaction with piperidine. The unchanged sulphone was recovered after the reaction was stopped and its activity was measured. The assay of radioactivity was carried out after each recrystallization until the activity disappeared or until the material was exhausted.

Solutions of 2,4-dinitrodiphenylsulphone and benzene-C^{14}-sulphinic acid in each of the reaction solvents, benzene, methanol, and acetonitrile, were placed in a constant temperature bath and maintained at 10°C. for three hours. Piperidine was added and reactions were

allowed to procede for times sufficient for approximately five per cent reaction. Perchloric acid was then added. The polar solvents were replaced by benzene using the solvent replacement technique described on page 135. The benzene solutions were each treated with aqueous permanganate and the resulting benzenesulphonic acid was removed by extraction with water. The benzene layer was dried and taken to dryness *in vacuo*. The recovered sulphone from each reaction system was recrystallized from one or more solvents and its activity determined after each recrystallization by a radioactive assay of the carbon dioxide produced by a wet-combustion method (132). Measurements were made by means of an ionization chamber-vibrating reed electrometer combination using the rate of drift method described by Raaen and Ropp (133).

The per cent apparent exchange is given by the expression,

$$\text{Per cent exchange} = \frac{S_{exp.}}{S_{calc.}} \times 100 \qquad \ldots(93).$$

where $S_{exp.}$ is the measured specific activity in millicuries per mole of the recovered sulphone, and $S_{calc.}$ is the specific activity which the sulphone would have if

equilibrium were complete. The quantity $S_{calc.}$ is given by

$$S_{calc.} = \frac{m_1}{m_1 + m_2} S_{orig.} \qquad \ldots(94).$$

where m_1 and m_2 are the number of moles of sulphone and sulphinic acid respectively and $S_{orig.}$ is the specific activity of the original sulphinic acid. The results of the exchange experiments are given in Table XVI. It can be seen that there is essentially no exchange in reactions carried out in either methanol or acetonitrile. Although the measured exchange in benzene may be real, it is still very small and certainly is not sufficient to give rise to any variation in the measured fractionation of sulphur isotopes.

Summary

On the basis of the results of the rather extensive tests which have been reported in the preceding sections, it may be concluded that no significant isotopic fractionation is introduced by the separation procedures, by the degradation reactions, or by any exchange phenomenon. Any observed isotopic fractionation, therefore, must have originated in the reaction of piperidine with the sulphone, that is, in the reaction whose isotope effect is being measured.

TABLE XVI

TESTS OF EXCHANGE BETWEEN BENZENE-C^{14}-SULPHINIC ACID AND 2,4-DINITRODIPHENYLSULPHONE

Solvent Reaction and Experiment Number	Sulphone Moles x 10^2	Sulphinic Acid(a) Moles x 10^4	Contact Time (min.)	$S_{calc.}$ m.curie/ mole x 10^2	Recrystallization	Solvent of Recrystallization	$S_{exp.}$ m.curie/ mole x 10^4	Per Cent "Apparent" exchange
Benzene IV 47 I	1.071	7.061	28	3.21	4th	Methanol	10.1	3.2
					5th	Ligroin	7.69	2.4
					6th	Methanol	5.99	1.9
Benzene IV 47 II	1.027	10.79	28	4.81	2nd	Ligroin	17.3	3.6
					3rd	Methanol	11.2	2.3
					4th	Methanol	8.23	1.7
Methanol IV 72 I	1.010	17.11	20	7.51	3rd	Methanol	0.98	0.1
					4th	Methanol	0.16	0.02
Acetonitrile IV 91 I	1.017	10.57	5	4.88	3rd	Methanol	3.38	0.7
					4th	Methanol	0.10	0.02

(a) The specific activity of the sulphinic acid, $S_{orig.}$, was 0.518 m.curie/mole.

Mass Spectrometry and Calculation of Isotope Effects

Analysis of sulphur dioxide samples was carried out using two different mass spectrometers. Samples originating from reactions in benzene were analyzed in a ninety-degree, simultaneous collection mass-spectrometer described by Wanless and Thode (134). This was a high-precision instrument capable of measuring changes of isotopic ratios with a precision of ± 0.02‰. The conventional collector of a single beam instrument had been modified to collect simultaneously the ion beams of masses 64 and 66. The current produced by the 66 beam was amplified and applied to a put-and-take potentiometer. Some fraction of the current from the put-and-take potentiometer was balanced against the separately amplified current from the 64 beam and the balance point was recorded on a Leeds and Northrup Co. Speedomax Type A Recorder. Since the position of balance will vary depending on the ratio of isotopes present in the sample, a shift of the balance point will be a measure of the 64/66 ratio relative to a standard sample. The ion current from mass 64 was used as a reference voltage and was adjusted to the same value for both the standard and the sample by changing the gas pressure of the sample until the peak height of mass 64, measured on single collection, was identical with that of

the standard. The instrument was switched to simultaneous collection operation, the put-and-take potentiometer was adjusted to give a balance near the centre of the recorder chart and the displacement of the null point of the sample from that of the standard was measured. The average of six displacements was used to calculate the per cent change in the isotope ratio of the sample relative to the standard. This gave the value of the 64/66 ratio.

Before the study of sulphur isotope effects had been completed, the simultaneous collection mass spectrometer was temporarily taken out of service and the isotope ratios of samples originating from reactions in methanol and in acetonitrile were measured with an older and somewhat less precise machine. This was a 180 degree directional-focusing mass spectrometer of the Nier type, fitted with an automatic recorder. The procedure using this instrument was to analyse a standard sample, the unknown sample and the standard again. An actual analysis consisted of a series of six double spectrograms. Each double spectrogram was obtained by scanning the 64 and 66 mass peaks in the order 64, 66, 66, 64. The 64/66 ratio for each spectrogram was calculated, and then the average value and the mean deviation were determined for the series of spectrograms. If the mean deviation was less than 0.1% of the average value, the measurement was considered

satisfactory. If the average value of the standard before and after the unknown had changed by less than 0.1‰, the average value of the unknown was accepted as a valid measure of the 64/66 ratio for the sample. An arbitrary value for the 64/66 ratio was assigned to the standard and the values of the 64/66 ratios of the unknown samples were normallized with respect to this standard value.

The mathematical relationship of the 64/66 ratio to the ion species present is:

$$\frac{64}{66} = \frac{S^{32}\,O_2^{16}}{S^{34}\,O_2^{16} + S^{32}\,O^{16}\,O^{18}} \qquad \ldots(95).$$

or,

$$\frac{66}{64} = \frac{S^{34}\,O_2^{16}}{S^{32}\,O_2^{16}} + \frac{S^{32}\,O^{16}\,O^{18}}{S^{32}\,O_2^{16}} \qquad \ldots(96).$$

the contribution of $S^{32}\,O_2^{17}$ being neglected. This can be expressed in terms of isotope abundance ratios as follows:

$$\frac{66}{64} = \frac{S^{34}}{S^{32}} + 2\,\frac{O^{18}}{O^{16}} \qquad \ldots(97).$$

or,

$$\frac{S^{32}}{S^{34}} = \frac{1}{\frac{66}{64} - 2\,\frac{O^{18}}{O^{16}}} \qquad \ldots(98).$$

The co-efficient 2 arises from the fact that sulphur dioxide contains two oxygen atoms and therefore the

probability of occurrence of $SO^{16}O^{18}$ will be twice the probability of occurrence of atomic O^{18}. A value of 0.002045 for the O^{18}/O^{16} ratio had been determined by Thode (135) and this value was used throughout the present work.

The sulphur isotope ratios calculated from the above expression were used to calculate the isotope effect of the reaction in benzene, acetonitrile, and methanol. An expression relating the isotopic ratios for the product of complete and partial reaction to the ratio of rate constants for reaction of species containing light and heavy isotopes, developed by Stevens and Attree (136), is:

$$\frac{k^{32}}{k^{34}} = \frac{\ln [1 - f]}{\ln \left[1 - \left[\frac{(S^{32}/S^{34})_c}{(S^{32}/S^{34})_p} \right] f \right]} \qquad \ldots(99).$$

for sulphur-32 and sulphur-34 isotopes where $(S^{32}/S^{34})_c$ is the isotopic ratio of the sulphur dioxide formed from the product of complete reaction, $(S^{32}/S^{34})_p$ is the corresponding ratio for the sulphur dioxide obtained from the product of partial reaction, and f is the mole fraction of the sulphone-S^{32} which has undergone reaction. For the low conversions used in the present study, no significant error is introduced by taking f as the total mole fraction of sulphone (S^{32} plus S^{34} species) which has undergone

reaction, that is,

$$f = \text{per cent reaction}/100$$

The ratio k^{32}/k^{34} was calculated from each individual pair of isotopic ratios obtained in separate experiments and the resulting values for each solvent system then were averaged. The 95 per cent confidence limits for these average values then were evaluated.

In discussion, it is convenient to refer to the per cent isotope effect. This is related to the k^{32}/k^{34} values by the following expression:

$$\text{per cent isotope effect} = 100\left[\frac{k^{32}}{k^{34}} - 1\right] \ldots (100).$$

Isotope Effect Results

The results of the isotope effect experiments for reaction of 2,4-dinitrodiphenylsulphone with piperidine in benzene solution are presented in Table XVII, in methanol in Table XVIII, and in acetonitrile in Table XIX.

Isotope ratios for the products of parallel partial and complete experiments were determined in all but two cases and were used to evaluate the individual rate constant ratios given in the tables. The products of the complete reactions run in conjunction with partials IV96P and

IV128P, Table XX, unfortunately were lost. For the calculation of isotope effects from the sulphur isotope ratios obtained for these partial reaction products, values of $(S^{32}/S^{34})c$ were used which were the average of all previous values obtained for the same sulphone preparation. This appeared to be a justifiable procedure since isotope effects calculated in this way were generally in close agreement with those calculated from the isotopic ratios of pairs carried through in parallel, as indeed they should be. It is of interest to note, however, that there appeared to be a significant difference in the $(S^{32}/S^{34})c$ ratios for the two different sulphone preparations used in the isotope effect experiments. This is not surprising since there is no reason why the sulphur isotope ratios should be the same for the reagents used in the two separate syntheses of the sulphone.

A summary of the kinetic and isotope effect results for reaction in the three solvents is presented in Table XX.

TABLE XVII

ISOTOPE EFFECT RESULTS FOR THE REACTION OF 2,4-DINITRODIPHENYLSULPHONE WITH PIPERIDINE IN BENZENE AT 10°C.

Experiment Number		Per Cent Reaction(a)	Per Cent Yield of $BaSO_4$(b)	S^{32}/S^{34} Ratios	$\frac{(S^{32}/S^{34})_p}{(S^{32}/S^{34})_c}$	k^{32}/k^{34}
IV 26	p	6.3	90.4	22.696	1.0134	1.0137
	c	100	104.3	22.396		
IV 27	p	6.3	88.3	22.635	1.0104	1.0108
	c	100	95.9	22.401		
IV 28	p	4.5	91.0	22.660	1.0118	1.0121
	c	100	85.2(c)	22.396		
IV 29	p	4.2	90.8	22.676	1.0123	1.0126
	c	100	97.0	22.401		
IV 102(d)	p	5.4	100.6	22.619	1.0125	1.0129
	c	100	95.0	22.344		
IV 103(d)	p	5.1	97.6	22.624	1.0131	1.0135
	c	100	97.4	22.324		

mean(e) = 1.0126 ± 0.0011

(a) Based on optical density measurements in the partial reactions; assumed to be 100 per cent in the complete reactions (7).

(b) Based upon the amount of benzenesulphinic acid known to be present in the reaction solution.

(c) Accidental mechanical losses suffered during conversion of cadmium sulphide to silver sulphide.

(d) The sulphone was from a different preparation than that used in preceding experiments.

(e) Precision expressed as 95% confidence limits.

TABLE XVIII

ISOTOPE EFFECT RESULTS FOR THE REACTION OF 2,4-DINITRODIPHENYLSULPHONE WITH PIPERIDINE IN METHANOL AT 10°C.

Experiment Number		Per Cent Reaction(a)	Per Cent Yield of $BaSO_4$(b)	S^{32}/S^{34} ratios	$\frac{(S^{32}/S^{34})_p}{(S^{32}/S^{34})_c}$	k^{32}/k^{34}
IV 82	p	8.1	90.4	22.493	1.0057	1.0059
	c	100	97.4	22.375		
IV 83	p	8.0	91.2	22.507	1.0052	1.0054
	c	100	100.1	22.391		
IV 86	p	5.1	96.3	22.555	1.0067	1.0069
	c	100	100.3	22.401		
IV 87	p	5.6	90.3	22.510	1.0046	1.0047
	c	100	98.7	22.407		
IV 88	p	6.7	90.4	22.448	1.0056	1.0058
	c	100	97.0	22.359		

$\text{mean}^{(c)} = 1.0057 \pm 0.0010$

(a) Based on optical density measurements in the partial reaction; assumed to be 100% in the complete reactions (7).

(b) Based on the amount of benzenesulphinic acid known to be present in the reaction solution.

(c) Precision expressed as 95 per cent confidence limits.

TABLE XIX

ISOTOPE EFFECT RESULTS FOR THE REACTION OF 2,4-DINITRODIPHENYLSULPHONE WITH PIPERIDINE IN ACETONITRILE AT 10°C.

Experiment Number		Per Cent Reaction(a)	Per Cent Yield of $BaSO_4$(b)	S^{32}/S^{34} Ratios	$\frac{(S^{32}/S^{34})_p}{(S^{32}/S^{34})_c}$	k^{32}/k^{34}
IV 93	p	5.9	93.5	22.849	1.0179	1.0185
	c	100	98.7	22.479		
IV 94	p	5.3	94.8	22.812	1.0163	1.0167
	c	100	99.3	22.435		
IV 95	p	5.9	90.2	22.795	1.0135	1.0139
	c	100	96.4	22.492		
IV 96	p	5.2	93.7	22.814	1.0178	1.0183
	c	--	--	22.417(d)		
IV 128(c)	p	5.6	91.2	22.618	1.0129	1.0133
	c	--	--	22.331(e)		
IV 129(c)	p	5.1	90.8	22.660	1.0145	1.0149
	c	100	95.3	22.344		

mean(f) = 1.0159 ± 0.0025

(a) Based on optical density measurements in the partial reactions; assumed to be 100 per cent in the complete reactions (7).

(b) Based on the amount of benzenesulphinic acid known to be present in the reaction solution.

(c) The sulphone was from a different preparation than that used in the preceding experiments.

(d) The product of the complete reaction carried out in parallel with partial reaction IV96P was lost. The value tabulated for $(S^{32}/S^{34})c$ was the average of the values obtained for the product of eight complete reactions (IV 82C, IV 83C, IV 86C, IV 87C, IV 88C, IV 93C, IV 94C, and IV 95C) performed on the same sulphone preparation and measured on the same mass-spectrometer.

(e) The product of the complete reaction carried out in parallel with partial reaction IV 128P was lost. The value tabulated for $(S^{32}/S^{34})c$ was the average of the values of IV 102C, IV 103C, IV 129C, and IV 130C (the last value = 22.314, is not incorporated in any table since the parallel partial result was lost) from the same sulphone preparation and measured on the same mass spectrometer.

(f) Precision expressed as 95% confidence limits.

TABLE XX

ACTIVATION HEATS AND ENTROPIES AND KINETIC ISOTOPE EFFECTS IN THE REACTION OF 2,4-DINITRODIPHENYLSULPHONE WITH PIPERIDINE

Solvent	$\Delta H^{\ddagger}$ k.cal./mole	$\Delta S^{\ddagger}$ e.u.	$100\left[\frac{k^{32}}{k^{34}} - 1\right]$ at 10°C.
Benzene	7.4 ± 0.3	-43.0 ± 0.9	1.26 ± 0.11
Acetonitrile	6.5 ± 0.4	-40.5 ± 1.6	1.59 ± 0.25
Methanol	11.8 ± 0.1	-28.4 ± 0.3	0.57 ± 0.10

RESULTS AND DISCUSSION

Kinetic Results

As outlined in the previous section, rate constants for reaction in methanol were measured under pseudo-first order conditions, those for reaction in benzene were determined under both pseudo-first and second order conditions while, in acetonitrile, only second order conditions were used. Pseudo-first order constants were converted to second order constants which were used to calculate the activation parameters for the reaction. For convenience, these data are re-tabulated below.

TABLE XXI

RATE AND ACTIVATION CONSTANTS FOR THE REACTION OF 2,4-DINITRODIPHENYLSULPHONE AND PIPERIDINE IN VARIOUS SOLVENTS

Solvent	Temp. °C.	Rate constant $l.mole^{-1} min.^{-1}$	Eexp K-cal./ mole	$\Delta H^{\ddagger}$ K-cal./ mole	$\Delta S^{\ddagger}$ e.u. (a)
Benzene	10	0.286			
	25	0.585	7.8	7.4	-43.0
	40	1.078			
Methanol	0	0.0836			
	25	0.558	12.3	11.8	-28.4
	40	1.493			
Acetonitrile	0	4.24			
	10	6.29			
	20	10.56	6.9	6.5	-40.5
	30	15.28			
	40	20.85			

(a) Calculated for reaction at 10°C.

An examination of the data in Table XXI shows that there is no apparent correlation between rates and the polarity of the medium. Methanol and acetonitrile have approximately the same dielectric constant, yet a change of

solvent from benzene to acetonitrile results in a roughly twentyfold increase in rate while for a change from benzene to methanol, rates are essentially unaffected. When the rate data is analysed in terms of the activation parameters, the origin of these rate changes becomes apparent. The activation entropies, $\Delta S^{\ddagger}$, follow the order, benzene > acetonitrile >> methanol and the activation heats, $\Delta H^{\ddagger}$, follow the order methanol >> benzene > acetonitrile. The entropies of activation clearly become less negative the greater the solvating power of the solvent while, except for benzene and acetonitrile where differences are small, the heats of activation are in the reverse order.

Such relationships between the nature of the solvent and the activation parameters have been observed before (137, 138, 139) and have been accounted for in the following way (140, 141).

Solvation of polar molecules generally is governed by the polarity of the medium; polar solvents solvate polar molecules efficiently, non-polar solvents do not. Solutions of polar reactants (the initial state) in polar solvents, therefore, are characterized by a high degree of ordering of solvent molecules, while in non-polar solvents, this degree of ordering is low. For a reaction producing ions, the transition state will involve a considerable development of charge and the charged centres will be

highly solvated. The "freezing out" of these solvent molecules by the charged centres results in a very high degree of organization of solvent molecules on forming the transition state and the entropy of activation is negative.

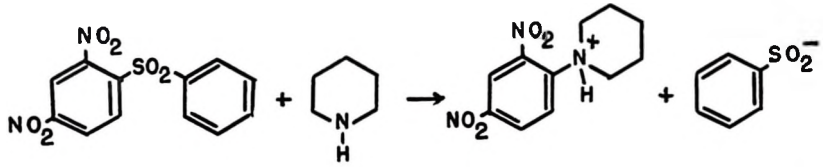
The magnitude of the activation entropy depends upon the polarity of the solvent. In non-polar solvents with a very small degree of organization in the initial state, the change in organization on forming the transition state will be large, while in polar solvents where the initial state is already highly organized, formation of the transition state results in a relatively much smaller change in the degree of organization. Activation entropies, therefore, tend to become less negative as the polarity of the medium is increased.

Heats of activation depend mainly upon the type of reaction and normally do not vary widely from solvent to solvent. To the extent, however, that the heat of activation is influenced by the medium the trend for a reaction proceeding through a highly polar transition state, usually, but not invariably, is that the more polar the solvent, the larger is the heat of activation. Although solvation of transition states is greater in the more polar solvents, solvation of initial states is greater as well. The extra stabilization conferred upon the transition state by a more polar solvent often is more than

compensated by the extra energy required to overcome the stronger intermolecular forces between solvent molecules and between solute and solvent molecules in the initial state. Consequently, the heat of activation is larger than in a less polar solvent.

Since these small increases in activation heats are accompanied by relatively large changes in entropies towards less negative values, the usual observation is that rates are faster in the more polar solvents.

The reaction of piperidine with 2,4-dinitrodiphenyl-sulphone:



...(101).

does produce ions and, hence, there is a development of charge in the transition state. With the non-polar solvent benzene, there will be little or no organization of solvent molecules in the initial state but, because of the highly polarizable π electron cloud of this solvent, there will be considerable interaction with the highly polar transition state. There is, therefore, a large change in the degree of ordering of solvent molecules on going from

the initial to the transition state and a large negative entropy of activation will result. With the solvent acetonitrile, a much more polar molecule, there will be some ordering of solvent in the initial state. In the transition state with its highly developed charge, the degree of organization of solvent molecules is greatly increased and again a large negative activation entropy results. Because of the solvation of the reactant molecules, however, the change in the degree of organization is not quite as large in this solvent as in benzene and the entropy of activation will be slightly less negative.

It is difficult to state a priori what will be the effect on the heat of activation on going from solvent benzene to acetonitrile, other than that it will be small. The observation of a smaller activation heat in the more polar solvent, however, is readily accounted for. Although in benzene there is a large increase in the degree of ordering of the solvent molecules on going from the initial to the transition state, the forces of interaction between solvent molecules and the transition state will be relatively small. With acetonitrile, however, for a somewhat smaller change in the degree of ordering of solvent molecules, the effect on the heat of activation actually will be larger since the energy of interaction between the highly polar solvent molecules and the charged transition

state will be of considerable magnitude. In other words, for every solvent molecule which is frozen out there will be a greater resulting stabilization of the transition state in acetonitrile than in benzene.

Very large changes in these activation parameters are observed when the solvent is changed to methanol. While this solvent is very polar, it also is hydroxylic and, obviously, is a special case since it is well known that hydroxylic solvents are characterized by their ability to form strong intermolecular hydrogen bonds. In this particular reaction, not only will there be strong solvent-solvent hydrogen bonds but, in addition, the solvent will be very powerfully hydrogen-bonded to the basic piperidine reactant. The initial state in methanol then is very highly ordered compared to this state in both benzene and acetonitrile and formation of the transition state results in a relatively small change in the degree of organization of the reaction system. The activation entropy then is much less negative in this solvent. Although the hydroxylic solvent will solvate and hence stabilize the transition state, nevertheless, on forming this state the powerful hydrogen bonds between methanol and piperidine and between methanol molecules themselves must be broken. The energy required to overcome these hydrogen bonding forces is much larger than that gained by stabilization of the

transition state and the heat of activation consequently is much larger than in benzene or in acetonitrile. Similar effects on heats and entropies of activation on going from a non-hydroxylic to a hydroxylic solvent have been observed previously in a number of reactions producing ions from neutral molecules (142, 143). The effects of benzene and acetonitrile are normal solvent effects, influencing reaction rates by interaction with the transition state. Methanol, on the other hand, exerts a specific solvent effect upon the reactants which quite outweighs its effects upon the transition state and, therefore, tends to retard the rate.

These effects of the various solvents on the heat of activation are shown in Fig. 13. No implication with respect to the mechanism is intended in drawing the potential energy curves in this figure.

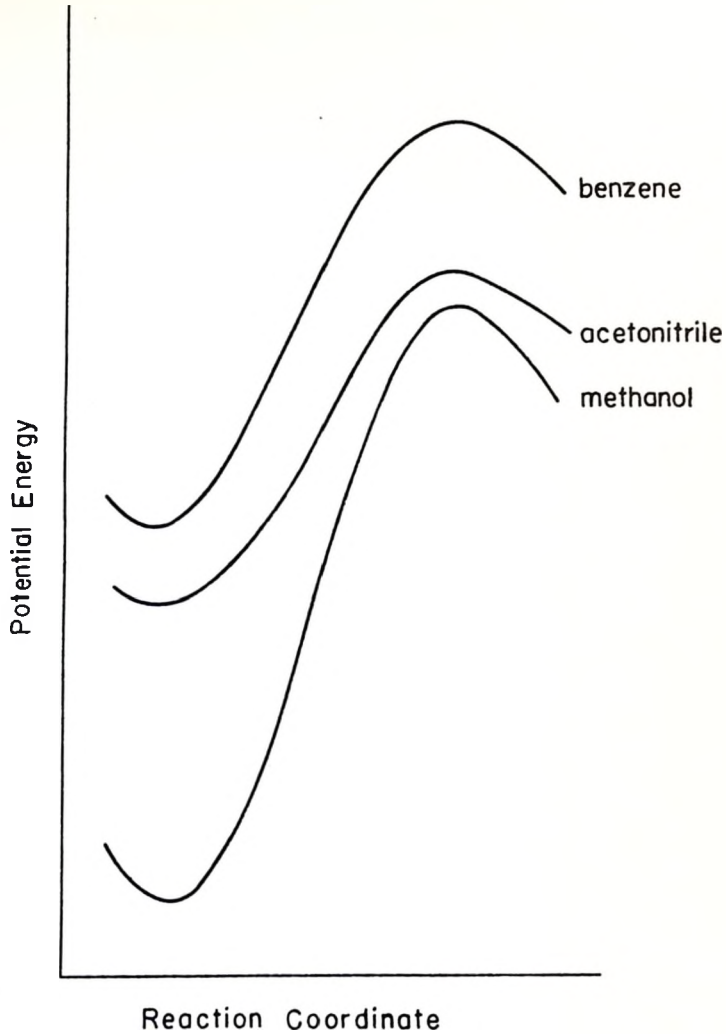


Fig. 13. Potential energy profiles for reaction in three solvents.

Kinetic Isotope Effect Results

An important objective of the present study of the kinetic sulphur isotope effect in the reaction of piperidine with 2,4-dinitrodiphenylsulphone in various solvents was to distinguish unequivocally between the concerted and stepwise mechanisms for a representative nucleophilic aromatic substitution. Of no lesser significance, however, is the fact that this study has provided the first direct measure of the extent to which the rupture of the bond to the leaving group is involved in a rate-determining step of the reaction.

The results of this investigation, which were presented in detail in the EXPERIMENTAL AND RESULTS section, are re-tabulated in Table XXII.

TABLE XXII

ISOTOPE EFFECTS FOR THE REACTION OF 2,4-DINITRODIPHENYL-SULPHONE WITH PIPERIDINE IN THREE SOLVENTS AT 10°C.

Solvent	Per Cent Isotope Effect	Relative Isotope Effect
Benzene	1.26 ± 0.11	2.2
Acetonitrile	1.59 ± 0.25	2.8
Methanol	0.57 ± 0.10	1.0

An isotope effect of appreciable magnitude is observed in each of these solvent systems and, therefore, carbon-sulphur bond rupture must be involved in a step which is partially or wholly rate-determining. The theoretical maximum effect expected for reaction in which carbon-sulphur bond rupture is wholly rate-determining is 1.7 per cent at 10°C. (The reader is referred to the APPENDIX for details of the calculation of this maximum effect). The 1.6 per cent isotope effect observed in the acetonitrile system approaches this maximum value very closely, showing that the carbon-sulphur bond is greatly weakened in the transition state of the rate-determining step. In benzene, the observed effect, 1.3 per cent, is only slightly smaller and, therefore, in this solvent also, the bond to sulphur is being broken in the slow step. Of particular interest is the smaller but quite significant effect, 0.6 per cent, observed for reaction in methanol. Here again, bond rupture plays a role in determining the reaction rate but to a considerably lesser degree than in the other solvents.

Methanol was the solvent used by Bunnett in his "element effect" study of the reaction of piperidine with a number of aromatic substrates, one of which was 2,4-dinitrodiphenylsulphone, the compound used in the present study. The observed isotope effect of 0.6 per cent, which is at least one third of the theoretical

maximum effect and is much too large for a secondary effect, shows clearly that Bunnett's conclusion that the formation of the intermediate is rate-determining is incorrect. Indeed, on the basis of this isotope effect, it is surprising that the reaction rates of Bunnett's substrates are so similar unless, as suggested in the HISTORICAL INTRODUCTION of this thesis, (Page 81) there is a large measure of cancellation of the inductive and conjugative effects associated with the different leaving groups.

The actual magnitude of the isotope effect in any one solvent, although showing the extent to which the reaction rate is determined by rupture of the bond to the leaving group, is of no value in establishing whether or not the reaction proceeds through a metastable intermediate. Both the large effect observed in acetonitrile and the relatively small effect in methanol can be accommodated by either the concerted or two-step mechanisms. The change in magnitude of the effect with change of solvent, however, provides an answer to this question as will be shown in the following discussion.

The Bigeleisen equation for the theoretical evaluation of an isotope effect from spectroscopic data, strictly speaking, holds only for reactions in the gas phase. Yet it has been applied quite successfully to reactions in the solid phase, in melts, and in solution. In other words,

the influence of intermolecular forces on the magnitude of an isotope effect associated with a single-stage process is small. Recently, this has been demonstrated quite convincingly by Bigeleisen and Riesz (26) who studied the carbon-13 isotope effect in the decarboxylation of trinitrobenzoate ion, a reaction which exhibits very large variations in rate and activation parameters with change in solvent. Their results are summarized in Table XXIII.

TABLE XXIII

CHANGES IN RATES, ACTIVATION PARAMETERS, AND ISOTOPE EFFECTS WITH SOLVENT IN THE DECARBOXYLATION OF TRINITROBENZOATE ION AT 50°C.

Solvent	Rate Constant sec.$^{-1}$	$\Delta H^{\ddagger}$ K-cal./mole	$\Delta S^{\ddagger}$ e.u.	Carbon-13 Isotope Effect Per Cent
Water	5.6×10^{-7}	35.8	25	3.6
90% Ethanol	2.95×10^{-4}	27.4	12	3.3

It is seen that in this one-step process, a change in solvent from water to 90 per cent ethanol brings about only a 10 per cent change in the magnitude of the isotope effect. In contrast to this, the sulphur isotope effect in the reaction of 2,4-dinitrodiphenylsulphone with piperidine shows an almost threefold change on going from solvent methanol to acetonitrile. In light of this, the one-step mechanism

for this nucleophilic aromatic substitution would appear to be definitely eliminated.

These large variations in the magnitude of the isotope effect, on the other hand, can be accommodated readily by the two-step mechanism:

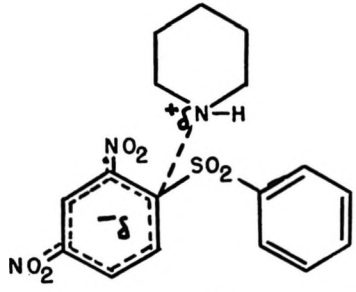
$$ArY + Z: \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \left[\overset{+}{Ar} \begin{matrix} \diagup Y^- \\ \diagdown Z \end{matrix} \right] \xrightarrow{k_2} \overset{+}{Ar}Z + Y: \qquad \ldots(102).$$

The magnitude of the observed isotope effect for Y can be expected to depend upon the relative rates with which the intermediate returns to reactants and proceeds to products. When k_2 is very large relative to k_{-1}, the rate-determining step is the formation of the intermediate. Since, in this step, the C-Y bond is still intact, there will be no isotope effect other than possibly a very small secondary one. Conversely, if k_{-1} is very much larger than k_2, the intermediate is essentially in equilibrium with the reactants and the rate-determining step then is the decomposition of the intermediate to products. Since this step does involve the rupture of the bond to Y, an appreciable isotope effect should result. Small k_{-1}/k_2 ratios, therefore, produce very small or zero isotope effects, large k_{-1}/k_2 ratios lead to quite significant isotope effects.

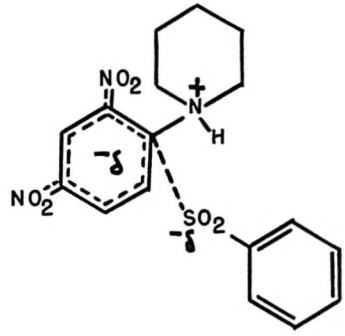
Since the transition states corresponding to the two steps of the reaction will differ in both the degree of

charge development and distribution, it can be expected that their relative energies will depend greatly upon the reaction medium. It follows, then, that a change in solvent can bring about a large change in the magnitude of the isotope effect.

An inspection of the two transition states, XXIII and XXIV, for the reaction of piperidine with 2,4-dinitrodiphenylsulphone reveals that charge is more highly developed and concentrated in XXIV, the transition state for decomposition of the intermediate to products.



XXIII



XXIV

Any change to a solvent of greater charge-stabilizing ability will, therefore, lower the energy of XXIV relative to XXIII, thus decreasing the k_{-1}/k_2 ratio, and reducing the isotope effect.

It is now clear why, if the two-step mechanism is being followed, the isotope effect is smallest in methanol.

This solvent is unique in that it alone of the three solvents used in this study is capable of forming hydrogen bonds. These hydrogen bonding interactions will be particularly strong for the transition state XXIV and will act between the hydroxylic hydrogen and the negatively charged oxygen atoms of the developing benzenesulphinate ion, and also between the oxygen of methanol and hydrogen on the positive nitrogen atom. One might think of the hydroxylic solvent as assisting, through hydrogen bond formation, in the elimination of the benzenesulphinate group as an anion. Because of this specific solvation effect, the ratio k_{-1}/k_2, and hence the isotope effect, should be smallest in methanol.

There is other evidence which points to a specific solvation of the transition state of the second step by a hydroxylic solvent. Hammond and Parks (100) found that the rates of reaction of different 1-halo-2,4-dinitrobenzenes with N-methylaniline are nearly constant in ethanol but vary widely in nitrobenzene. Although there is more than one way of interpreting these observations, the results are readily understood in terms of a two-step mechanism. In nitrobenzene, a very polar solvent but one which is not capable of showing specific solvation effects, the rate-determining step is the decomposition of the intermediate to products and, therefore, rates will depend upon the nature of the departing halogen atom. In ethanol,

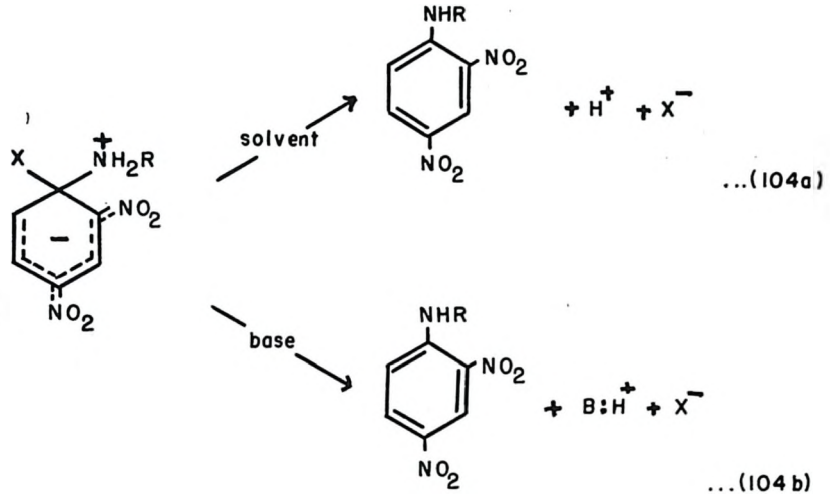
a much less polar solvent, the specific solvation of the second transition state so speeds up the decomposition step that the slow step now is formation of the intermediate. Since this step does not involve the rupture of the carbon-halogen bond, the reaction rates will be little influenced by the nature of the halogen atom. It should be recalled that in this connection Bunnett's "element effect" study in which similar rates and activation parameters were found for a series of 1-substituted-2,4-dinitrobenzenes involved the solvent methanol.

The work of Ross (106) on base catalysis in nucleophilic aromatic substitution reactions provides further support for the hypothesis that a polar solvent may speed up the decomposition of an intermediate in a stepwise process. Ross found the reaction of 1-halo-2,4-dinitrobenzenes with various amines to follow the kinetic expression,

$$\text{rate} = k_1 [\text{ArX}] [\text{RNH}_2] + k_3 [\text{ArX}] [\text{RNH}_2]^2 \quad \ldots(103).$$

To the additional molecule of amine in the second term, he assigned the role of base catalyst which accepts a proton from the positively charged nitrogen of the intermediate. The relative importance of this base catalysis term was found to depend greatly upon solvent, being smallest in

in solvents of high polarity. For a stepwise mechanism, this may be interpreted in terms of two different pathways for decomposition of the intermediate to products, one involving the base and the other not:



As the solvating power of the solvent for hydrogen and halide ions increases, the unimolecular decomposition of the intermediate (equation 104a) competes more effectively with the bimolecular process involving base (equation 104b) and, as a result, the k_1/k_3 ratio increases.

On the basis of this interpretation of the low isotope effect in methanol in terms of preferential stabilization of the transition state for the decomposition of an intermediate, one would logically expect the isotope effect to be largest in benzene since it is the least solvating of the three solvents studied. Yet this is not the case; the isotope effect in benzene actually is slightly less than that for reaction in the much more polar solvent acetonitrile[1]. It follows then that either the reasoning relating to the mechanism of the reaction and the effect of solvent on the relative energies of the two transition states is incorrect, or that there is some additional factor which is responsible for the somewhat smaller isotope effect in the solvent benzene. It is believed that the latter is the explanation and that the responsible factor is the so-called "built-in-solvation" effect of the ortho-nitro group.

The concept of "built-in-solvation" was invoked a few years ago by Bunnett (144, 145) to account for the relative constancy of rate and activation parameters of

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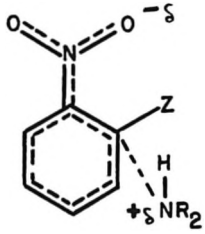
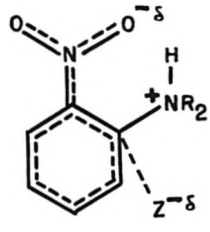
1. The standard deviation for the observed isotope effects in the two solvents is such that there is a slight overlap in values (1.26 ± 0.11 in benzene, 1.59 ± 0.25 in acetonitrile). Application of Students "t" test, however, has shown that there is a better than 99 per cent probability that the isotope effect in acetonitrile is higher than that in benzene.

reactions of ortho-nitrohalobenzenes with the piperidine as the solvent is varied, as compared to the large variations found for reaction of the corresponding para-nitrohalobenzenes. It was proposed that this effect is a consequence of the interaction between the negatively charged oxygen atom of the ortho-nitro group and the reaction centre of the nucleophilic reagent. This interaction, which may act directly between the oxygen atom and the positive nitrogen or may be a hydrogen bonding effect or even a combination of the two, satisfies in part the tendency of the charged atoms to surround themselves with solvent molecules and plays an increasingly important role as the solvating power of the medium decreases. "Built-in-solvation", like solvation by methanol, is a specific solvation effect and can be expected to be very much more important in stabilizing the second transition state, XXV, than the first, XXVI, partly because the positive charge on nitrogen is more fully developed but, more importantly, because the

geometry of the second transition state brings a negative oxygen atom into closer proximity to nitrogen and its attached hydrogen atom.



XXV



XXVI

Applying this hypothesis to the reaction of 2,4-dinitrodiphenylsulphone with piperidine, it can be seen why the isotope effect might be smaller in benzene than in acetonitrile. The latter, a highly polar solvent, will solvate and hence stabilize both transition states by a general medium effect and "built-in-solvation" will play only a minor role. In the much less polar benzene, however, "built-in-solvation" will be the important stabilizing factor but, being a specific effect, it will operate much more effectively in stabilizing the second transition state than the first. As a consequence, the change in solvent from acetonitrile to benzene decreases the k_{-1}/k_2 ratio and hence reduces the isotope effect.

One may think of the situation in benzene as being very much like that in methanol except that in the former the specific solvation of the transition state for decompsition is provided internally rather than by external solvent molecules.

Having established that the reaction under investigation follows the two-step mechanism, it is of interest to attempt to use the isotope effect results to calculate the relative rate of return of the intermediate to reactants and of its decomposition to products.

Steady state treatment of the kinetics of the two-step process leads to the rate expression,

$$\text{rate} = \frac{k_1 \; k_2}{k_{-1} + k_2} [\text{sulphone}][\text{piperidine}] \quad \ldots(105).$$

from which it follows that,

$$\left[\frac{k^{32}}{k^{34}}\right]_{obs} = \frac{k_1^{32} \; k_2^{32} \left[k_{-1}^{34} + k_2^{34}\right]}{k_1^{34} \; k_2^{34} \left[k_{-1}^{32} + k_2^{32}\right]} \quad \ldots(106).$$

As a first approximation, it may be assumed that there is no isotope effect associated either with formation of the intermediate or with its reversion to reactants, that is, the ratios k_1^{32}/k_1^{34} and k_{-1}^{32}/k_{-1}^{34} are unity. This would seem

reasonable since secondary isotope effects involving the isotopes of sulphur can be expected to be very small. Equation 106 then reduces to

$$\left[\frac{k^{32}}{k^{34}}\right]_{obs} = \frac{k_2^{32}\left[k_{-1}^{32} + k_2^{34}\right]}{k_2^{34}\left[k_{-1}^{32} + k_2^{32}\right]} \qquad \ldots(107).$$

which may be written as

$$\left[\frac{k^{32}}{k^{34}}\right]_{obs} = \frac{\left[\frac{k_2^{32}}{k_2^{34}}\right]\left[\frac{k_{-1}^{32}}{k_2^{32}}\right] + 1}{\left[\frac{k_{-1}^{32}}{k_2^{32}}\right] + 1} \qquad \ldots(108).$$

Equation 108, on rearrangement, gives

$$\frac{k_{-1}^{32}}{k_2^{32}} = \frac{\left[\frac{k^{32}}{k^{34}}\right]_{obs} - 1}{\left[\frac{k_2^{32}}{k_2^{34}}\right] - \left[\frac{k^{32}}{k^{34}}\right]_{obs}} \qquad \ldots(109).$$

The only quantities required for the calculation of k_{-1}^{32}/k_2^{32}, the ratio of the rates of return of the sulphur-32

containing intermediate to reactant and of its decomposition to products, are the observed isotope effect and k_2^{32}/k_2^{34}, the isotope effect for the step involving carbon-sulphur bond rupture. The latter can be estimated in the following way.

The theoretical maximum isotope effect for the decomposition of the intermediate can be calculated by substituting into the Bigeleisen equation the maximum vibrational stretching frequency to be expected for the carbon-sulphur bond in this intermediate and assuming a zero force constant for this bond in the transition state. The value for k_2^{32}/k_2^{34} so obtained is 1.0169 (see APPENDIX for details of this calculation). Now the isotope effect observed for reaction in acetonitrile is 1.0159 which is very close to this theoretical maximum value. It would seem reasonable, therefore, to assume that in this solvent, the second step is very nearly, if not entirely, rate-controlling and that this observed isotope effect is that associated with the decomposition of the intermediate. In any case, the true k_2^{32}/k_2^{34} ratio should not differ by more than one or two tenths of a per cent from 1.016 and the error introduced by the use of this value should be relatively small.

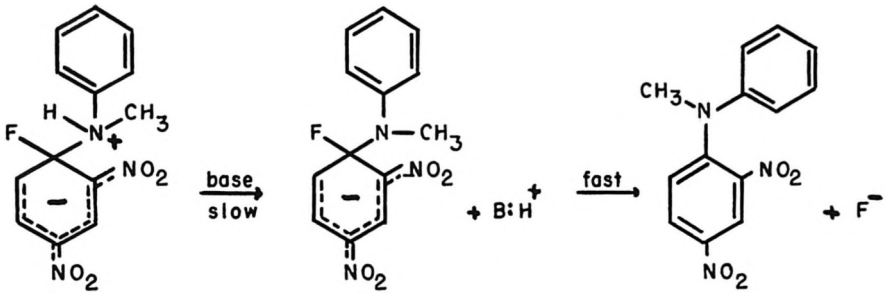
One may now calculate the k_{-1}^{32}/k_2^{32} ratio for the reaction in methanol by substituting into equation 109 the value 1.016 for k_2^{32}/k_2^{34} and 1.0069 for $[k^{32}/k^{34}]_{obs}$, the observed isotope effect in this solvent. The value so

obtained is 0.55. Because of the assumptions made in this calculation, namely, no secondary isotope effect in the formation of the intermediate and a k_2^{32}/k_2^{34} ratio of 1.016, the value of 0.55 may be in error by as much as fifty per cent. Nevertheless, it can be stated with considerable confidence that the rates of decomposition of the intermediate to products and to reactants are of comparable magnitudes.

A similar calculation can be performed for reaction in benzene although the resulting value for k_{-1}^{32}/k_2^{32} probably is not particularly meaningful since the difference between 1.0126, the isotope effect observed in this solvent, and 1.016, the value assumed for k_2^{32}/k_2^{34} is small. If one does carry out such a calculation, however, the value obtained for k_{-1}^{32}/k_2^{32} is 3.57.

It will be recalled that prior to the present study, the most convincing evidence in support of a metastable intermediate in nucleophilic aromatic substitution was the work of Bunnett and Randall (109) relating to the non-linear base catalysis of the reaction of 1-fluoro-2,4-dinitrobenzene with N-methylaniline. There was, however, one important question concerning mechanism which could not be answered by their study. This is whether or not the bond to fluorine is broken in the rate-determining step. Bunnett favoured a two-step process for decomposition of the

intermediate, the first and rate-determining being the abstraction of the proton from nitrogen and the second a fast elimination of fluoride ion:

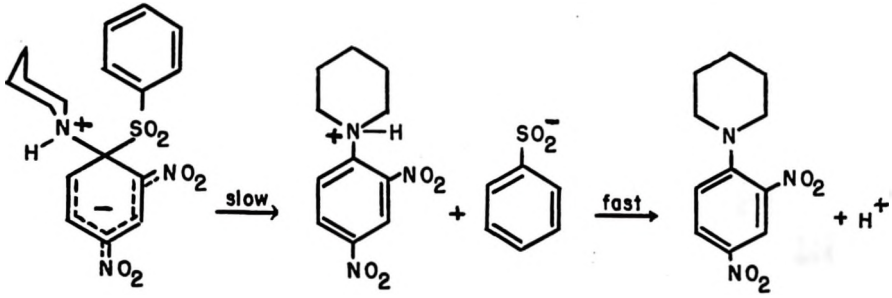


...(110)

Equally compatible with his results, however, is a one-step decomposition of the intermediate in which departure of fluoride ion is concurrent with proton abstraction by base.

The present study has been able to resolve the question of the detailed pathway of decomposition of the intermediate in the reaction of piperidine with 2,4-dinitrodiphenylsulphone. Since carbon-sulphur bond rupture clearly has been shown to be involved in the rate-determining step of this reaction, the mechanism of decomposition obviously is not that proposed by Bunnett for his reaction system. Two other possibilities remain. One is a one-step process in which carbon-sulphur bond rupture and proton-abstraction are synchronous and the

other a stepwise process in which rapid proton abstraction follows a rate-determining elimination of the benzene-sulphinate ion (equation 111),



...(111).

The first of these possible pathways should be subject to base catalysis and the second should not.

It will be recalled from Ross' studies that solvent itself can function as a base, this function becoming of increasing importance as the solvating ability of the medium is increased. Even if proton abstraction is involved in the rate-determining step, one might not expect to find base catalysis in the reaction of piperidine with the sulphone in such polar solvents as methanol and acetonitrile. In benzene, however, a poor solvent for ions, base catalysis should be observed if proton abstraction is part of the rate-determining step. Since the nucleophilic reagent

piperidine is a strong base, in fact much stronger than the amines used by Ross, a synchronous proton abstraction and carbon-sulphur bond rupture should give rise to a kinetic dependence upon piperidine concentration of a power higher than one. A comparison of the rate constants for reactions in benzene in which appreciably different initial concentrations of piperidine were used (reactions under pseudo-first order and second order conditions) are shown in Table XXIV.

TABLE XXIV

EFFECT OF PIPERIDINE UPON REACTION RATE OF 2,4-DINITRODIPHENYLSULPHONE WITH PIPERIDINE IN BENZENE

Temp °C.	Reaction Conditions	Sulphone Concentration m./l.	Piperidine Concentration m./l.	Rate Constant[a] l.mole.$^{-1}$ min.$^{-1}$
25	Pseudo-first order	0.00100	0.0405	0.586 ± 0.003
	Second Order	0.0165	0.0101	0.600 ± 0.007
40	Psuedo-first order	0.000685	0.0203	1.078 ± 0.010
	Second order	0.0186	0.0101	1.032 ± 0.031

(a) Experimentally observed deviations.

It can be seen that the rate constants obtained under these different reaction conditions are the same within experimental error. These results clearly eliminate a concerted process for the decomposition of the intermediate and strongly support a two-step process in which rapid proton abstraction follows a rate-determining departure of the benzenesulphinate ion.

It should be emphasized that this sequence of steps for the decomposition of the intermediate need not hold for other substitutions involving an amine as the nucleophile. Indeed, such a sequence obviously is not followed in reactions which are subject to base catalysis. In these, nitrogen-hydrogen bond rupture is part of the rate-determining step; whether the rupture of the bond to the leaving group occurs concurrently or in a subsequent fast step can only be determined by a study of the kinetic isotope effect associated with the atom whose bond to carbon is broken in the reaction.

SUMMARY

1. The rate constants and activation parameters for the reaction of 2,4-dinitrodiphenylsulphone with piperidine have been measured in three solvents, benzene, acetonitrile, and methanol.

2. The S^{32}/S^{34} isotope effects associated with the reaction have been measured in these three solvents. The magnitude of the effect was found to be strongly solvent dependent, being 1.26 per cent in benzene, 1.59 per cent in acetonitrile, and 0.57 per cent in methanol.

3. An extensive series of tests were carried out to ensure that the separation and degradation procedures did not introduce a spurious isotope effect, and also that the effect did not arise from an equilibrium rather than a rate process.

4. The large variation in the magnitude of the effect with change in solvent has been shown to be entirely incompatible with a concerted mechanism but is readily explicable in terms of the relative stabilization, through solvation, of the transition states for the formation and decomposition of a metastable intermediate. The first isotope effect

study of nucleophilic aromatic substitution has thus provided strong evidence in support of the stepwise mechanism for this reaction.

5. From the magnitude of the observed isotope effect in methanol and the theoretical value for a fully rate-determining carbon-sulphur bond rupture process, it has been estimated that the rates of return of the intermediate to reactants and of its decomposition to products are approximately equal in this solvent.

6. The absence of base catalysis for reaction in benzene strongly suggests that the decomposition of the intermediate to products proceeds through a rate-determining carbon-sulphur bond rupture step followed by a rapid abstraction of a proton from nitrogen.

APPENDIX

Theoretical Calculation of Isotope Effects

Kinetic isotope effect studies provide one of the most useful tools for obtaining information on the nature of the transition states in chemical reactions. With relatively few exceptions, most isotope effect studies have involved reactions in which a bond to hydrogen is broken. The rate differences with isotopes of this element are large and ordinary kinetic methods may be used to evaluate the isotope effect. Isotope effects associated with heavier elements are very much smaller but, using the modern mass spectrometer for the measurement of isotope ratios, they may be evaluated with approximately the same precision as the hydrogen effects.

During the past twelve years, a number of workers, (19, 146, 147) have attempted to give a theoretical basis for the rate differences found for isotopic molecules and equations, based upon the "absolute rate theory" of chemical reactions, have been developed for the evaluation of kinetic isotope effects from vibrational frequency data.

The most familiar treatment is that due to Bigeleisen (146, 147) and the present discussion will be restricted to his equation and its application to the theoretical calculation of the sulphur isotope effect to be expected in a reaction involving carbon-sulphur bond rupture in a rate-determining step.

The Bigeleisen equation takes the form

$$\frac{k_1}{k_2} = \left[\frac{m_2^*}{m_1^*}\right]^{\frac{1}{2}} \left[1 + \sum_i Gu_i \Delta u_i - \sum_i Gu_i^{\ddagger} \Delta u_i^{\ddagger}\right] \qquad \ldots(112).$$

The subscripts 1 and 2 refer to light and heavy isotopic molecules, respectively, and the double dagger, ‡, designates a property of the transition state. The term m_2^*/m_1^* is the ratio of the "effective masses" of the isotopically different species along the reaction co-ordinate. The symbol $\sum_i Gu_i$ is a convenient representation of the complex function

$$\frac{1}{2} - \frac{1}{u_i} - \frac{1}{e^{u_i} - 1}$$

where u_i is related to the normal vibration frequency of the molecule as follows,

$$u_i = \frac{hc}{kT} \omega_i \qquad \ldots(113).$$

(h = Plancks constant, k = Boltzmann constant, c is the velocity of light and T is the absolute temperature). The term Δu_i then is

$$\Delta u_i = \frac{hc}{kT}\left[\omega_{1_i} - \omega_{2_i}\right] \qquad \ldots(114).$$

The effective mass term, $\left[m_2^*/m_1^*\right]^{\frac{1}{2}}$, sometimes referred to as the temperature-independent term, expresses the relative rates at which the two isotopic molecules pass over the potential energy barrier. The second term, $\left[1 + \sum_i Gu_i \Delta u_i - \sum_i Gu_i^* \Delta u_i^*\right]$, frequently referred to as the temperature-dependent term, expresses the free energy differences of the isotopic molecules in the ground and in the transition states.

A complete evaluation of Bigeleisens equation requires a knowledge of the "effective masses" and of all the fundamental vibration frequencies of the isotopic reactants and transition states. For the vast majority of molecules, such information is not available. It is possible, nevertheless, to use the Bigeleisen equation to calculate an isotope effect by making certain simplifying assumptions.

One approximation frequently used to evaluate the "effective mass" term is to consider only the masses of the atoms comprising the bond to be ruptured. The reduced mass, μ, of this imaginary diatomic molecule then is used in

place of m^* (148). The validity of this approximation has been discussed elsewhere (149). To evaluate the temperature-dependent term, it is normally assumed that all vibration frequencies except that of the bond being broken are the same in the reactant and in the transition state and, therefore, cancel. It is further assumed that the force constant of the bond being ruptured is very nearly zero in the transition state and hence the factor $\sum_i Gu_i^* \Delta u_i^*$ is negligible. The Bigeleisen equation then becomes

$$\frac{k_1}{k_2} = \left[\frac{\mu_2}{\mu_1}\right]^{\frac{1}{2}} \left[1 + \sum_i Gu_i \Delta u_i\right] \qquad \ldots(115).$$

The above, are, of course, gross approximations but their use has given isotope effect values in surprisingly good agreement with experimental results (150, 151, 152, 153).

Using the simplifying assumptions outlined above, it is possible to estimate the maximum isotope effect[1] to be expected for rupture of the carbon-sulphur bond in the reaction of 2,4-dinitrodiphenylsulphone with piperidine. The reduced masses of the C^{12}-S^{32} and C^{12}-S^{34} bonds yield a value 1.0081 for the temperature-independent term.

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1. This is a maximum value only when the assumptions used in simplifying Bigeleisens equation are valid.

The temperature-dependent term is rather more difficult to estimate. The initial state in this reaction is the metastable intermediate, for which no spectral data is available. Its structure is, however, analogous to that of an aliphatic sulphone. The carbon-sulphur bond vibration frequencies of such sulphones (and of a wide variety of other sulphonyl compounds) have been found to lie in the range 750 to 790 cm.$^{-1}$ (154, 155). Using 790 cm.$^{-1}$ for the frequency of the C^{12}-S^{32} bond, a frequency of 784 cm.$^{-1}$ is calculated for the C^{12}-S^{34} bond from the expression

$$\frac{\nu_1}{\nu_2} = \left[\frac{\mu_2}{\mu_1}\right]^{\frac{1}{2}} \qquad \ldots(116).$$

These frequencies then lead to a value of 0.0087 for $Gu_i \Delta u_i$ and hence to the value 1.0087 for the temperature-dependent term of the Bigeleisen equation. The product of the temperature-dependent and temperature-independent terms, equalling k^{32}/k^{34}, is 1.0169. In other words, the assumption of a C^{12}-S^{34} bond frequency of 790 cm.$^{-1}$ and a complete bond rupture in the transition state leads to the prediction of a maximum isotope effect of 1.7 per cent for this reaction.

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