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CARBANION AND ENOL INTERMEDIATES IN C-NITROSATION AND HALOGENATION

Alan Graham

ABSTRACT

A kinetic study of the nitrosation of ethyl cyanoacetate, diethyl malonate and malononitrile, in acidic water/dioxan solution, by nitrous acid, at 25° C, was undertaken. Catalysis of this reaction was obtained by the addition of nucleophilic catalysts; chloride ion, bromide ion, thiocyanate ion and thiourea. The results were consistent with a mechanism where malononitrile reacted exclusively via the carbanion intermediate. Within the pH range used, pH 0.7 to pH 3.3, ethyl cyanoacetate and diethyl malonate reacted either through a carbanion intermediate, at higher acidity, or an enol intermediate, at lower acidity. Values of the second order rate constant for the attack of the nitrosating species upon the carbanions were obtained. The carbanions of malononitrile and diethyl malonate reacted at the diffusion limit, in the presence of catalysts. Nitrosation of ethyl cyanoacetate, via its carbanion, showed an already established trend in the reactivity of the nitrosating species, $\text{NO}^+\text{SC}(\text{NH}_2)_2 < \text{NOSCN} < \text{NOBr} < \text{NOCl}$.

A kinetic study of the nitrosation of malonic and methylmalonic acids, and of the iodination and bromination of these two acids as well as ethylmalonic and phenylmalonic acids, in aqueous acidic solutions, at 25° C, was also undertaken. At high acidity nitrosation was shown to proceed via an enol intermediate and at lower acidities via a carbanion. Nitrosation of the intermediate was rate determining. Under certain conditions, in nitrosation, it was possible to make the enolisation rate limiting. Iodination and bromination, by the halogen molecules, involved rate determining enol formation. Iodination by triiodide ion involved rate determining iodination of the enol. Values of the enolisation rate constant, k_e , were obtained for all four of the acid substrates, these were in reasonable agreement for the different electrophilic processes. Between pH 0 and pH 2 the results fitted an intramolecular acid catalysed enolisation mechanism. At higher pH values (2 to 4) the results fitted a change in mechanism to include, additionally, base catalysed enolisation and enol carboxylate formation pathways.

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Carbanion and Enol Intermediates in C-Nitrosation and Halogenation

by

Alan Graham, B.Sc. (Keele), Graduate Society.

A thesis submitted for the degree of Doctor of Philosophy of the
University of Durham, October 1991.



- 9 JUL 1992

To my wife Alison,
mum, dad and Steve.

Memorandum

The work for this thesis has been carried out in the Department of Chemistry at the University of Durham between October 1988 and July 1991. It is the original work of the author unless otherwise stated. None of this work has been submitted for any other degree.

Acknowledgements

To my supervisor, Professor D.L.H.Williams, I am deeply indebted for all of his expertise, guidance and encouragement over the last three years.

I would like to thank my fellow physical organic researchers; Hanif, John, Shirlene, Andrew, Paula, Simon, Tim, Jav and John, for their advice and continued friendship. Thanks are also due to Mr.C. Greenhalgh for the maintenance of all of the spectrophotometers and especially for writing some of the computer software. I would also like to extend my thanks to Mrs.M.Butterfield for her persistence and aid in maintaining a clean and tidy laboratory.

In conclusion, I would like to thank the Science and Engineering Research Council (S.E.R.C.) for providing the funding for this research.

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CHAPTER 1

INTRODUCTION



1.1 Nitrosation

Nitrosation is the chemical process by which the nitroso group ($-\text{NO}$) is incorporated into a molecule. In the 1840's Piria¹ reacted aliphatic primary amines with nitrous acid and in the 1850's Hofmann² performed similar reactions with aromatic amines, both isolating the deamination products. In 1873 Victor Meyer³ produced nitrolic acids from aliphatic nitro compounds, the first example of nitrosation at carbon.

Since these early nitrosation reactions the field of study has expanded greatly, to the extent that certain nitrosation reactions have become standard procedures, not only in the laboratory but also in industrial processes. The nitrosation products or their decomposition products may be of great use themselves, as in the formation of azo dyes from the diazotisation of amines^{4,5}, or the use of alkyl nitrites as vasodilators in medicine⁶. Alternatively the nitrosation species may be an important intermediate in the synthesis of other products, for example the use of nitroso compounds in rubber production or the nitrosation of cyclohexane derivatives to produce ϵ -caprolactam^{7,8,9,10} which in turn is used in the production of nylon-6.

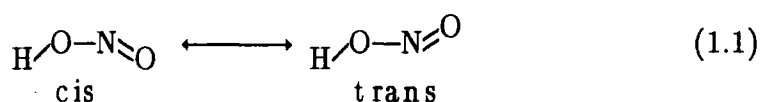
The discovery in 1956¹¹ that nitrosamines were potent carcinogens generated tremendous interest in their chemistry. Nitrosamines can be formed in the stomach under acidic conditions from ingested nitrites or nitrates with some naturally occurring amines and amino acids.

Nitrosation reactions can be performed by a great many differing nitrosating species under a wide range of reaction conditions.

1.2 Nitrosating species

1.2.1 Nitrous acid

Of all the reagents used to perform nitrosation and diazotisation reactions, by far the most commonly used is nitrous acid. Solutions of nitrous acid can be made easily from the combination of nitrite salts (most commonly sodium nitrite) and an aqueous mineral acid. The molecular structure of nitrous acid is well known^{1 2} and exists in solution in both the cis and trans forms, (equation 1.1). It is the trans form that predominates as it is more stable than the cis form.

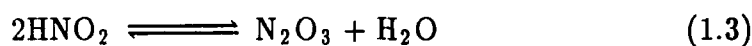


Nitrous acid is a weak acid, with a pKa of 3.148 at 25°C^{1 3}, which has been determined by several different methods; conductometric^{1 4}, potentiometric^{1 5} and kinetic^{1 6}, which are all in good agreement.

In solution nitrous acid decomposes quite readily in the presence of acid, (equation 1.2).

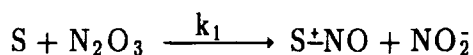
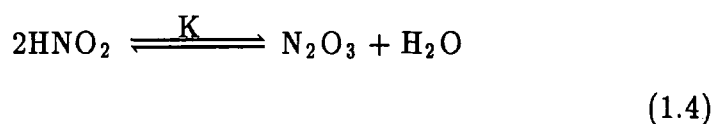


Another important equilibrium of nitrous acid in solution is the formation of dinitrogen trioxide, (equation 1.3).



Dinitrogen trioxide is itself a nitrosating species, its reactions with amines being the most commonly studied^{1 7}. Fairly high nitrous acid concentrations and low acidities produce sufficient dinitrogen trioxide for nitrosation via this species to

have been identified in a kinetic study. Under conditions of lower nitrous acid concentrations and higher acidities, reactions proceed via an electrophilic acid catalysed reaction pathway¹⁸. Experimentally it is easy to differentiate between reaction via dinitrogen trioxide and the acid catalysed pathway, due to the different rate equations. The reaction of dinitrogen trioxide with a substrate (S), (equation 1.4), has a second order dependence upon the nitrous acid concentration, (equation 1.5).

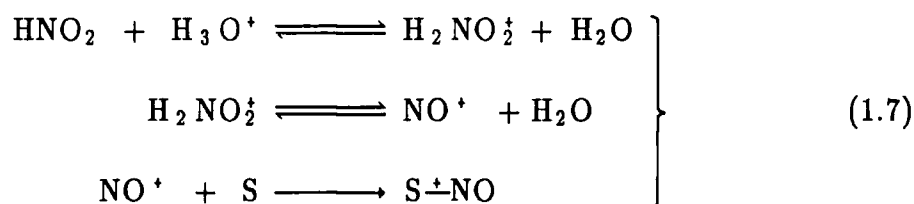


$$\text{Rate} = k_1 \text{K}[\text{S}][\text{HNO}_2]^2 \quad (1.5)$$

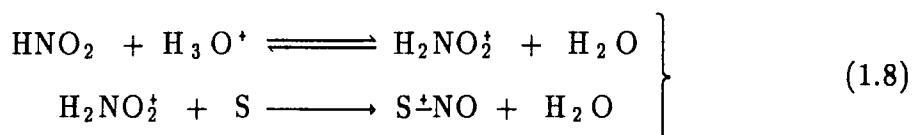
The acid catalysed pathway however only has a first order dependence upon the nitrous acid concentration, (equation 1.6).

$$\text{Rate} = k[\text{S}][\text{H}_3\text{O}^+][\text{HNO}_2] \quad (1.6)$$

Two possible mechanisms have been proposed which both correspond to the rate equation. One is that reaction is through the nitrosonium ion¹⁹, (equation 1.7),

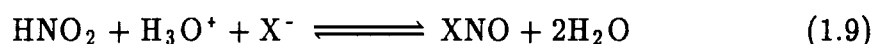


the other is that the reaction goes through the hydrated nitrosonium ion (or nitrous acidium ion), (equation 1.8).



Although there has been no clear evidence to date, to distinguish between these possibilities, a first order dependence upon nitrous acid concentration has been shown for a large number of substrates^{20 - 24}. In fact the only clear evidence is for solutions of very high acidity, i.e. 60% perchloric acid²⁵. In this case the presence of the nitrosonium ion has been shown spectroscopically. The nitrosonium and nitrous acidium ions are indistinguishable and for the rest of this work the nitrosonium ion only will be quoted for the reactions of nitrous acid.

The addition of a non-basic nucleophile (X^-), (equation 1.9), to the acidic nitrous acid solution will generate another equilibrium, giving equilibrium concentrations of a nitrosyl species (XNO) which can then act in solution as an additional nitrosating species, such as the nitrosyl halides²⁶.



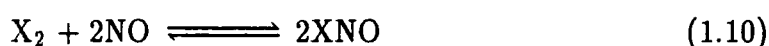
1.2.2 Nitrosyl halides, nitrosyl thiocyanate and S-nitrosothiuronium ion

Nitrosyl fluoride, nitrosyl chloride and nitrosyl bromide have all been characterised fully²⁷ and there is spectroscopic evidence for the existence of nitrosyl iodide, in both solution and the gas phase. All nitrosyl halides are gaseous at room temperature and pressure. Some of their physical properties are shown in table 1.1.

TABLE 1.1: Some physical properties of the nitrosyl halides.

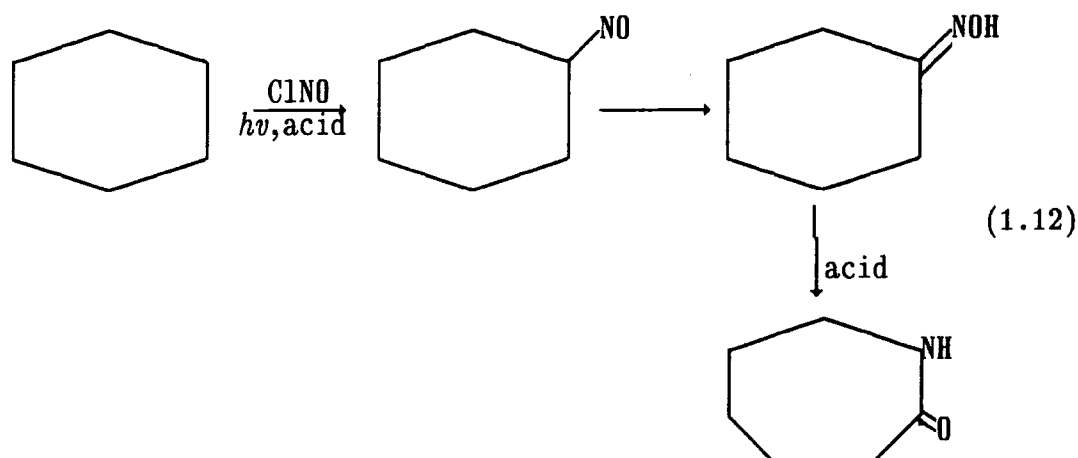
Nitrosyl halide	Colour	Melting point/ ^o C	Boiling point/ ^o C
FNO	Colourless	-133	-60
ClNO	Yellow/orange	-62	-6
BrNO	Red	-56	0

As they are all gases their use as nitrosating species has involved bubbling the gas into a range of different organic solvents²⁸. This is beneficial in the nitrosation of substrates which are not soluble in water. Nitrosyl chloride has been used to nitrosate a wide range of substrates for example alcohols²⁹, carbonyl compounds^{30,31,32,33} and primary amines²⁰. The nitrosyl halides can be generated by the direct reaction of the halogen with nitric oxide, (equation 1.10), or they can be generated *in situ* using nitrous acid and the halide ion, (equation 1.11).



The nitrosyl halides can react either as electrophilic^{34,35} or free radical nitrosating species⁷, depending upon the experimental conditions. The free radical process involves irradiation of the nitrosyl halide by ultra-violet light. The synthesis of nylon-6 involves the synthesis of ϵ -caprolactam which can be formed by irradiating an acidic solution of cyclohexane and nitrosyl chloride. The product is the oxime, (equation 1.12), which can undergo a Beckmann rearrangement to give ϵ -caprolactam. There is no detailed mechanism for this process, but it seems

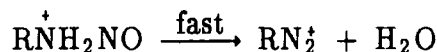
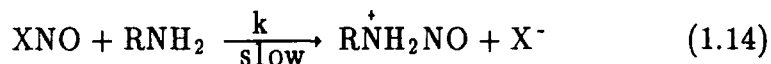
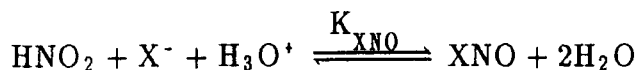
reasonable to assume that free radicals are involved.



As electrophilic nitrosating species the nitrosyl halides are usually formed, *in situ*, from aqueous acidic nitrous acid solutions with halide ions present. The nitrosyl halides, present in equilibrium concentrations, then act as nitrosating species. Spectrophotometric determinations, by Schmid and coworkers^{36,37}, of the equilibrium constants, (equation 1.13), were performed for nitrosyl chloride and nitrosyl bromide. No values for nitrosyl fluoride and nitrosyl iodide have been calculated. The nitrosyl iodide case is due to the ready formation of iodine.

$$K_{\text{XNO}} = \frac{[\text{XNO}]}{[\text{HNO}_2][\text{H}_3\text{O}^+][\text{X}^-]} \quad (1.13)$$

The early work of Schmid³⁸ showed catalysis due to added hydrochloric acid in the nitrosation of anilines. Hammett³⁹ later gave a mechanistic interpretation of these data involving the rate limiting attack of the nitrosyl halide upon the amine, (equation 1.14).



The overall rate equation for this process, (equation 1.15), is

$$\text{Rate} = kK_{\text{XNO}}K_a[\text{X}^-][\text{HNO}_2]_{\text{T}}[\text{RNH}_2]_{\text{T}} \quad (1.15)$$

where $[\text{HNO}_2]_{\text{T}}$ and $[\text{RNH}_2]_{\text{T}}$ are the total stoichiometric concentrations of the nitrous acid and amine respectively, K_{XNO} is the equilibrium constant for the nitrosyl halide formation and K_a is the acid dissociation constant for the protonated amine. Values for k , the second order rate constant, can only be calculated accurately if both K_{XNO} and K_a are known. For certain substrates, aniline derivatives⁴⁰ and some sulphur compounds⁴¹ that are very reactive, the rate determining step changes to that of the formation of the nitrosyl halide. The third order rate constants for the attack of the halide ion upon the nitrosonium (or nitrous acidium) ion can readily be found.

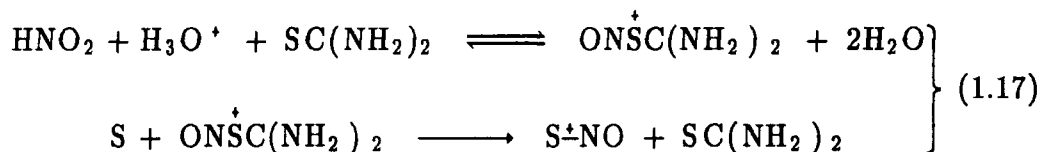
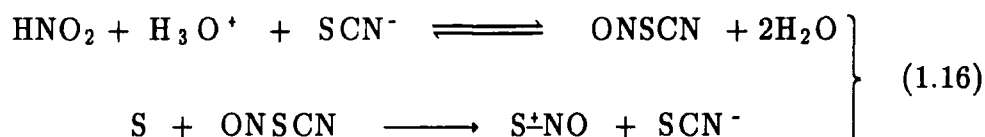
Bromide ion catalysis has been shown always to be greater than chloride ion catalysis, this is due to the difference in the K_{XNO} values being more substantial than the differences in the k values. However, with respect to intrinsic reactivity $\text{ClNO} > \text{BrNO}$, due to the difference in electronegativity between chlorine and bromine, a trend expected for an electrophilic process.

Nitrosyl thiocyanate is believed to be a covalent compound with a sulphur bound nitroso group⁴², although due to its instability the structure has not been shown conclusively.

S-nitrosothiouronium ion is known as a nitrosating species. This was clearly

demonstrated by the addition of thiourea, to a reaction solution, in the nitrosation of morpholine resulting in catalysis⁴³.

Nitrosyl thiocyanate and S-nitrosothiouronium ion have been shown to nitrosate several different substrates^{44,45,46}. The initial step of the mechanism, the formation of these nitrosating species, and the subsequent rate limiting attack upon the substrate (S) by these species, (equations 1.16 and 1.17), are similar to those ascribed to nitrosation by nitrosyl halides.



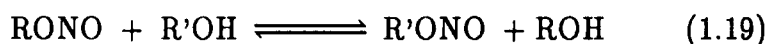
As with the nitrosyl halides the equilibrium constants, K_{XNO} , have been found for the formation of nitrosyl thiocyanate⁴⁷ and S-nitrosothiouronium ion⁴⁸. The series of the reactivity of the nitrosating species, $\text{ClNO} > \text{BrNO} > \text{ONSCN} > \text{ON}^+\text{SC}(\text{NH}_2)_2$, is the reverse of the catalytic activity of the nucleophilic species, $\text{SC}(\text{NH}_2)_2 > \text{SCN}^- > \text{Br}^- > \text{Cl}^-$. Comparison of the equilibrium constants of these reagents, table 1.2, shows that the size of K_{XNO} is the dominant factor in the catalytic effect of each of the nitrosating agents.

Table 1.2: Equilibrium constants and second order rate constants, for attacks on substrates, for some nitrosating species, at 25° C.

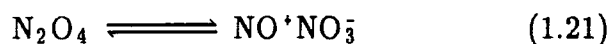
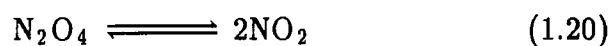
Nitrosating species	K_{XNO}/l^2mol^{-2}	2-nitropropane $k_2/ l mol^{-1}s^{-1}$	aniline $k_2/ l mol^{-1}s^{-1}$
NOCl	1.1×10^{-3}	8.8×10^7	2.2×10^9
NOBr	5.1×10^{-2}	5.1×10^6	1.7×10^9
NOSCN	30	8.6×10^3	1.9×10^8
$NO\overset{+}{S}(NH_2)_2$	5000	—	1.3×10^6

1.2.3 Other nitrosating species

There are other species which can effect nitrosation, but perhaps are not as widely used as those previously mentioned. Alkyl nitrites are formed by the nitrosation of an alcohol⁴⁹, (equation 1.18). Their only advantage over nitrous acid is their ability to transfer the nitroso group to a substrate (such as an alcohol), in non-aqueous media, (equation 1.19). This is known as transnitrosation.



There are three oxides of nitrogen which are known to nitrosate, dinitrogen trioxide in equilibrium with nitrous acid in solution has been discussed previously. Dinitrogen tetroxide, although usually known for its equilibrium with nitrogen dioxide, (equation 1.20), involved in free radical nitrations⁵⁰ can also under certain conditions effect electrophilic nitrosations⁵¹, (equation 1.21). This has been reported for alcohols, thiols and amines⁵².



Nitric oxide, NO, has been reported as a nitrosating species⁵³ but this reaction possibly involved aerial oxidation of the nitric oxide to dinitrogen trioxide or dinitrogen tetroxide and then subsequent reaction via these species. However, with careful exclusion of oxygen, under basic conditions, in the presence of a metal or other catalyst, nitric oxide can be an effective nitrosating agent^{54,55}.

Nitrosyl acetate, formed from the addition of sodium nitrite to glacial acetic acid has proved useful for nitrosation in organic solvents^{19,56}.

Finally nitrosonium salts, X^-NO^+ , have also been shown as effective nitrosating agents (eg. BF_4^- , BCl_4^- , HSO_4^- , ClO_4^-) under anhydrous conditions, hence avoiding hydrolysis to give nitrous acid.

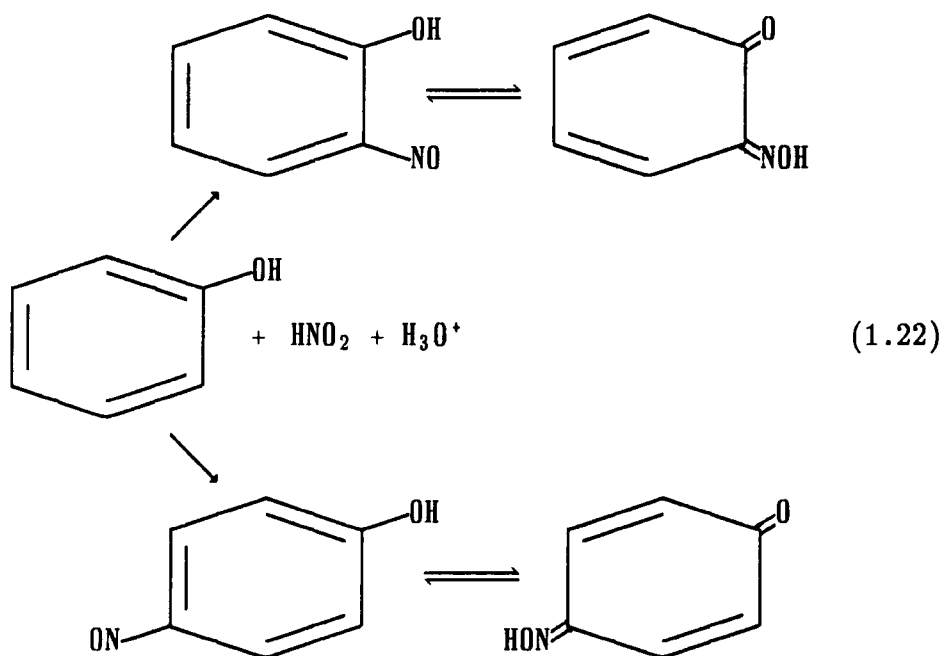
1.3 C-Nitrosation

C-nitroso compounds are known to exist as monomers, dimers or in the tautomeric oxime form. The oxime and dimer are considered to be more stable, but steric and other features of the compound may stabilise the monomer, for example secondary nitro compounds upon nitrosation form α -nitro nitroso compounds which exist as the monomer in solution³. Oximes from both primary and secondary nitroso compounds are widely used by synthetic chemists as intermediates in many standard procedures, for example the hydrogenation of the oximino group to an amine group, as in the synthesis of alanine⁵⁷, which involves 2-oximinopropanoic acid (from the nitrosation of methylmalonic acid) as an intermediate. However due to the reaction dependence upon many factors including the solvent and temperature the products can be obtained in either monomeric, dimeric or oximino forms.

1.3.1 Aromatic C-nitrosation

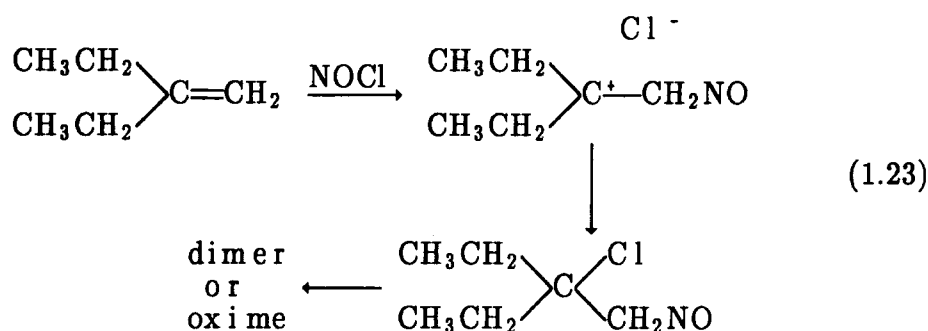
Nitrosation at carbon in a molecule has been predominantly studied for aliphatic and alicyclic compounds, which will be discussed in some detail later.

Aromatic C-nitrosation however is a less studied subject as the nitrosating species are either not powerful enough electrophiles or are not present in sufficiently high concentrations to facilitate nitrosation. The substrates under nitrosation have largely been substituted aromatics, the most commonly studied being phenol which undergoes C-nitrosation at room temperature with nitrous acid in mildly acidic solution^{5,8}, (equation 1.22). The product is predominantly 4-nitroso-phenol but the 2-nitrosophenol isomer does form a small part of the product mixture ($\approx 10\%$ at 40°C). In solution both of the nitroso-phenols exist mainly in the tautomeric benzoquinone monooxime form.



1.3.2 Nitrosation of alkanes and alkenes

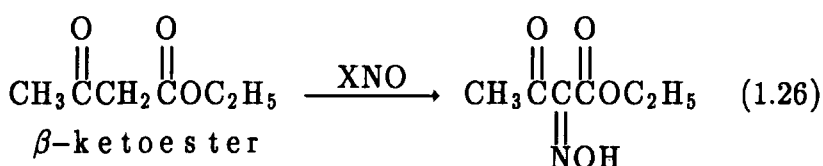
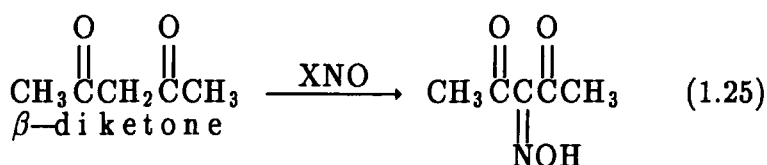
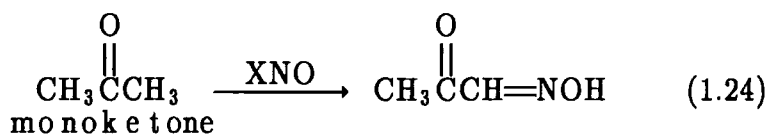
In 1919^{5,9} a solution of nitrosyl chloride and heptane was unintentionally left exposed to sunlight; this led to the discovery that alkanes and nitrosyl chloride will yield a C-nitroso product (or an oxime). The free radical mechanism is not a selective method and so many different products are possible. In cyclohexane the hydrogen atoms are all equivalent and hence the synthesis of ϵ -caprolactam⁷ has an industrial application, previously mentioned in section 1.2.2. Nitrosyl halides have been used as electrophilic nitrosating species in the nitrosation of alkanes. The pioneering work of Tilden and Stenstone^{6,0} first showed the nitroso chloro products of nitrosation of alkenes by nitrosyl chloride. Addition goes via the more stable carbocation as expected for an electrophilic addition reaction, (equation 1.23). The products are most usually the dimer or oxime due to the relative instability of the nitroso chloro compound.



Alkenes are also known to undergo nitrosation by dinitrogen tetroxide and dinitrogen trioxide^{5,0,6,1}. The nitrosating abilities of both species has been covered earlier in this chapter. In the case of dinitrogen trioxide attack upon alkenes, giving a nitroso nitro product, can involve a free radical mechanism. Evidence has been produced for the electrophilic nitrosation involving dinitrogen trioxide as NO^+NO_2^- , in dilute aqueous solution.

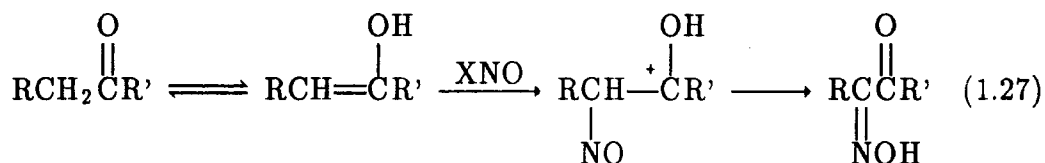
1.3.3 Nitrosation of ketones

Ketones can be thought of as compounds containing an active methyl or methylene group, that is a methyl or methylene group adjacent to the carbonyl group. Nitrosation at this active methyl or methylene is widely known for a large range of ketones^{62,63}. The product is usually the α -oximino ketone. Not only is nitrosation of monoketones known (aromatic as well as aliphatic) but also that of other compounds with an active methyl or methylene group adjacent to more than one carbonyl group, β -diketones⁶⁴, β -ketoacids⁶⁵, β -ketoesters⁶⁶. Some examples are shown in equations 1.24, 1.25 and 1.26.



Most of the nitrosating species are effective in reactions with ketones, but the most commonly used preparatively, have been the nitrogen oxides, nitrosyl chloride, nitrosyl sulphuric acid, alkyl nitrites (mainly in organic solvents) and aqueous acidic nitrous acid solutions. Unlike in N-nitrosation, the quantity of work carried out to establish the reaction mechanisms for the nitrosation of ketones is relatively small. Recent work⁶⁷, however, has provided evidence that reaction proceeds via the tautomeric enol form of the ketone. The keto-enol equilibrium will be discussed more thoroughly later in this chapter. The mechanism, (equation

1.27), is of course analogous to those of the halogenation and deuteration of ketones.

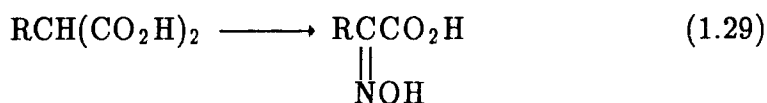
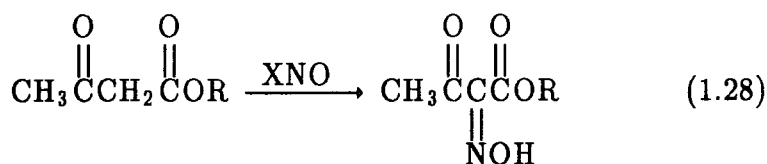


Singer and Vamplew⁶⁸ did propose an alternative mechanism involving electrophilic attack on the keto form followed by internal –NO transfer. The grounds for this mechanism were that the rate of the nitrosation was far faster than that of the enolisation under the same reaction conditions effectively ruling out enol involvement. The error in this case was to compare second and third order rate constants.

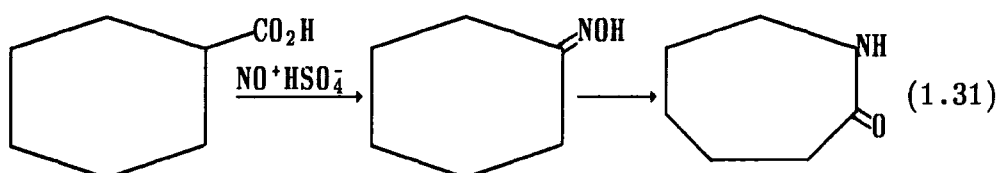
Nitrosation of ketones has been shown to involve the enol. In the presence of nucleophilic catalysts the reaction has been shown to be zero order in $[\text{HNO}_2]$ and $[\text{X}^-]$. These correspond to rate limiting enol formation. Again this has been seen in the halogenation of ketones and the agreement between the rate constants is good. The nitrosation can be made rate limiting by adjusting $[\text{H}_3\text{O}^+]$, $[\text{X}^-]$ or $[\text{HNO}_2]$ and hence the rate constant for the attack of XNO can be obtained.

1.3.4 Nitrosation of other carbonyl compounds

Other carbonyl compounds, most significantly β -keto esters⁶⁹, (equation 1.28), alkyl malonic acids⁷⁰, (equation 1.29), and esters⁷¹, (equation 1.30), have been shown to undergo nitrosation. As with ketones the products are the corresponding oximes. Nitrosation of alkylmalonic acid has also been shown to involve decarboxylation, (equation 1.29).



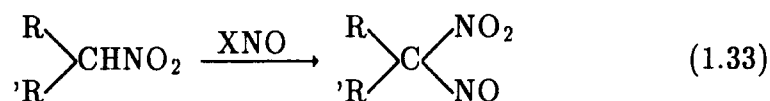
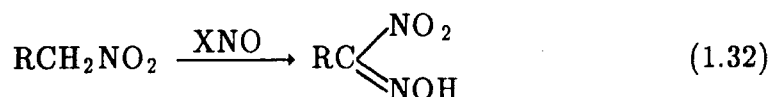
The Snia-Viscosa process¹⁰, (equation 1.31), is another industrially viable process to ϵ -caprolactam formation. Japanese patent literature suggests that a ketene intermediate is formed, but it is more likely that the enol tautomer is involved, this will be discussed further in chapter 3.



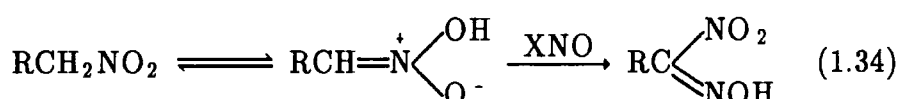
1.3.5 Nitrosation of compounds containing other electron withdrawing group

An active methyl or methylene group does not necessarily have to be adjacent to a carbonyl group to undergo nitrosation. Other electron withdrawing species, nitro, aryl, cyano, halo and imino, have been seen to be effective in promoting nitrosation. A nitro compound was the first substrate (in 1873)³ to undergo C-nitrosation. This work by Victor Meyer led to his colour test for distinguishing between primary, secondary and tertiary structures. Primary nitro compounds form α -nitro oximes upon nitrosation which are red in basic solution, (equation 1.32). Secondary nitro compounds form α -nitro nitroso compounds which are blue

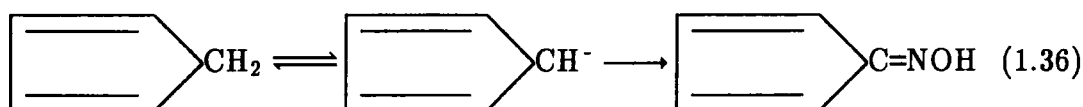
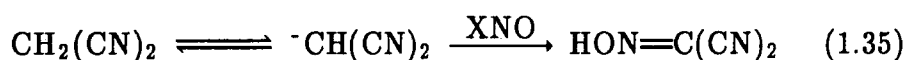
in basic solution, (equation 1.33). Tertiary nitro compounds do not react and so do not involve a colour change.



The mechanism almost certainly occurs via the nitronic acid, (equation 1.34) and is analogous to the mechanism for carbonyl reactions involving the enol intermediate.



With cyano groups as the electron withdrawing part of the molecule a mechanism involving the carbanion as the reactive intermediate has been shown⁷² to occur at relatively low acidities, (equation 1.35). This is also thought to be the intermediate in the nitrosation of cyclopentadiene⁷³, (equation 1.36).



1.4 Halogenation

The halogens, fluorine, chlorine, bromine and iodine have all been studied for many years and their physical properties are well known^{74,75}. Some are displayed in table 1.3.

TABLE 1.3: Some physical properties of the halogens.

Halogen	Appearance	m.p./ C°	b.p./ C°	Electro- negativ- ity	Ionisation enthalpy $\Delta H_{298}/\text{kJmol}^{-1}$	Standard red.pot. E°/V
F ₂ (g)	yellow / green	-223	-188	4.1	1682	+2.65
Cl ₂ (g)	yellow / green	-103	-34.6	2.8	1255	+1.36
Br ₂ (l)	red/ brown	-7.2	58.8	2.7	1142	+1.07
I ₂ (s)	grey/ black	113.5	184.4	2.2	1008	+0.54

Fluorine is often the most reactive halogen followed by chlorine, bromine and iodine, in a number of reaction types. The standard reduction potential of the halogens, (equation 1.37) decreases from X = F to X = I.

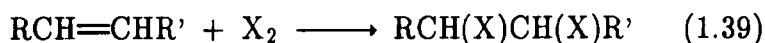


There are many properties of the halogens that can be discussed and are very comprehensively studied^{76,77}. In organic chemistry halogenation can occur by two processes. A halogen molecule upon irradiation will form free radicals which will halogenate a substrate⁷⁸, (equation 1.38).

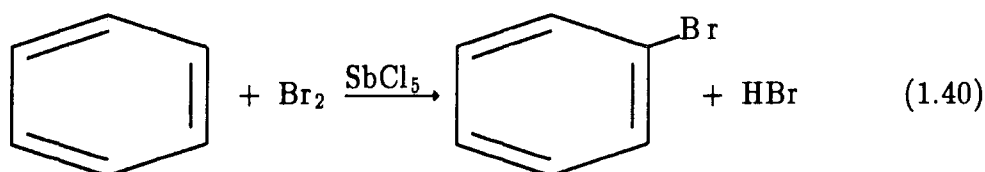


The other process is electrophilic halogenation and this can also be considered

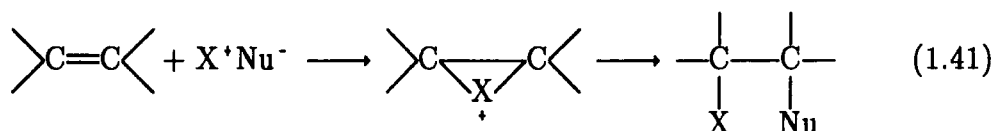
in two broad categories. There is an addition reaction, most commonly associated with halogenation of an olefin⁷⁹, (equation 1.39).



The other process is electrophilic substitution, similar to other electrophilic reactions such as nitration, where another electrophile (commonly a proton) is replaced by the halogen⁸⁰. Under certain conditions this may require the presence of a Lewis acid⁸¹, (equation 1.40), or other co reagents able to enhance the electrophilic capabilities of the halogens⁷⁵.



Halogenation can be carried out directly by the halogen molecule, X_2 , or by the trihalide species, X_3 . Electrophilic addition reactions involving halogenating species are considered to involve a two step process. The most common halogenating species considered is the halogen molecule⁸². The partially polarised halogenating species attacks the olefinic substrate with its positive end thus forming a carbocation intermediate. The carbocation can then react with any nucleophilic species present in solution, (equation 1.41)



Theoretical considerations would indicate rate limiting electrophilic attack by the halogenating species rather than nucleophilic attack by its 'negative end'. Carbocations appear to be relatively more stable than the carbanions, which would be the intermediate in nucleophilic attack. Nucleophilic attack would also be

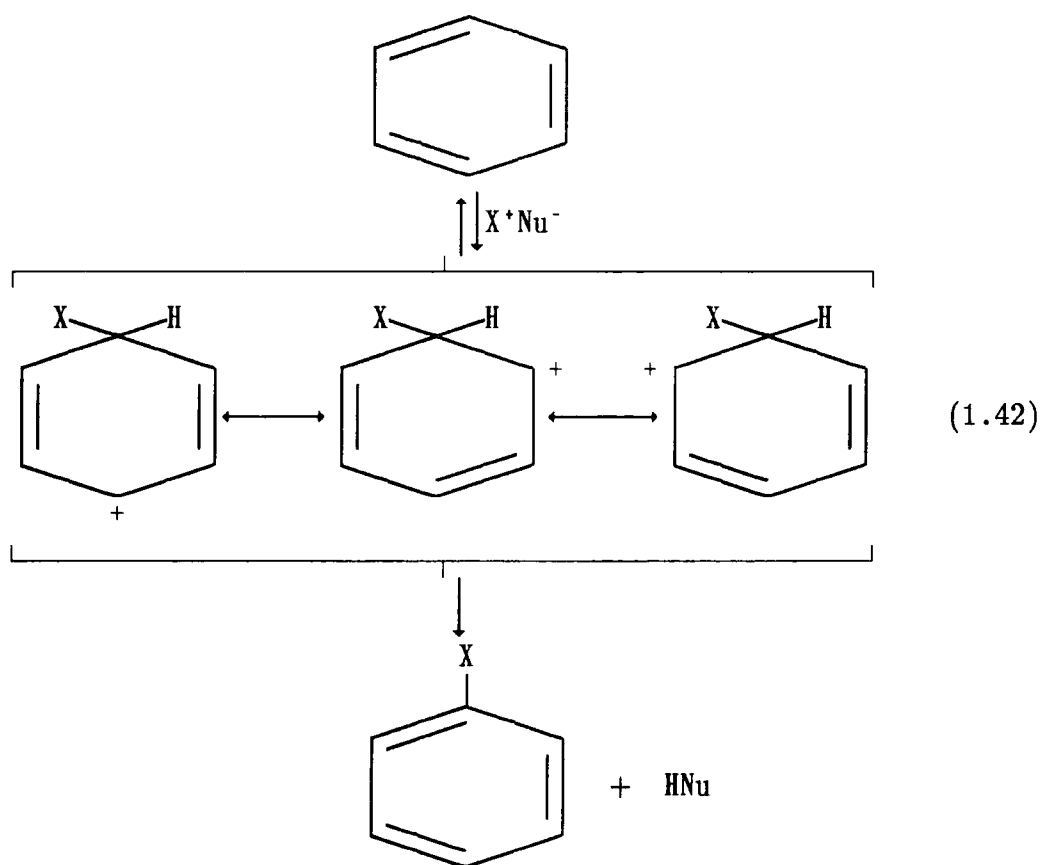
hindered by the unsaturated electrons of the olefin double bond, which would favour attack by an electrophile. Experimentally the addition of other nucleophiles to a reaction mixture, thus diverting reaction products is indicative of an initial electrophilic attack. An example of this is the addition of bromide ions to a solution where chlorination by Cl_2 is occurring, this gives progressively more chloro bromo addition product. Often the solvent is the nucleophile (particularly for reactions in water). In equation 1.41 the intermediate is represented as a bridged ion which is more favoured than the bare carbocation. This helps to explain why these addition reactions give trans addition products.

Experimental evidence favouring the electrophilic attack of the halogen has been documented⁸³, and it is now generally accepted that a two stage process is involved^{84,85}.

Electrophilic substitution reactions, nitration and halogenation, are examples from a significant area in physical organic chemistry. These reactions are most commonly associated with aromatic systems⁸⁶ and have been much studied.

As with the addition reactions, substitution reactions of the halogens are thought of as two step processes. Firstly there is the addition of the electrophilic halogen to give the relatively stable carbocation sometimes called the σ -complex or Wheland intermediate, followed by the loss, usually, of a proton, (equation 1.42), to give the halo product.

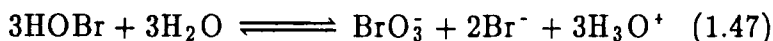
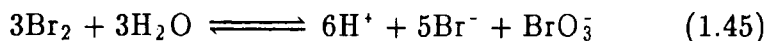
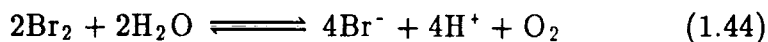
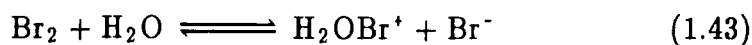
Early work on the mechanism by Melander⁸⁷ involved the study of isotope effects which has now become a standard procedure and is well discussed in the literature^{88,89,90}. Melander showed that there was no isotope effect for the nitration and bromination of some aromatic compounds, indicative of a two step process. Although unlikely, it was postulated⁹¹, that a one step process could also show no isotope effect. Later work^{92,93,94}, using electrophilic substitution processes other than halogenation did show that Melander was correct in postulating that the reaction was a two step process.



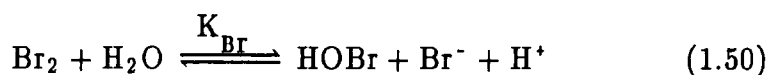
1.4.1 Bromine in aqueous solution

Electrophilic brominations can be performed on a very wide range of unsaturated compounds, simple and substituted olefins⁹⁵, acyclic and cyclic polyenes⁹⁶ and their substituted derivatives, conjugated heterocycles⁹⁷ and compounds containing other types of double bond⁹⁸.

Of course in aqueous solution the number of substrates that can undergo bromination is limited because of solubility problems. Bromine itself has limited solubility in water⁹⁹, but the exact solubility value is confused due to the equilibria the bromine forms in solution. Bromine in solution is involved in several equilibria^{100,101,102}, (equations 1.43 to 1.49).



The combination of these equilibria can make the interpretation of reaction mechanisms complicated. Variation of different reaction conditions makes it possible to repress or enhance different equilibria. It is known¹⁰⁰ that the bare cation, Br^+ , cannot exist in solution but the formation of a covalent bond to a water molecule forms a more stable hydrated cation, H_2OBr^+ , which is the protonated form of hypobromous acid, represented by equations 1.43 and 1.46, and is more commonly represented by equation 1.50.



The value for the equilibrium constant, K_{Br} , has been found to be 5.8×10^{-9} at 25°C ^{101,102}. Increasing the acid concentration of the solution is known to decrease the hydrolysis.

The production of the bromate, (equations 1.45 and 1.47), is not a significant reaction but can be made sufficiently slow with quite high bromide ion and acid

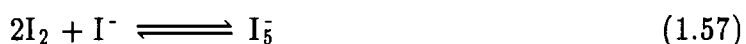
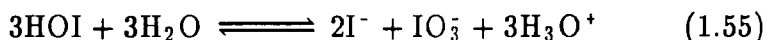
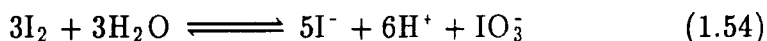
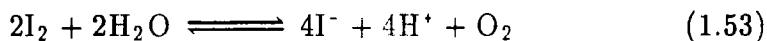
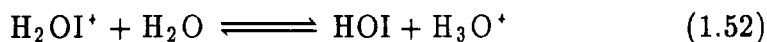
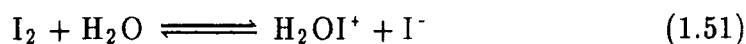
concentrations. The quantity of the tribromide and pentabromide can be reduced by using dilute solutions of bromine, thus significantly reducing the concentration of bromide ion present. Under these conditions electrophilic bromination takes place mainly through molecular bromine. It has been shown that the tribromide also accounts for a small amount of the halogenation^{103,104}. Addition of bromide ion (usually in the form of potassium bromide) to bromine solutions that are well below saturation will enhance the quantity of tribromide.

The tribromide can react either electrophilically, nucleophilically or by bromide ion catalysis¹⁰⁵. The predominant mode of attack has been shown to be as an electrophile. It has been shown that the tribromide is a significantly weaker electrophile than bromine, as expected. An exception to this is the demonstration¹⁰⁶ that the tribromide is a better electrophile than bromine in its reaction with α,β -unsaturated sulphones.

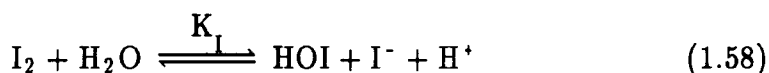
Bromination reactions in aqueous acidic solutions largely occur via the reaction of the bromine molecule upon the substrate¹⁰⁷, although addition of an alkali bromide salt in excess usually results in the effective brominating species being the tribromide¹⁰⁸. The brominations discussed later, chapter 6, fall into the former case.

1.4.2 Iodine in aqueous solution

Electrophilic iodinations, like brominations, can take place with a large number of substrates^{109,110,111}. In aqueous solutions solubility is once again a important factor. Iodine is far less soluble in water¹¹² than bromine⁹⁹, its saturation concentration being approximately 1.3×10^{-3} M compared to 0.2 M for bromine. Iodine addition to water also sets up several important equilibria, (equations 1.51 to 1.57).



The bare iodine cation cannot exist in aqueous solution, but the hydrated iodine cation, (equation 1.51), unlike those of chlorine and bromine, is sufficiently stable to be an appreciable part of a dilute aqueous solution of iodine. In solution the hydrated cation reacts rapidly to form the hypoiodous acid, (equation 1.52), this being part of the hydrolysis of iodine, (equation 1.58).



The equilibrium constant¹¹⁵ for the hydrolysis of iodine is approximately 10^{-13} .

For reactions to take place without the interference of the production of iodate, (equations 1.54 and 1.55), then acidic solutions are used. These push the equilibria to the left and repress the iodate formation. The equilibrium concentration of pentaiodide, (equation 1.57), can be reduced by similar means to the pentabromide mentioned previously, by the use of low halogen concentrations.

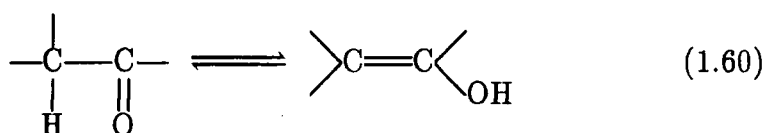
The formation of the triiodide is more substantial than the corresponding tribromide formation in aqueous solution and the equilibrium constant, (equation 1.59), has been measured^{116,117} as $714 \text{ mol}^{-1} \text{ l}$.

$$K_{\text{eq}} = \frac{[\text{I}_3^-]}{[\text{I}_2][\text{I}^-]} \quad (1.59)$$

The triiodide concentration can be vastly enhanced by addition of an alkali iodide (sodium, potassium) to the aqueous iodine solution. Spectrophotometric studies¹¹⁸ have shown a distinctive absorbance peak in the ultraviolet region due to the triiodide upon addition of excess iodide. This also causes a disappearance of the peak of iodine, present for solutions of iodine alone in water. Molecular iodine is the electrophilic reagent in acidic aqueous solutions, the hydrolysis and iodate formation are sufficiently repressed at high acidity to become negligible. If iodide is added in excess then the effective halogenating species becomes the triiodide, which is a much weaker electrophile than iodine. The effectiveness and use of iodine and triiodide as electrophilic halogenating species will be used and discussed in chapters 4 and 5.

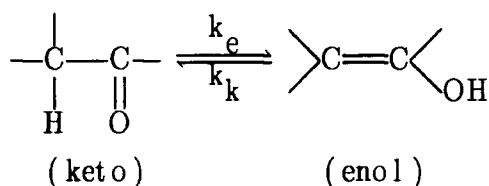
1.5 The keto-enol equilibrium

The involvement of the enol tautomer of carbonyl compounds, (equation 1.60), has been known and studied in chemistry¹¹⁹ since the turn of the century.



Many reactions of carbonyl compounds initially involve the formation of the enolic tautomers¹²⁰, which act as reaction intermediates. This of course means

that the size of the equilibrium constant, for the keto-enol equilibrium, (scheme 1.1), can be crucial to the reaction taking place.



$$K_E = \frac{k_e}{k_k}$$

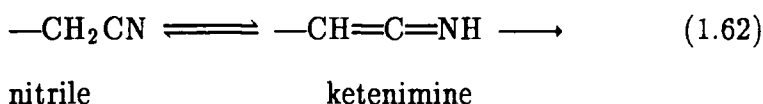
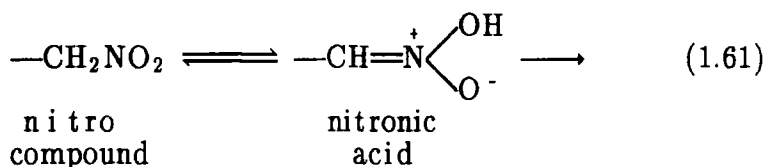
k_e – enolisation rate constant

k_k – ketonisation rate constant

K_E – keto-enol equilibrium constant

Scheme 1.1

There are other equilibria known that are analogous to the keto-enol type, (equations 1.61 and 1.62), and reactions are known to proceed via the enol analogues^{121,122}.



Although much of the early work has centred upon aldehydes and ketones, any carbonyl containing compound should, in theory, be capable of existing in the enol form. Such compounds include esters¹²³, carboxylic acids¹²⁴ and amides¹²⁵. Recent work has demonstrated the existence of such tautomers, in some cases they exist only fleetingly. Even with simple ketones the value of K_E can vary drastically

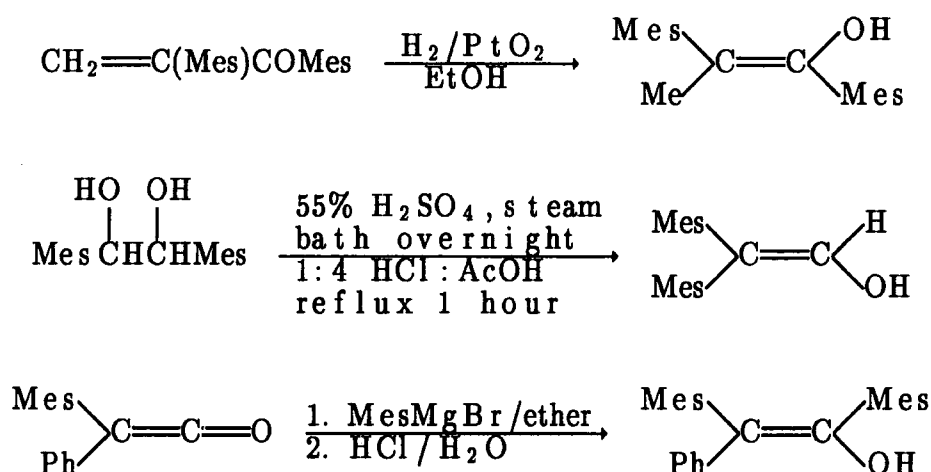
as can be seen by the K_E values of 6.0×10^{-9} and 1.0×10^{-2} for acetone¹²⁶ and chloroacetone¹²⁷ respectively. Structural and solvent¹²⁸ effects are extremely important. Molecular structure, whether the compound is aliphatic, alicyclic or aromatic, or is a mono-, di-, or tri- carbonyl, can also effect K_E . Other substituents within the molecule can also exert influences. All of these effects can be substantial and are briefly discussed in the remainder of this chapter. A recent review, however, gives a very comprehensive treatise of many aspects of enol chemistry¹²⁹.

Early measurements of K_E centred around the removal of the enol tautomer, usually by reaction with bromine¹³⁰. These suffer from an obvious drawback, they require the rate of enolisation to be negligible with respect to the rate of bromination. Consequently many of these early K_E values have been found to be in error. Spectroscopic methods, initially employed by Bell^{131,132} and Dubois¹³³, do not suffer from this drawback. They do however require that the enol content is at least 1%.

For bromination and other reactions, enolisation is often the rate limiting step. Many workers have reported zero order rate dependencies on the substrate attacking species concentration. Thus it is relatively easy to obtain k_e values. Recently Kresge and co-worker¹³⁴ have developed a method for measuring k_k values. This involves enol generation by flash photolytic techniques and observation of the ketonisation of these enols. This has enabled K_E values to be calculated with more accuracy, for example, K_E for acetone is now thought to be approximately 10^{-9} whereas early work calculated it as 10^{-6} .

1.5.1 Enols of monocarbonyl compounds

The volume of research into enols of monocarbonyl compounds is significantly less than that of dicarbonyls, probably due to the instability of many monocarbonyl enols relative to dicarbonyl enols. In 1964 the first structural evidence¹³⁵ for the existence of a simple aliphatic enol was presented. It is worth noting here 'simple' is used to define compounds where the carbonyl is the only active site in the molecule. The enol of acetone was detected using a photochemical process, although its presence had previously been postulated¹³⁶. Although this was the first case reported of a simple aliphatic enol, the enols of some monocarbonyl compounds were already known. These compounds contained large aryl groups (usually mesityl), sterically hindering the structure. This destabilises the keto form and stabilises the enol, hence the enol can be isolated. These enols are commonly known as Fuson's enols after the man who pioneered this work. Examples of the synthesis of some Fuson's enols¹³⁷⁻¹⁴⁰ can be seen in scheme 1.2.

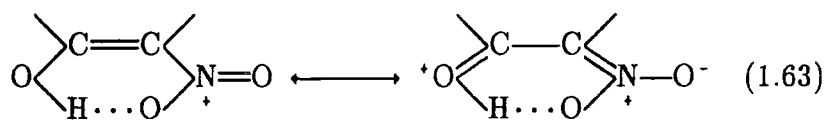


Scheme 1.2

In simple aliphatic monocarbonyls the major effects controlling the equilibrium are hyperconjugative stabilisation, this is an effect of alkyl groups which stabilises the carbonyl form, and cis interactions which are the major factor stabilising the enol tautomer, within the molecule, across the enol double bond to

the hydroxyl group. Additionally in aromatic monocarbonyls polar and resonance effects are more significant in the stabilisation of either the keto or enol forms.

Substituents in both aliphatic and aromatic monocarbonyls can be very important. For example, α -nitro or α -cyano¹⁴¹ groups destabilise the keto form because of their electron withdrawing inductive effect and stabilise the enol form by a resonance effect. There is also the possibility of hydrogen bonding in the enolic form, (equation 1.63).



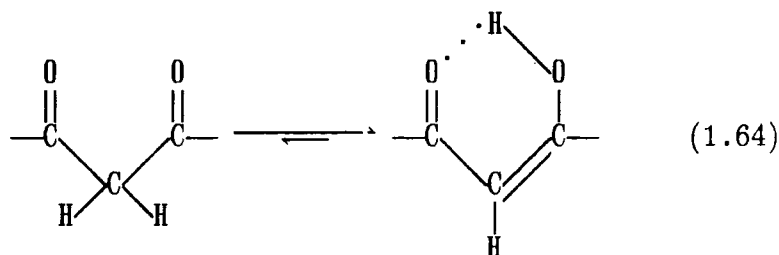
For all of those monocarbonyl compounds the K_E values have a dependence upon the solvent. The keto form is expected to have a larger dipole moment than the enol, hence K_E would be larger in less polar solvents. A hydrogen bond donating solvent would be expected to stabilise the keto form but a hydrogen bond accepting solvent would be expected to stabilise the enol.

1.5.2 Enols of dicarbonyl compounds

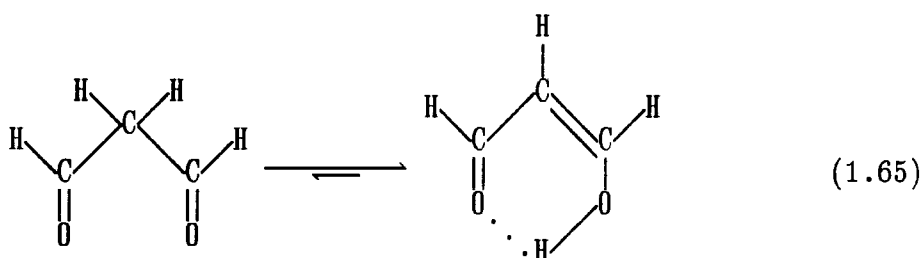
By far the most comprehensively studied compounds are those with the carbonyl β to each other. Aliphatic α -dicarbonyls in water have been reported to exist predominantly in the keto form¹⁴², here the formation of a stabilising intramolecular hydrogen bond is disfavoured. Alicyclic α -dicarbonyls however can form these hydrogen bonds¹⁴³ and hence are as stable as the β -dicarbonyls for which a hydrogen bonded cyclic enol form is well documented.

β -dicarbonyl (diketo-, ketoester-, ketoamide-, diester-, carboxylic acid) compounds have been more widely studied than the enols previously mentioned due to much larger K_E values for these enols. This is largely because the

β -dicarbonyls can form cyclic intramolecular hydrogen bonded compounds, stabilising the enol tautomers, (equation 1.64).



The simplest β -dicarbonyl is malondialdehyde and it is known to exist almost exclusively in the enol form¹⁴⁴, (equation 1.65).



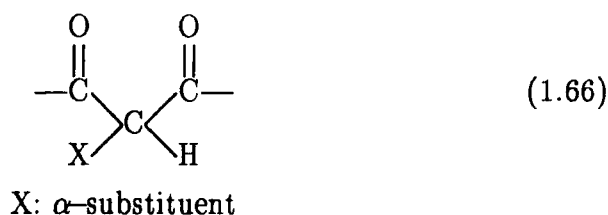
Although the intramolecular hydrogen bonding stabilises the enol tautomer, and enol contents are high for other β -dicarbonyl compounds, they are not as high as those for the parent aldehydes. Hyperconjugative stabilisation due to more alkyl groups stabilises the keto form (as mentioned for monocarbonyls earlier), hence decreasing the size of the equilibrium constant.

TABLE 1.4: Enol contents of pentane-2,4-dione in different solvents.

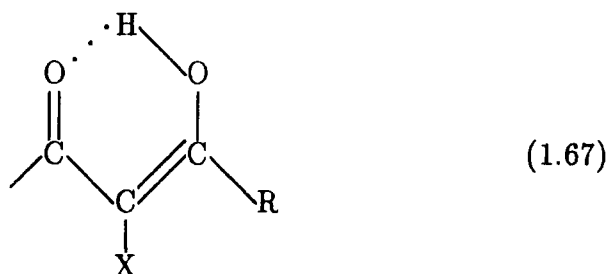
Solvent	C ₆ H ₆	CCl ₄	THF	CHCl ₃	EtOH	MeOH	H ₂ O
% Enol	97	94.6	87.5	82.6	74.4	68.0	12.9

Just as for the monocarbonyls there is quite a substantial solvent effect upon the equilibrium constant. The enol structures are of lower polarity than the keto structures and hence a less polar solvent increases the percentage of enol present. This difference can be quite marked, and is displayed in table 1.4, on previous page. This gives the enol content of pentane-2,4-dione (acetylacetone) in different solvents¹⁴⁵.

The effect of having other substituents in the β -dicarbonyl is dominated by the effect of α -substituents, (equation 1.66), and γ -substituents have been shown to only have small effects on the equilibrium¹⁴⁶.



Alkyl α -substituents have been shown to decrease the enol content of β -dicarbonyls¹⁴⁷. This effect is commonly associated with non bonding interactions between the substituted group X and R in the enol form, (equation 1.67), and not the loss of planar structure in the hydrogen bonded cyclic enol structure.

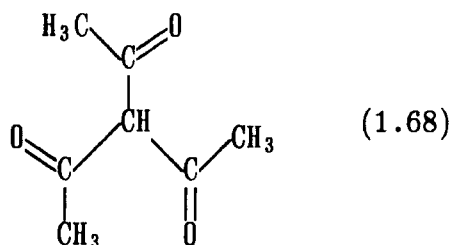


The larger the alkyl substituent the more dramatic the drop in enol content^{148,149}. α -Substituents other than alkyl groups have more complicated effects. The main factors on the equilibrium are due to the substituents size, its effect on polarity and resonance. For example if X in equation 1.67 is a halogen¹⁵⁰

(inductively electron withdrawing) this can destabilise the keto form, increasing the enol content. If X is an unsaturated species¹⁵¹ this could conjugate to the enol double bonds, stabilising the enol.

1.5.3 Enols of tricarbonyl compounds

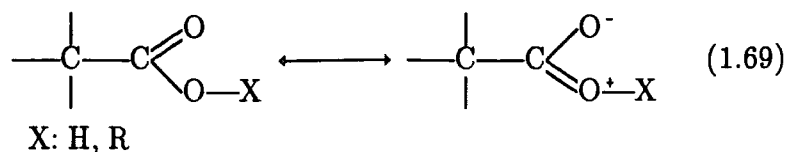
The simplest β,β' tricarbonyl, triacetylmethane, (equation 1.68), has been found to exist almost completely in the enol form and even in water the amount of keto form is relatively much smaller than that present for its corresponding β -dicarbonyl¹⁵².



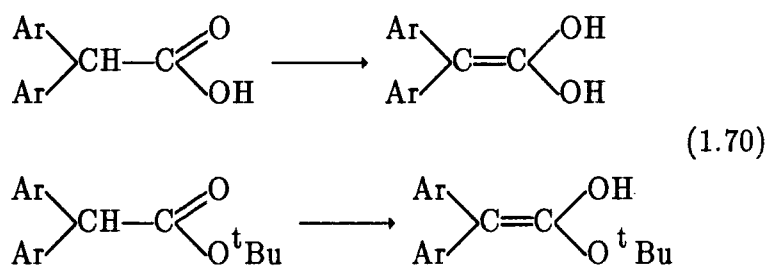
The study of tricarbonyl enol formations has predominantly been to look at the possible formation of different enols and their interconversions. ¹H NMR spectroscopy has been the major tool used in these studies.

1.5.4 Enolisation of carboxylic acids and esters

Enols derived from carboxylic acids and esters have not been as widely studied as those from ketones and aldehydes. This is possibly due to the much smaller K_E values carboxylic acids and esters appear to have. The electron donating powers of the oxygen attached to the carbonyl group can stabilise the keto form, (equation 1.69), reducing the size of K_E .



Ketene hydration is a reaction where enediol intermediates have been postulated; 1,1-enediols have also been discussed as intermediates in the decarboxylation and debromination of dicarboxylic acids¹⁵³. Following similar techniques to those employed by Fuson¹⁵⁴, for sterically hindered enols of ketones, Hegarty and O'Neill¹⁵⁵ have isolated and characterised the acid and ester enols shown in equation 1.70.



Ketene acetals derived from acids and esters have also been used to show the involvement of ester enols in the reaction^{156,157,158}.

Bafna and coworkers¹⁵⁹⁻¹⁶² considered the enol form of malonic acid to be important in its halogenation. Again more recently^{163,164} the halogenation of substituted alkylmalonic acids has been proposed to proceed via the enol intermediate. Under some conditions the enolisation has been made the rate limiting step of the reaction.

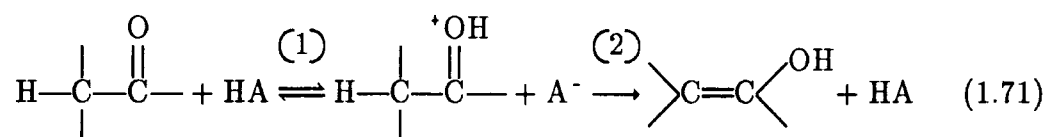
Only very recently the ketonisation of acid enols has been studied¹⁶⁵. The use of flash photolytic techniques to generate excess enol has made it possible to gain values of K_E for substrates where the magnitude of K_E has been too small to be studied by previous methods.

As kinetic methods are improved the study of the synthesis of acid and ester enols and also their role as reaction intermediates is set to receive a significant influx of interest.

1.6 Mechanism of enolisation

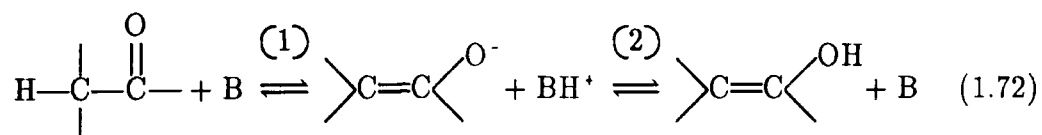
Enolisation is known to occur via mechanisms involving acid and base catalysis¹⁶⁶. Bell and coworkers^{167,168,169} looked at the enolisation of acetone and other substrates in the halogenation of these substrates. They and later authors have shown that enolisation can be a general acid and general base catalysed process^{170,171,172}. More recently several authors have shown^{173,174,175} that dicarbonyl substrates were able to undergo enolisation via intramolecular catalysis. Initially this catalysis was not observed as it is far quicker than intermolecular catalysis. Advances in NMR spectroscopy, amongst others, have enabled workers to identify rapid reactions.

Acid catalysis firstly involves proton transfer to the oxygen, (equation 1.71), then removal of the proton from an adjacent carbon.



It is possible for either of these steps to be made rate determining, both give general acid catalysis, but can be differentiated between by a primary isotope effect. If (1) is rate determining the primary isotope effect is small, if, however, (2) is rate determining the primary isotope effect is large. The evidence from isotope studies¹⁷⁶ show that the proton loss from the carbon (step 2), instead of protonation of oxygen (step 1), is the favoured rate determining step. Bronsted correlations have also been used¹⁷⁷ to establish the nature of the rate limiting step. This again points to the mechanism involving rate limiting proton loss from the carbon.

Base catalysis firstly involves the removal of a proton from a carbon, (equation 1.72), to give an enolate ion, this is followed by protonation of the oxygen atom.



As with the acid catalysed mechanism there are in principle two possible rate determining steps, a) when the proton removal (step 1) is rate determining, or b) when the protonation (step 2) is rate determining. Experimental evidence indicates that the former case, rate determining proton removal, to give the enolate, is the mechanism that occurs. Similar K_E values are obtained^{178,179,180} for both the acid and base catalysed systems. This corroborates step 1 being rate limiting. If step 2 is rate limiting then the enolate will be present in solution, for relatively more time, and so open to attack by other species in solution. A calculated K_E value should therefore be appreciably different to the acid catalysed case. This is not so, and the experimental evidence favours base catalysis proceeding via rate limiting proton removal

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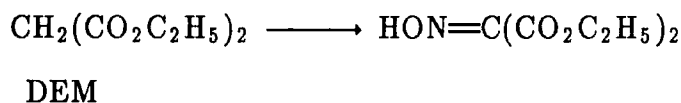
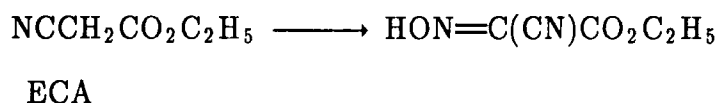
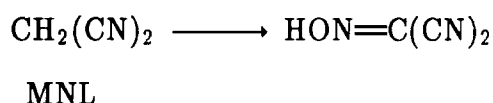
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CHAPTER 2
NITROSATION OF ETHYL CYANOACETATE
DIETHYL MALONATE AND MALONONITRILE

2.1 Introduction

Kinetic studies of the C-nitrosation of compounds containing electron withdrawing groups other than a carbonyl group have not been substantial. Very recently an investigation into the nitrosation of malononitrile was performed¹, yielding some very interesting results. The work in this chapter is an attempt to observe the effect of change of the cyano group for another electron withdrawing species, an ethyl ester group. Malononitrile (MNL), ethyl cyanoacetate (ECA) and diethyl malonate (DEM) are all known to react with nitrous acid or its derivatives yielding the α -oximino products, (scheme 2.1).



Scheme 2.1

The work of Iglesias and Williams showed that the nitrosation of malononitrile, within the pH range 1 to 4, involved attack by the nitrosating species upon the malononitrile carbanion. Aqueous acidic solutions were used at all times, as under basic conditions the hydrolysis of the malononitrile could be a competitive reaction, also the effective nitrosating species, under basic conditions, is substantially converted to nitrite ion, which is unreactive.

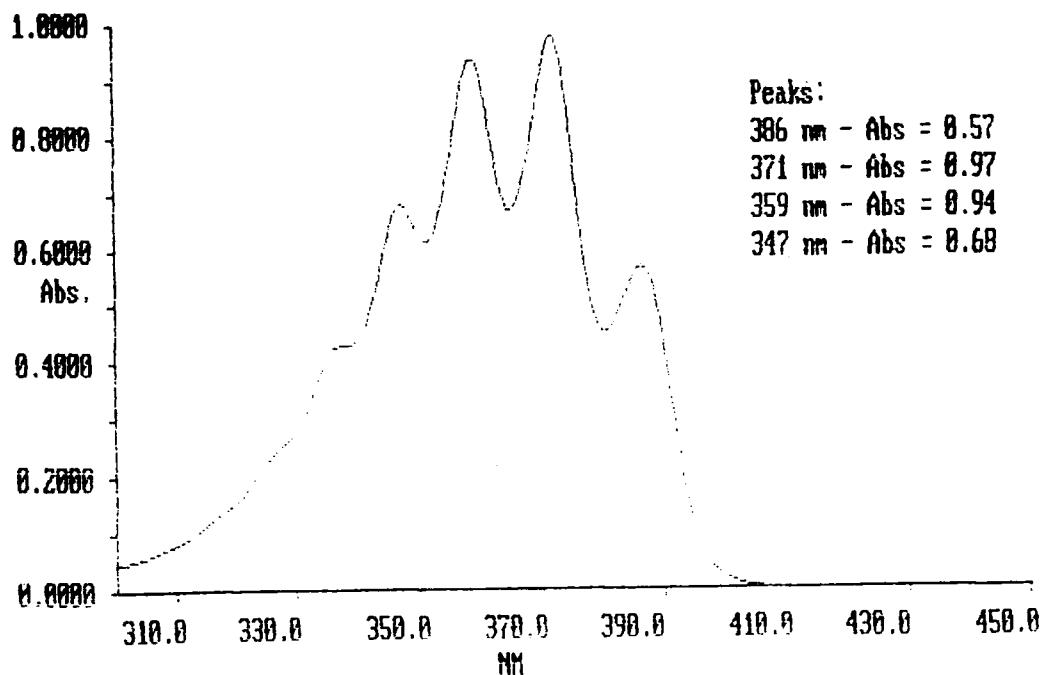
2.2 Results

The reactions of ethyl cyanoacetate and diethyl malonate were carried out in acidic dioxan/water solvent. This was in the ratio 70% distilled water to 30% dioxan by volume. A mixed solvent was necessary because of solubility problems, in water, encountered with both substrates. For consistency between the results obtained for these substrates and those quoted for malononitrile, malononitrile was also studied in a mixed solvent system to observe the effect of the change of solvent.

Reactions were performed in acidic solutions up to pH 4, using acetic acid/acetate or chloroacetic acid/chloroacetate buffers. All reagent concentrations were in at least a twenty fold excess to that of the nitrous acid. Experimentally it was found that this gave first order reaction kinetics with respect to the nitrous acid concentration. The reactions were usually followed by noting the disappearance of absorbance due to the nitrous acid at one of its characteristic peaks, (graph 2.1).

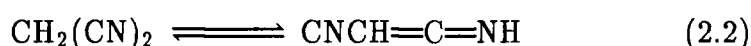
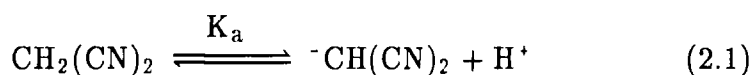
GRAPH 2.1: The distinctive absorbance scan of nitrous acid between 300 nm and 450 nm.

X: USER001; absc 500.0- 190.0; pts 311; int 1.00; ord 0.0002-3.6068;

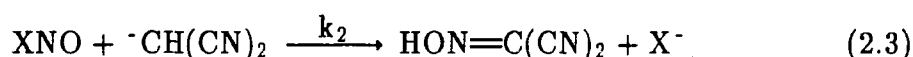


The nitrosation products were synthesised using literature methods^{2,3,4} and purified to enable u.v./visible spectra to be taken, prior to the kinetic studies.

It was more convenient to follow the nitrosation of malononitrile at 310 nm, noting the increase in absorbance due to the formation of the oxime product. The malononitrile nitrosation was shown to proceed via the carbanion intermediate, (equation 2.1), and not through the possible ketenimine intermediate, (equation 2.2), at all times under the reaction conditions used.



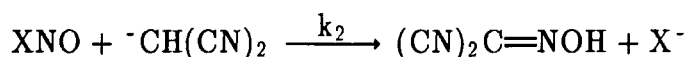
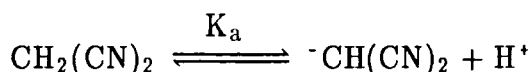
Nitrosation in the presence of nucleophilic catalysts; bromide ion, thiocyanate ion and thiourea (giving nitrosyl bromide, nitrosyl thiocyanate and S-nitroso-thiouronium ion as the respective nitrosating species) involved the rate limiting attack of these species upon the carbanion derived from malononitrile, (equation 2.3).



Interestingly all three nitrosating species appear to attack at the diffusion limit. The second order rate constants, k_2 , for the attack of the nitrosating species upon the carbanion, were all in the region of $10^9 \text{ l mol}^{-1} \text{ s}^{-1}$. This has previously been shown in some nitrosation reactions⁵, but this was the first occasion it had been seen for the less reactive nitrosating agents, ONSCN and $\text{ON}^+\text{SC}(\text{NH}_2)_2$. This suggests that, not surprisingly, the carbanion of malononitrile is the most reactive substrate studied in this way.

In this work initially the effect of changing solvent from water to a dioxan/water mixture was studied. The proposed stepwise process, (scheme 2.2), also took

into consideration the dissociation of the nitrous acid, necessary for work above pH 2.



Scheme 2.2

The overall rate equation, (equation 2.4), can be derived from this mechanism, where K_N is the dissociation constant for nitrous acid, K_{XNO} the equilibrium constant for XNO formation, K_a is the dissociation constant for malononitrile and k_2 is the second order rate constant for the attack of XNO upon the carbanion.

$$\text{Rate} = \frac{k_2 K_a K_{\text{XNO}} [\text{MNL}] [\text{X}^-] [\text{HNO}_2]_{\text{T}} [\text{H}^+]}{K_N + [\text{H}^+]} \quad (2.4)$$

The literature values, $K_N^6 = 7.1 \times 10^{-4}$, $K_{\text{ClNO}}^7 = 1.1 \times 10^{-3}$, $K_{\text{BrNO}}^7 = 5.1 \times 10^{-2}$, $K_{\text{NOSCN}}^7 = 30$, $K_{\text{ONS}(\text{NH}_2)_2}^7 = 5000$, $K_a = 4.1 \times 10^{-12}$ for malononitrile⁸, were used in calculations of k_2 . Under the reaction conditions used, $\text{rate} = k_{\text{obs}}[\text{HNO}_2]_{\text{T}}$, and substitution in equation 2.4 gives the expression for k_{obs} , (equation 2.5).

$$\text{Rate} = k_{\text{obs}}[\text{HNO}_2] = \frac{k_2 K_a K_{\text{XNO}} [\text{MNL}] [\text{X}^-] [\text{HNO}_2]_{\text{T}} [\text{H}^+]}{K_N + [\text{H}^+]}$$

$$k_{\text{obs}} = \frac{k_2 K_a K_{\text{XNO}} [\text{MNL}][\text{X}^-][\text{H}^+]}{K_{\text{N}} + [\text{H}^+]} \quad (2.5)$$

Plots of k_{obs} against both malononitrile and catalyst concentrations gave straight lines and from the slopes values for k_2 were obtained, (equation 2.6).

$$\text{Slope} = \frac{k_2 K_a K_{\text{XNO}} [\text{MNL}][\text{H}^+]}{K_{\text{N}} + [\text{H}^+]} \quad (2.6)$$

for $[\text{X}^-]$ variation

These reactions were performed using bromide ion and thiocyanate ion catalysts and also by varying both substrate and XNO concentrations, keeping all other conditions constant. These are represented in graphs 2.2, 2.3 and 2.4. The subsequently calculated k_2 values are shown in table 2.1 along with the literature values for the reaction in water¹.

TABLE 2.1: Values of k_2 for the nitrosation of malononitrile in different solvents.

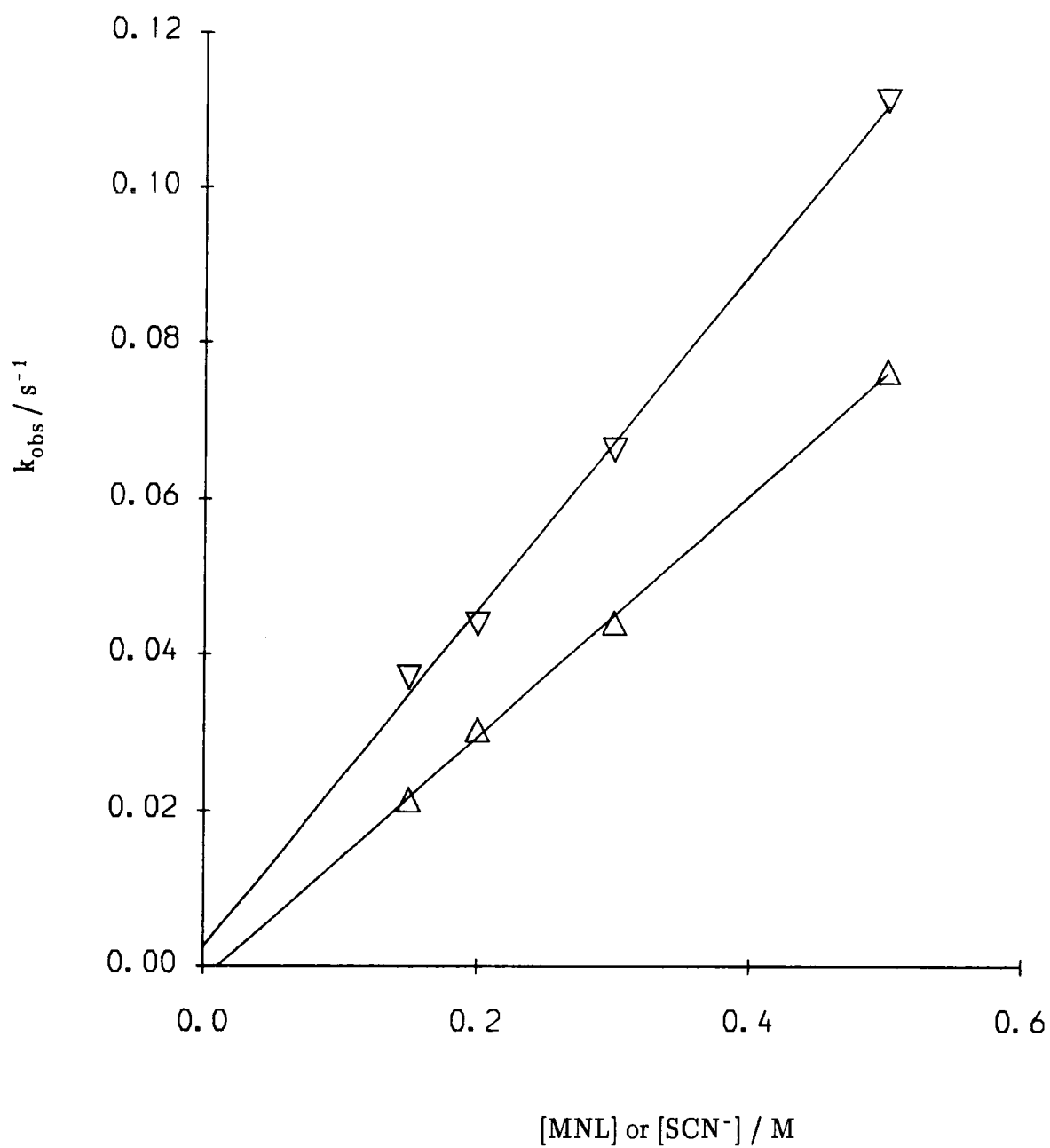
	SCN ⁻ catalysed $k_2/1 \text{ mol}^{-1}\text{s}^{-1}$	Br ⁻ catalysed $k_2/1 \text{ mol}^{-1}\text{s}^{-1}$
100% water	4.2×10^9 (a) (lit.)	1.1×10^{10} (c) (lit.)
85% water 15% dioxan	7.3×10^9 (a) 6.8×10^9 (b)	—
70% water 30% dioxan	7.0×10^9 (a) 6.7×10^9 (b)	7.4×10^9 (c) 2.5×10^9 (b)

(a) – variation of $[\text{SCN}^-]$

(b) – variation of $[\text{MNL}]$

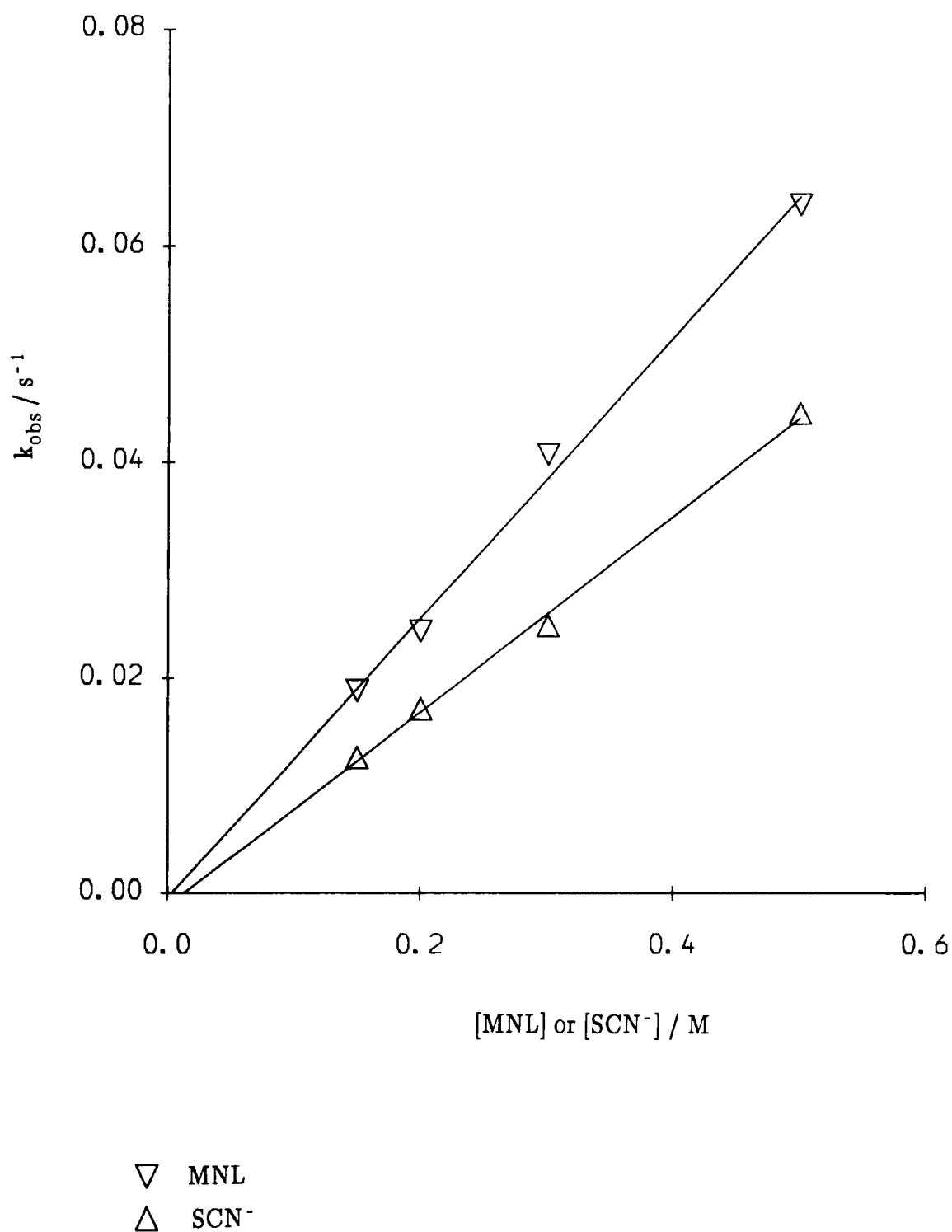
(c) – variation of $[\text{Br}^-]$

GRAPH 2.2: Thiocyanate ion catalysed nitrosation of malononitrile in 85% water, 15% dioxan solvent.

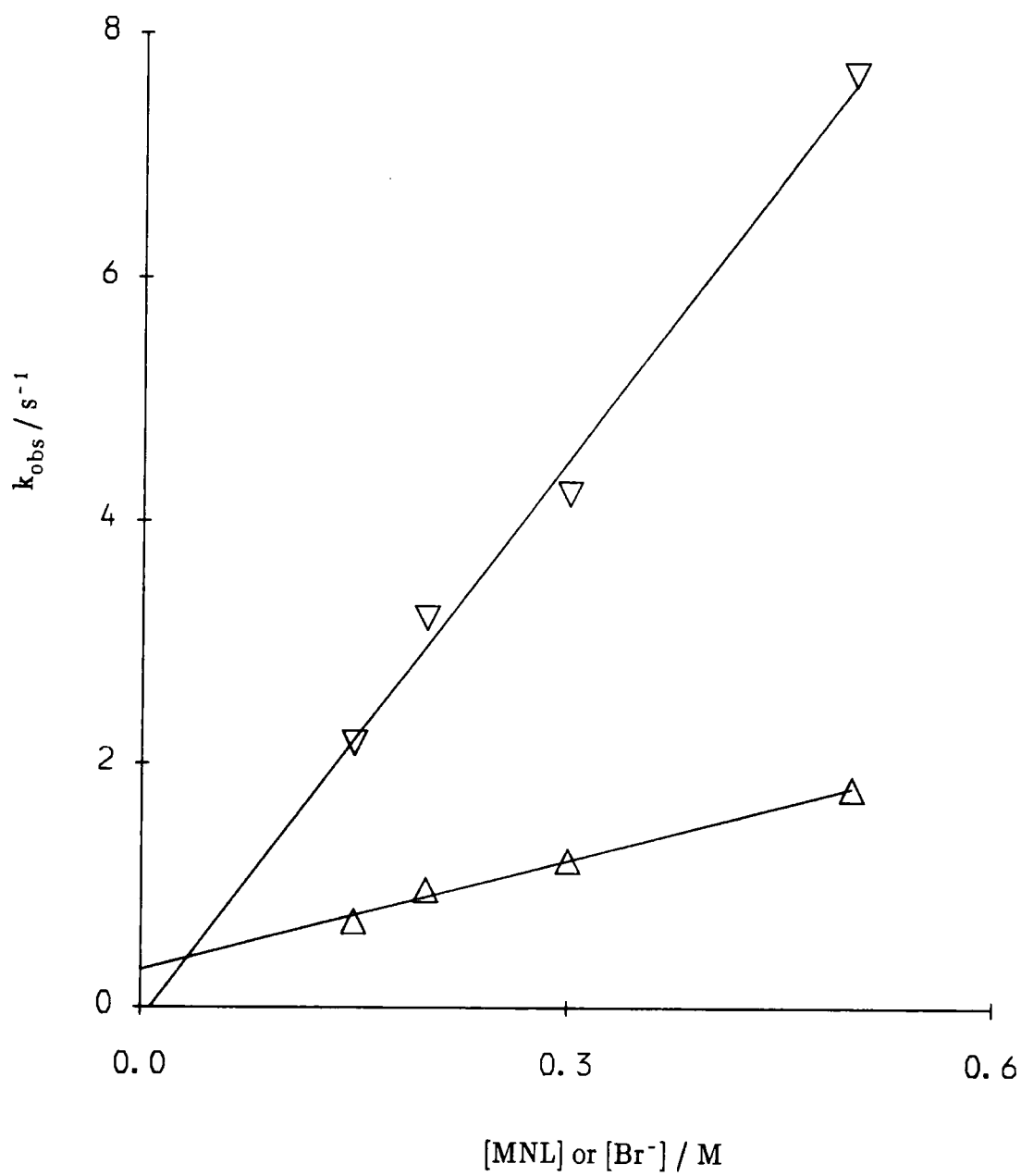


∇ MNL
 \triangle SCN^-

GRAPH 2.3: Thiocyanate ion catalysed nitrosation of malononitrile in 70% water, 30% dioxan solvent.



GRAPH 2.4: Bromide ion catalysed nitrosation of malononitrile in 70% water,
30% dioxan solvent.



▽ MNL
△ Br^{-}

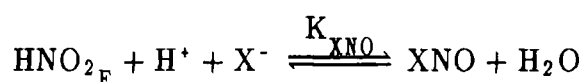
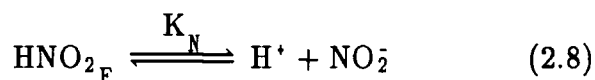
The variation of solvent composition within this range appears to have only a small effect upon the rate constants. Therefore comparisons of rate constants for reactions in water with those obtained in a dioxan/water mixed solvent are valid.

Ethyl cyanoacetate and diethyl malonate were both reacted with nitrous acid in the presence of thiocyanate ions as catalyst. Effectively the nitrosating species is nitrosyl thiocyanate, (equation 2.7).



All reaction components were kept constant except for the pH of the reaction solution. The change in observed rate constant with change in acid concentration is shown in tables 2.2 and 2.3, for ethyl cyanoacetate and diethyl malonate respectively. Plots of k_{obs} versus acid concentration can also be seen in graphs 2.5 and 2.6.

At lower acid concentrations (above pH 2 approximately) the ionisation of nitrous acid (to nitrite ion) needs to be taken into account, (equation 2.8).



The total concentration of nitrous acid, $[\text{HNO}_2]_{\text{T}}$, can be represented by equation 2.9.

$$[\text{HNO}_2]_{\text{T}} = [\text{HNO}_2]_{\text{F}} + [\text{NO}_2^-] \quad (2.9)$$

We also know that,

$$K_N = \frac{[H^+][NO_2^-]}{[HNO_2]_F} \quad (2.10)$$

and a combination of equations 2.9 and 2.10 gives a new expression for the total nitrous acid concentration, (equation 2.11).

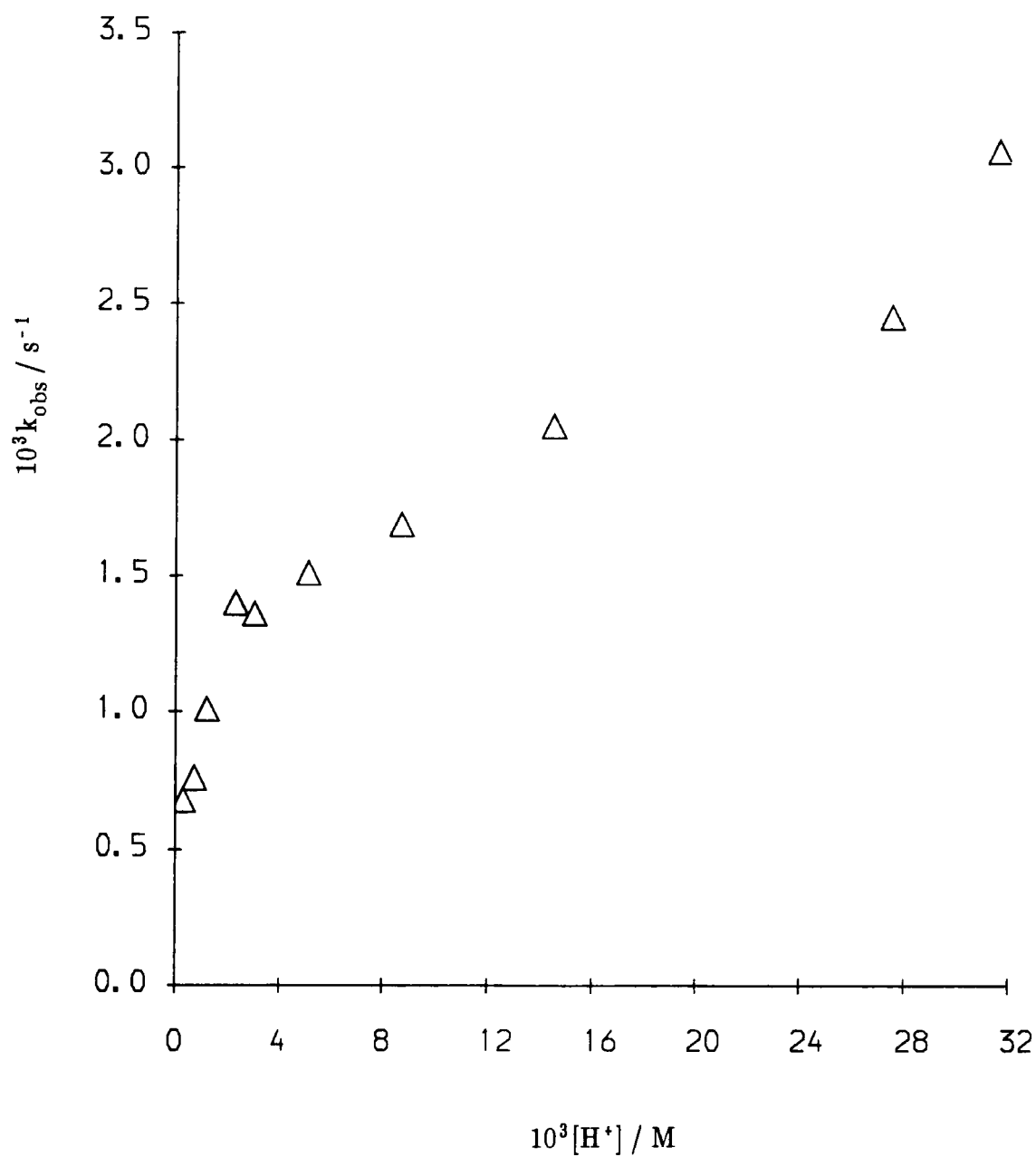
$$[HNO_2]_T = [HNO_2]_F \left[1 + \frac{K_N}{[H^+]} \right] \quad (2.11)$$

TABLE 2.2: Thiocyanate ion catalysed nitrosation of ethyl cyanoacetate at various acidities.

$[HNO_2] = 5.0 \times 10^{-3}M$, $[ECA] = 0.247M$, $[SCN^-] = 0.19M$, $T = 298K$.

pH	$10^3 [H^+] / M$	$10^3 k_{obs} / s^{-1}$	$10^3 k_{corr} / s^{-1}$
1.50	31.6	3.06	3.13
1.56	27.5	2.45	2.51
1.84	14.5	2.05	2.15
2.06	8.7	1.69	1.83
2.29	5.1	1.51	1.72
2.52	3.0	1.36	1.68
2.64	2.3	1.40	1.83
2.92	1.2	1.01	1.61
3.14	0.7	0.76	1.51
3.53	0.3	0.68	2.29

GRAPH 2.5: Variation of acid concentration for the thiocyanate ion catalysed nitrosation of ethyl cyanoacetate.



GRAPH 2.6: Variation of acid concentration for the thiocyanate ion catalysed nitrosation of diethyl malonate.

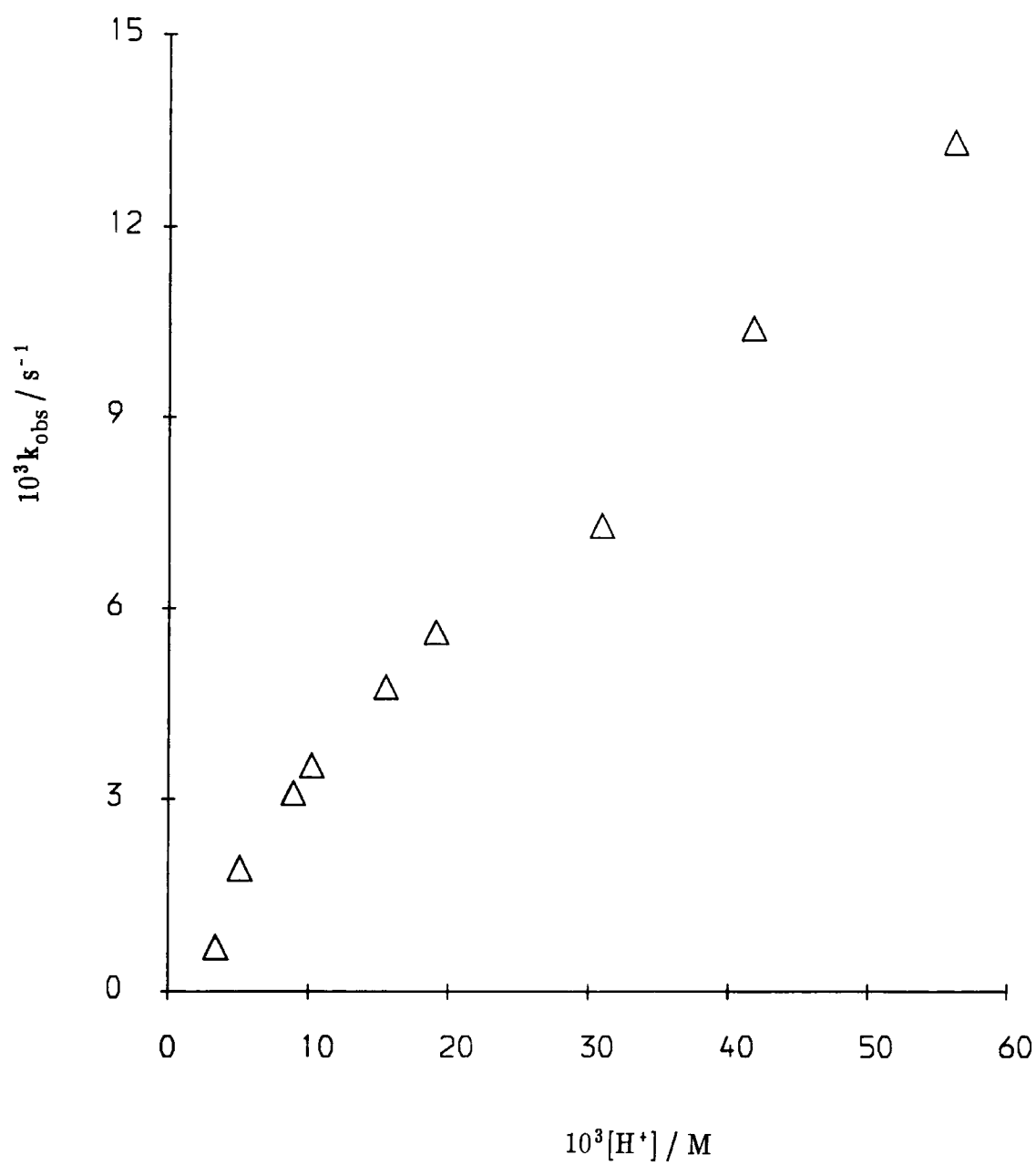


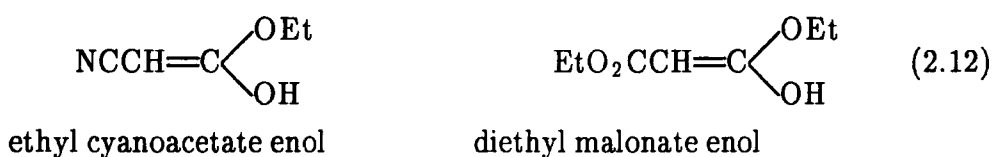
TABLE 2.3: Thiocyanate ion catalysed nitrosation of diethyl malonate at various acidities.

$[\text{HNO}_2] = 5.0 \times 10^{-3} \text{ M}$, $[\text{DEM}] = 0.125 \text{ M}$, $[\text{SCN}^-] = 0.40 \text{ M}$, $T = 298 \text{ K}$.

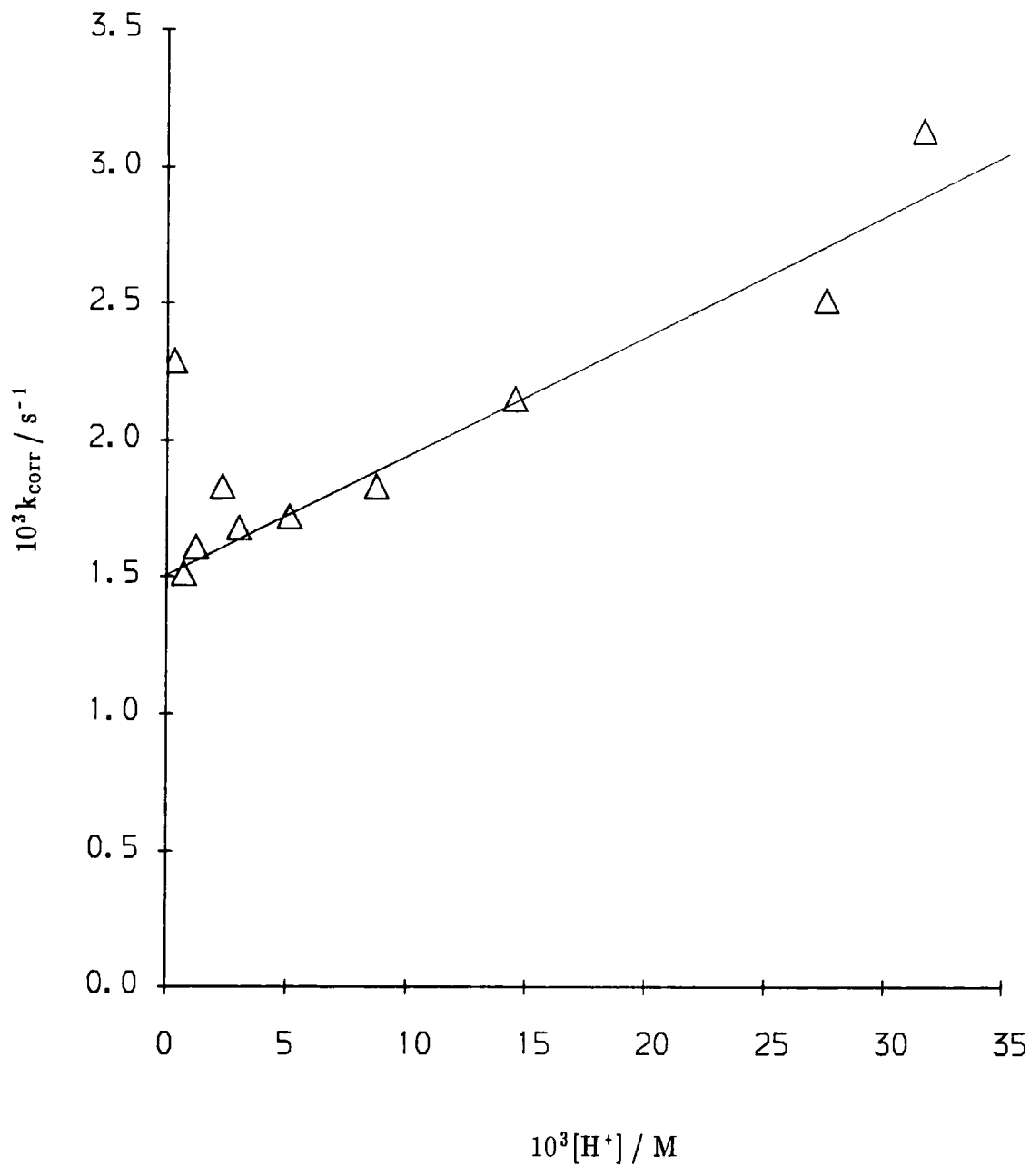
pH	$10^3 [\text{H}^+] / \text{M}$	$10^3 k_{\text{obs}} / \text{s}^{-1}$	$10^3 k_{\text{corr}} / \text{s}^{-1}$
1.25	56.2	13.3	13.5
1.38	41.7	10.4	10.6
1.51	30.9	7.30	7.47
1.72	19.1	5.62	5.83
1.81	15.5	4.76	4.98
1.99	10.2	3.52	3.77
2.05	8.9	3.09	3.34
2.29	5.1	1.92	2.19
2.47	3.4	0.69	0.83

A corrected first order rate constant, k_{corr} , can be obtained, to account for the nitrous acid ionisation, by multiplying the observed first order rate constant by $\left[1 + \frac{K_{\text{N}}}{[\text{H}^+]}\right]$. These values are in the final column of tables 2.2 and 2.3. They are also graphically represented, (graphs 2.7 and 2.8).

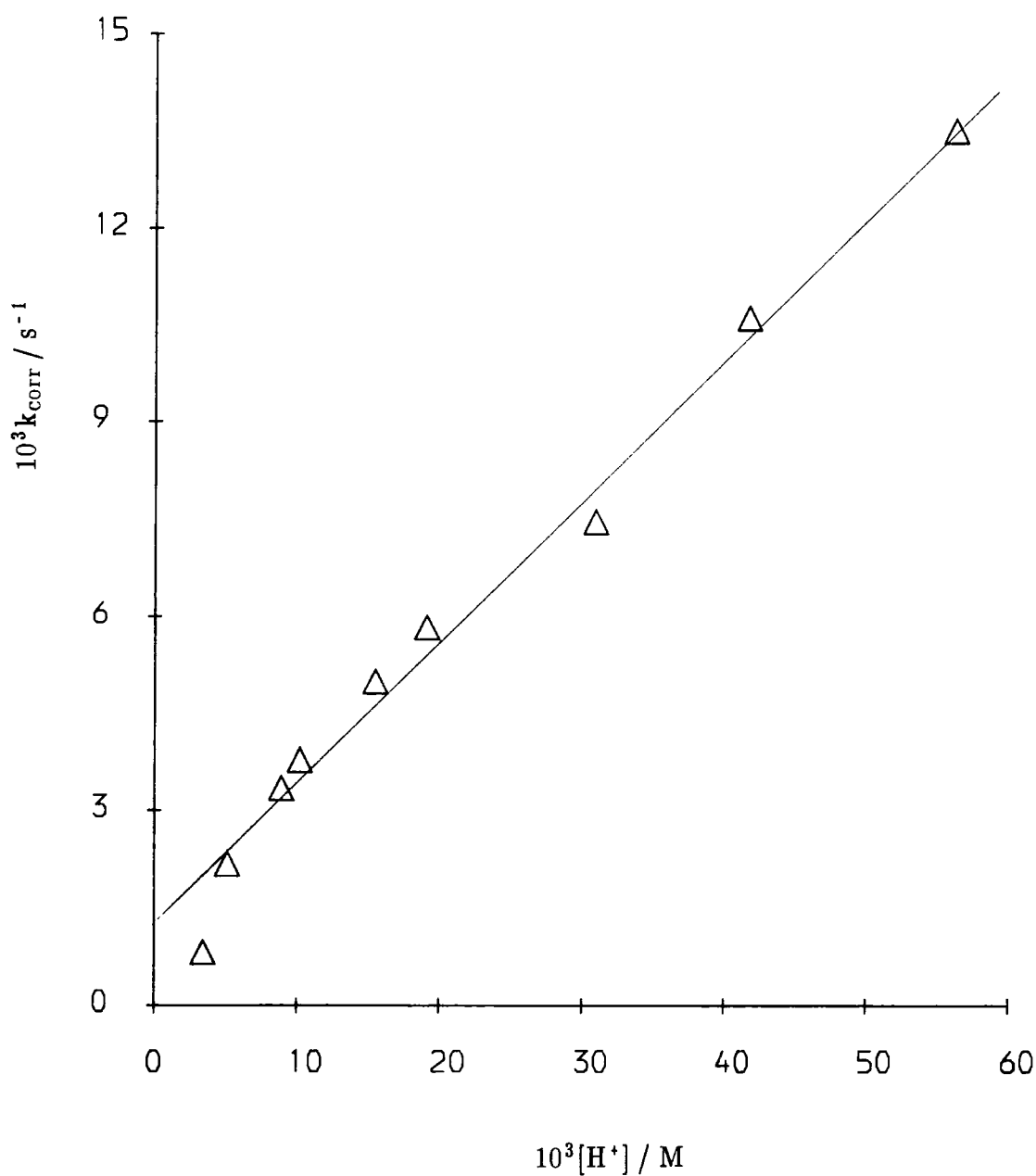
Unlike the nitrosation of malononitrile, where the reaction proceeds exclusively via the carbanion, the possibility exists, with both ethyl cyanoacetate and diethyl malonate, for the reaction to take place via an enol intermediate, (equation 2.12).



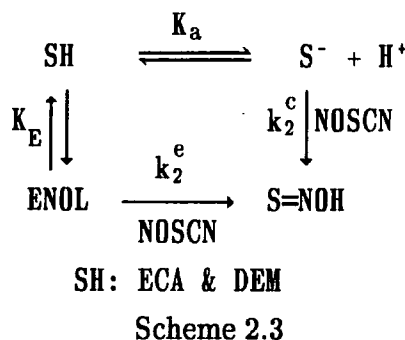
GRAPH 2.7: Variation of the corrected first order rate constant with acid concentration, for the thiocyanate ion catalysed nitrosation of ethyl cyanoacetate.



GRAPH 2.8: Variation of the corrected first order rate constant with acid concentration, for the thiocyanate ion catalysed nitrosation of diethyl malonate.



Scheme 2.3 shows the possible reaction pathways for the thiocyanate catalysed nitrosation of ethyl cyanoacetate or diethyl malonate.



Where K_a is the dissociation constant of the substrate ($K_a = 1.82 \times 10^{-12}$ for ethyl cyanoacetate⁹ and $K_a = 1.26 \times 10^{-13}$ for diethyl malonate¹⁰), K_E is the keto-enol equilibrium constant for both substrates (unknown), k_2^c and k_2^e are the second order rate constants for the attack of the nitrosating species upon the carbanion and enol intermediates respectively. The rate of reaction is represented in equation 2.13.

$$\text{Rate} = k_2^e[\text{ENOL}][\text{NOSCN}] + k_2^c[\text{S}^-][\text{NOSCN}] \quad (2.13)$$

The following equalities are also known, $[\text{S}^-] = \frac{[\text{SH}] K_a}{[\text{H}^+]}$, $[\text{ENOL}] = K_E[\text{SH}]$, $[\text{NOSCN}] = K_{\text{XNO}}[\text{SCN}^-][\text{H}^+][\text{HNO}_2]$ and can be substituted into equation 2.13, yielding a new expression for the rate equation, (equation 2.14).

$$\begin{aligned}
 \text{Rate} = k_{\text{obs}}[\text{HNO}_2] = & k_2^e K_E K_{\text{NOSCN}} [\text{SCN}^-] [\text{SH}] [\text{H}^+] [\text{HNO}_2] \\
 & + k_2^c K_a K_{\text{NOSCN}} [\text{SCN}^-] [\text{SH}] [\text{HNO}_2]
 \end{aligned} \quad (2.14)$$

$$k_{\text{obs}} = k_2^e K_E K_{\text{NOSCN}} [\text{SCN}^-] [\text{SH}] [\text{H}^+] + k_2^c K_a K_{\text{NOSCN}} [\text{SCN}^-] [\text{SH}] \quad (2.15)$$

All of the experiments gave good first order kinetics with respect to nitrous acid concentration. This fits with the rate equation which predicts this first order

dependence upon nitrous acid concentration. Equation 2.15 predicts a straight line dependence between the corrected rate constant and acid concentration, with a positive intercept as is found experimentally, for both substrates. For both substrates the intercept value on the ordinate can be used in conjunction with the intercept term to calculate values of k_2^c , (equation 2.16).

$$\text{Intercept} = k_2^c K_a K_{\text{NOSCN}} [\text{SCN}^-] [\text{SH}] \quad (2.16)$$

Similarly values of $k_2^e K_E$ can be obtained from the slopes of the plots in graphs 2.7 and 2.8 along with part of equation 2.15, (equation 2.17).

$$\text{Slope} = k_2^e K_E K_{\text{NOSCN}} [\text{SCN}^-] [\text{SH}] \quad (2.17)$$

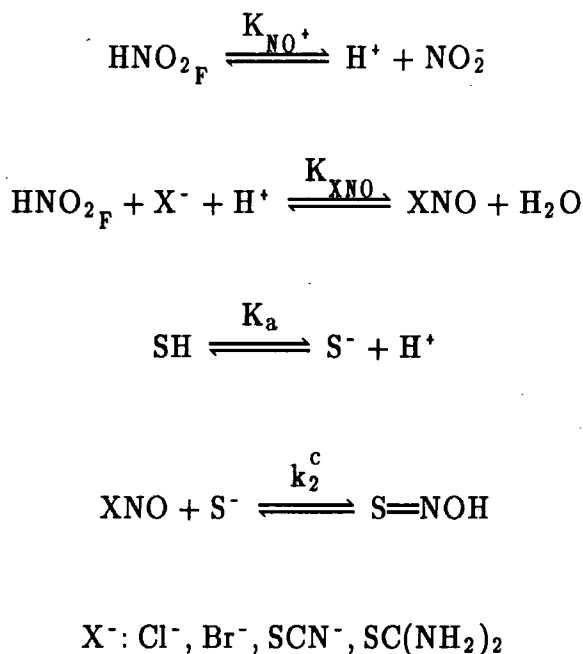
An approximate value for K_E , for ethyl cyanoacetate and diethyl malonate, can be obtained if k_2^e is assumed to be at the diffusion limit, although perhaps nitrosyl thiocyanate is not a sufficiently reactive nitrosating species for the assumption to be fully justified, so no comparison, of the K_E values, has been made. All k_2^c , $k_2^e K_E$ and K_E values are shown in table 2.4.

TABLE 2.4: Values of k_2^c , $k_2^e K_E$ and K_E obtained from the thiocyanate ion catalysed nitrosation of ethyl cyanoacetate and diethyl malonate.

	Ethyl cyanoacetate	Diethyl malonate
k_2^c	$6.11 (\pm 0.11) \times 10^8$	$5.36 (\pm 0.76) \times 10^9$
$k_2^e K_E$	$2.50 (\pm 0.14) \times 10^{-2}$	$0.140 (\pm 0.004)$
K_E	3.6×10^{-12}	2.0×10^{-11}

Further experiments were carried out with ethyl cyanoacetate and diethyl malonate in the presence of thiocyanate ions, at constant pH whilst varying

substrate or thiocyanate ion concentrations. The pH of the reaction solution was at the higher end of the range previously used (pH = 3.2) and the assumption was made that the reaction proceeded exclusively via the carbanion. Scheme 2.4 shows the general stepwise process is a catalysed reaction via the carbanion and equation 2.18 is the rate equation derived from scheme 2.4.



Scheme 2.4

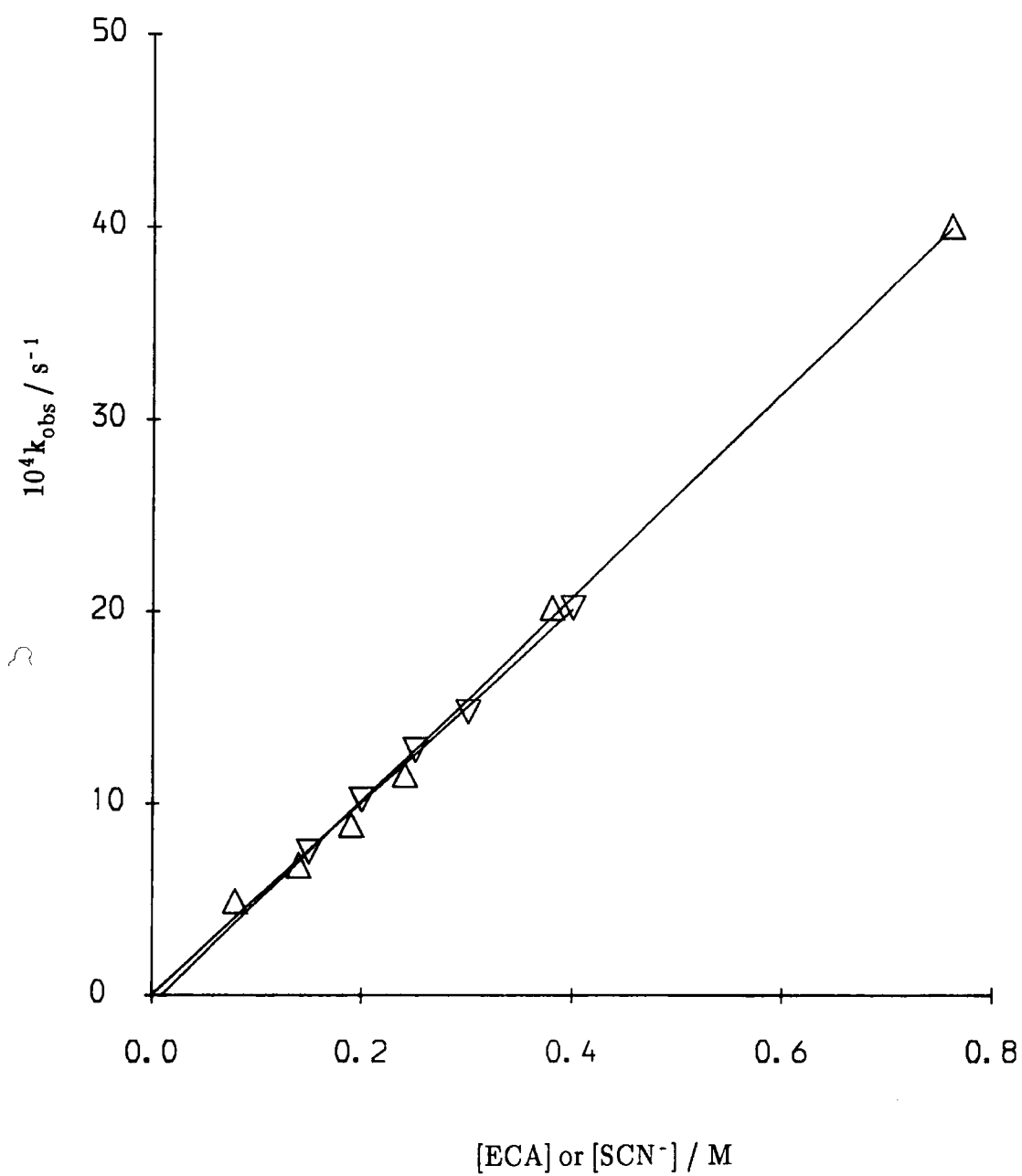
$$\text{Rate} = \frac{k_2^c K_a K_{\text{XNO}} [\text{SH}][\text{X}^-][\text{H}^+][\text{HNO}_2]}{K_N + [\text{H}^+]} \quad (2.18)$$

Equation 2.19 gives the expression for the observed rate constant.

$$k_{\text{obs}} = \frac{k_2^c K_a K_{\text{XNO}} [\text{SH}][\text{X}^-][\text{H}^+]}{K_N + [\text{H}^+]} \quad (2.19)$$

Thiocyanate ion catalysed nitrosation of ethyl cyanoacetate was carried out with variation of thiocyanate ion concentration and separately with the variation

GRAPH 2.9: Thiocyanate ion catalysed nitrosation of ethyl cyanoacetate,
variation of ethyl cyanoacetate and thiocyanate ion concentrations.



▽ ECA
△ SCN^-

of ethyl cyanoacetate concentration. These results have been tabulated, (table 2.5), and graphically represented, (graph 2.9).

TABLE 2.5: Nitrosation of ethyl cyanoacetate by nitrosyl thiocyanate.

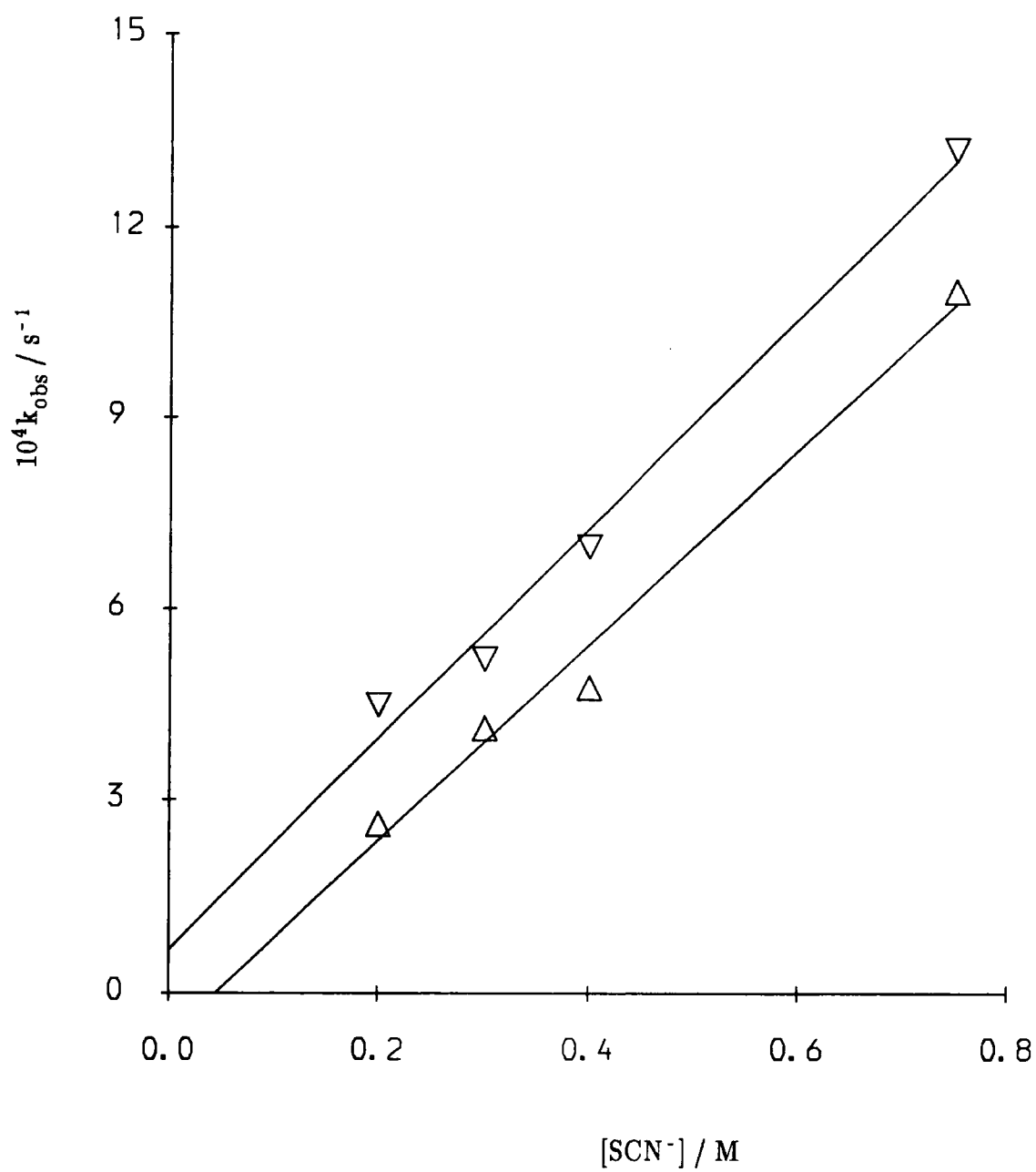
$$[\text{HNO}_2]_{\text{T}} = 2.5 \times 10^{-3} \text{M}, T = 298\text{K}, \text{pH} = 3.2$$

$\frac{[\text{ECA}]}{[\text{SCN}^-]} = 0.25\text{M},$	0.08	0.14	0.19	0.24	0.38	0.76
$10^4 k_{\text{obs}} / \text{s}^{-1}$	4.90	6.76	8.88	11.5	20.2	40.0
$\frac{[\text{SCN}^-]}{[\text{ECA}]} = 0.24\text{M},$	0.15	0.20	0.25	0.30	0.40	
$10^4 k_{\text{obs}} / \text{s}^{-1}$	7.47	10.2	12.8	14.8	20.2	

Both plots are linear meaning that the reaction has a first order dependence upon the concentrations of both ethyl cyanoacetate and thiocyanate ion. Values for k_2^c of $8.28 (\pm 0.44) \times 10^8 \text{ l mol}^{-1} \text{s}^{-1}$ and $8.18 (\pm 0.12) \times 10^8 \text{ l mol}^{-1} \text{s}^{-1}$ were obtained from the two plots. Both values are in very good agreement which is to be expected as they represent the same reaction system and also compare well with the value of k_2^c in table 2.4.

The effect of ionic strength was examined for the thiocyanate ion catalysed nitrosation of diethyl malonate. This was carried out by varying only the thiocyanate ion concentration in an identical fashion to the reactions performed with ethyl cyanoacetate. Results are reported in table 2.6 and graph 2.10.

GRAPH 2.10: Thiocyanate ion catalysed nitrosation of diethyl malonate.



▽ - at non-constant ionic strength

△ - at constant ionic strength

TABLE 2.6: Nitrosation of diethyl malonate by nitrosyl thiocyanate.

$$[\text{DEM}] = 0.125\text{M}, [\text{HNO}_2]_{\text{T}} = 5.0 \times 10^{-3}\text{M}, T = 298\text{K}, \text{pH} = 2.8.$$

$[\text{SCN}^-] / \text{M}$	0.20	0.30	0.40	0.75
$I = 0.9^*$ $10^4 k_{\text{obs}}/\text{s}^{-1}$	2.62	4.11	4.75	11.0
$10^4 k_{\text{obs}}/\text{s}^{-1}$	4.48	5.20	6.97	13.2

* NaClO_4 used to give constant ionic strength

The plots are linear indicating that the thiocyanate ion catalysed reaction has a first order dependence upon $[\text{SCN}^-]$ and the k_2^c values, $3.22 (\pm 0.03) \times 10^9 \text{ l mol}^{-1} \text{ s}^{-1}$ and $5.05 (\pm 0.20) \times 10^9 \text{ l mol}^{-1} \text{ s}^{-1}$, for the constant ionic strength and non-constant ionic strength cases respectively. These values are reasonably close showing that the ionic strength effect, upon the nitrosyl thiocyanate reaction, is very small and are in reasonable agreement with the k_2^c value for diethyl malonate in table 2.4.

The assumption that the reaction takes place exclusively via the carbanion derived from either ethyl cyanoacetate and diethyl malonate was used again for the catalysed nitrosation of ethyl cyanoacetate and diethyl malonate at pH 3.2. The catalysts used were chloride ion, bromide ion and thiourea (the effective nitrosating species being nitrosyl chloride, nitrosyl bromide and nitrosothiuronium ion respectively).

The observed rate constants, for the nitrosation of ethyl cyanoacetate and diethyl malonate (by NOBr), as a function of bromide ion concentration are shown in tables 2.7 and 2.8 and plots of k_{obs} versus $[\text{Br}^-]$ are shown in graph 2.11. These plots are linear showing a first order reaction dependence upon bromide ion concentration.

TABLE 2.7: Nitrosation of ethyl cyanoacetate by nitrosyl bromide

$[\text{ECA}] = 0.25\text{M}$, $[\text{HNO}_2]_{\text{T}} = 2.5 \times 10^{-3}\text{M}$, $T = 298\text{K}$, $\text{pH} = 3.2$

$[\text{Br}^-]/\text{mol l}^{-1}$	0.10	0.14	0.19	0.24	0.38	0.76
$10^5 k_{\text{obs}}/\text{s}^{-1}$	4.40	4.88	5.25	6.03	7.03	10.6

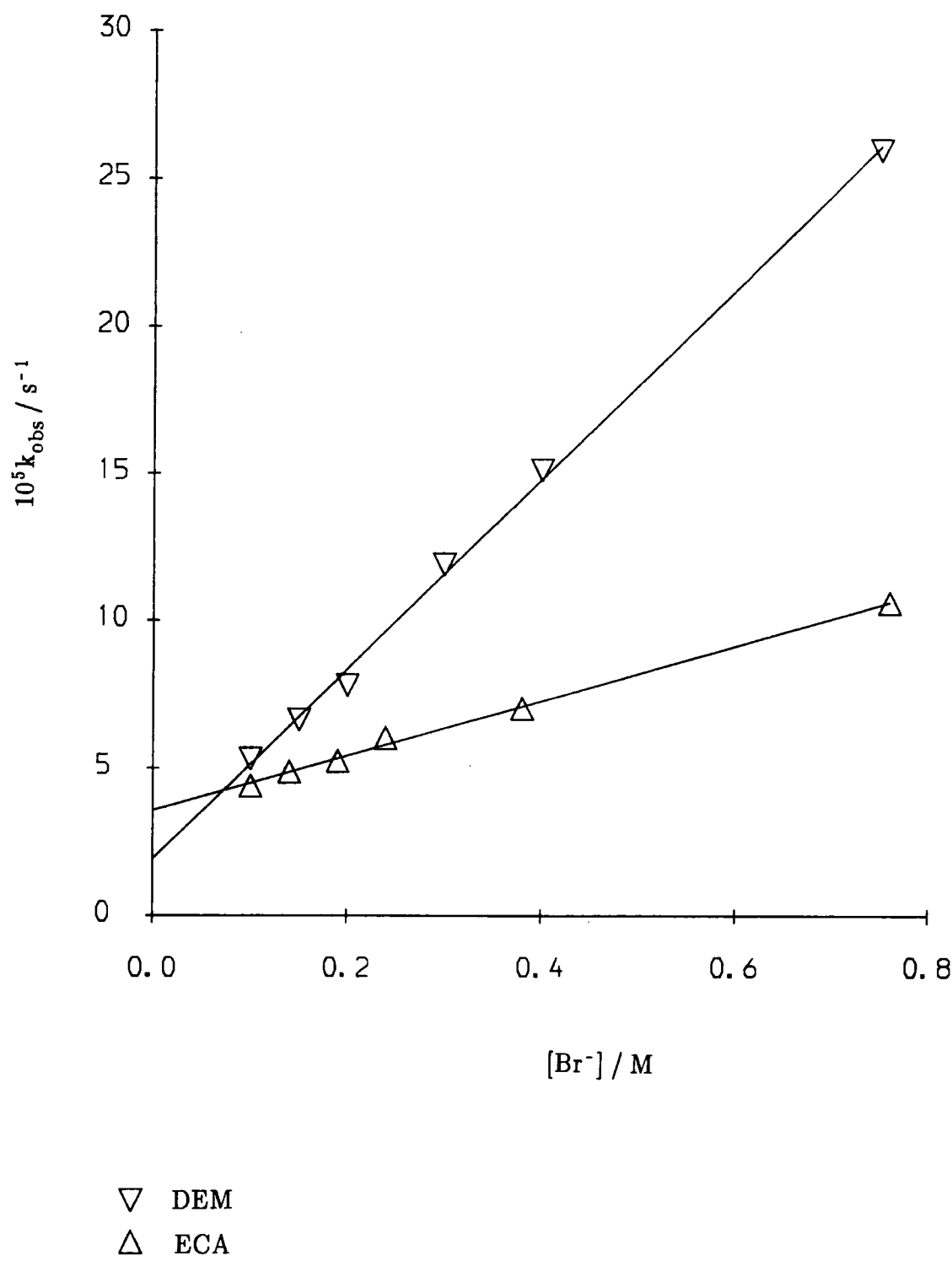
TABLE 2.8: Nitrosation of diethyl malonate by nitrosyl bromide

$[\text{DEM}] = 0.125\text{M}$, $[\text{HNO}_2]_{\text{T}} = 5.0 \times 10^{-3}\text{M}$, $T = 298\text{K}$, $\text{pH} = 2.8$

$[\text{Br}^-]/\text{mol l}^{-1}$	0.10	0.15	0.20	0.30	0.40	0.75
$10^5 k_{\text{obs}}/\text{s}^{-1}$	5.32	6.64	7.81	11.89	15.11	25.94

From the slopes of the plots in graph 2.11 k_2^c values of $8.55 (\pm 0.46) \times 10^9 \text{ l mol}^{-1} \text{ s}^{-1}$ and $4.91 (\pm 0.04) \times 10^{11} \text{ l mol}^{-1} \text{ s}^{-1}$, were obtained, for the attack of nitrosyl bromide upon ethyl cyanoacetate and diethyl malonate respectively.

GRAPH 2.11: Bromide ion catalysed nitrosation of ethyl cyanoacetate and diethyl malonate.



Thiourea catalysis was also investigated for ethyl cyanoacetate and diethyl malonate, where the nitrosating species is now the S-nitrosothiuronium ion, $\text{ONSC}^+(\text{NH}_2)_2$. The rate constants were measured over a range of thiourea concentrations and the results are in table 2.9 and graphically shown in graph 2.12.

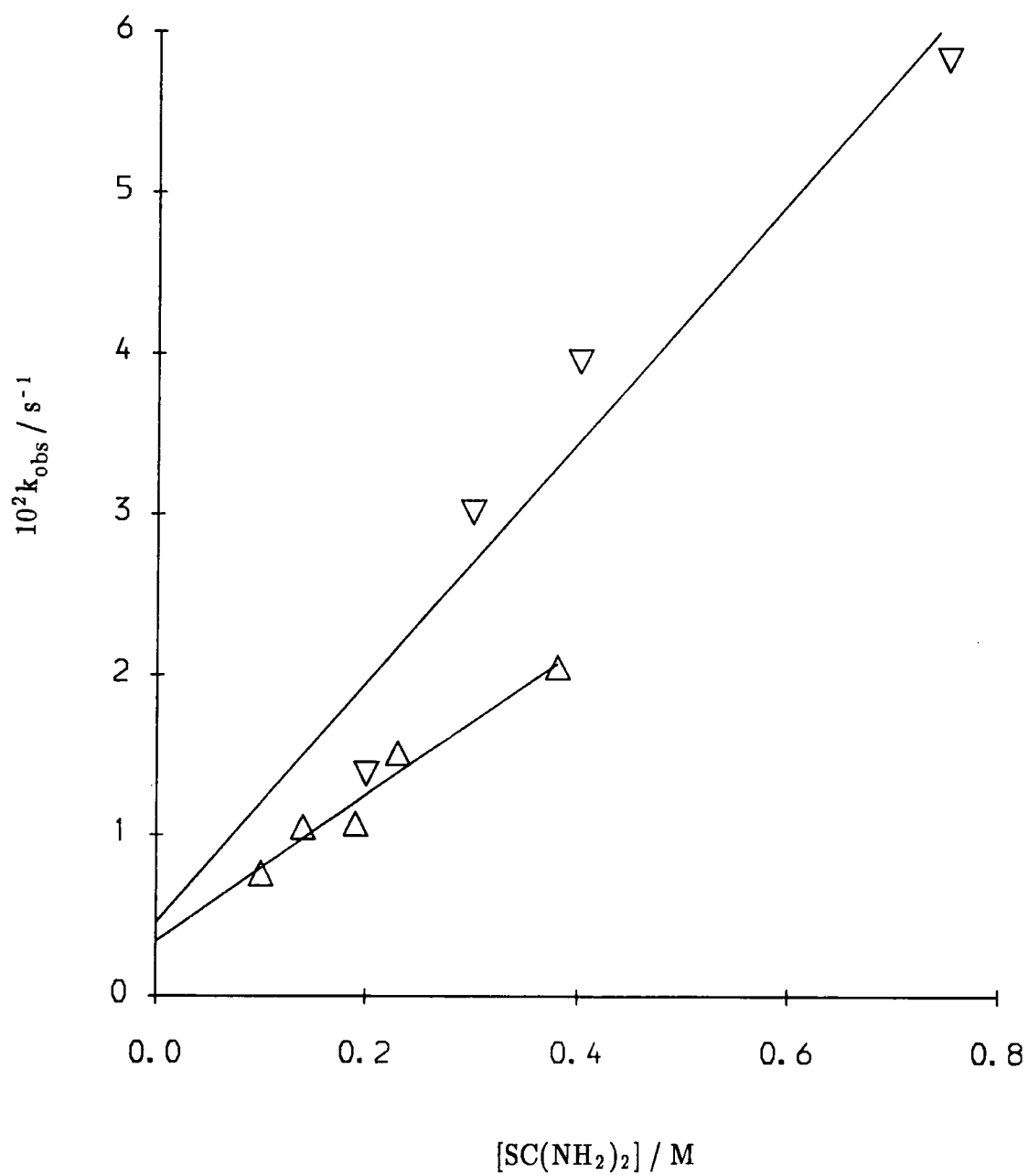
TABLE 2.9: Reaction of S-nitrosothiuronium ion with ethyl cyanoacetate and diethyl malonate.

- (i) $[\text{ECA}] = 0.25\text{M}$, $[\text{HNO}_2]_{\text{T}} = 2.5 \times 10^{-3}\text{M}$, $\text{pH} = 3.2$, $T = 298\text{K}$.
(ii) $[\text{DEM}] = 0.125\text{M}$, $[\text{HNO}_2]_{\text{T}} = 5.0 \times 10^{-3}\text{M}$, $\text{pH} = 2.8$, $T = 298\text{K}$.

$[\text{SC}(\text{NH}_2)_2] / \text{M}$	ECA, $10^2 k_{\text{obs}} / \text{s}^{-1}$	DEM, $10^2 k_{\text{obs}} / \text{s}^{-1}$
0.10	0.76	—
0.14	1.05	—
0.19	1.07	—
0.20	—	1.38
0.23	1.51	—
0.30	—	3.01
0.38	2.05	—
0.40	—	3.95
0.75	—	5.83

The k_{obs} versus $[\text{SC}(\text{NH}_2)_2]$ plots are both linear indicating a first order dependence on the thiourea concentration and the calculated k_2^c values are $4.27 (\pm 0.63) \times 10^7 \text{ l mol}^{-1} \text{ s}^{-1}$ and $2.29 (\pm 0.27) \times 10^9 \text{ l mol}^{-1} \text{ s}^{-1}$ for the reactions with ethyl cyanoacetate and diethyl malonate respectively.

GRAPH 2.12: Thiourea catalysed nitrosation of ethyl cyanoacetate and diethyl malonate.



▽ DEM
△ ECA

Reactions via nitrosyl chloride were examined at different chloride ion concentrations. The results are displayed in table 2.10.

TABLE 2.10: Nitrosation of ethyl cyanoacetate and diethyl malonate by nitrosyl chloride.

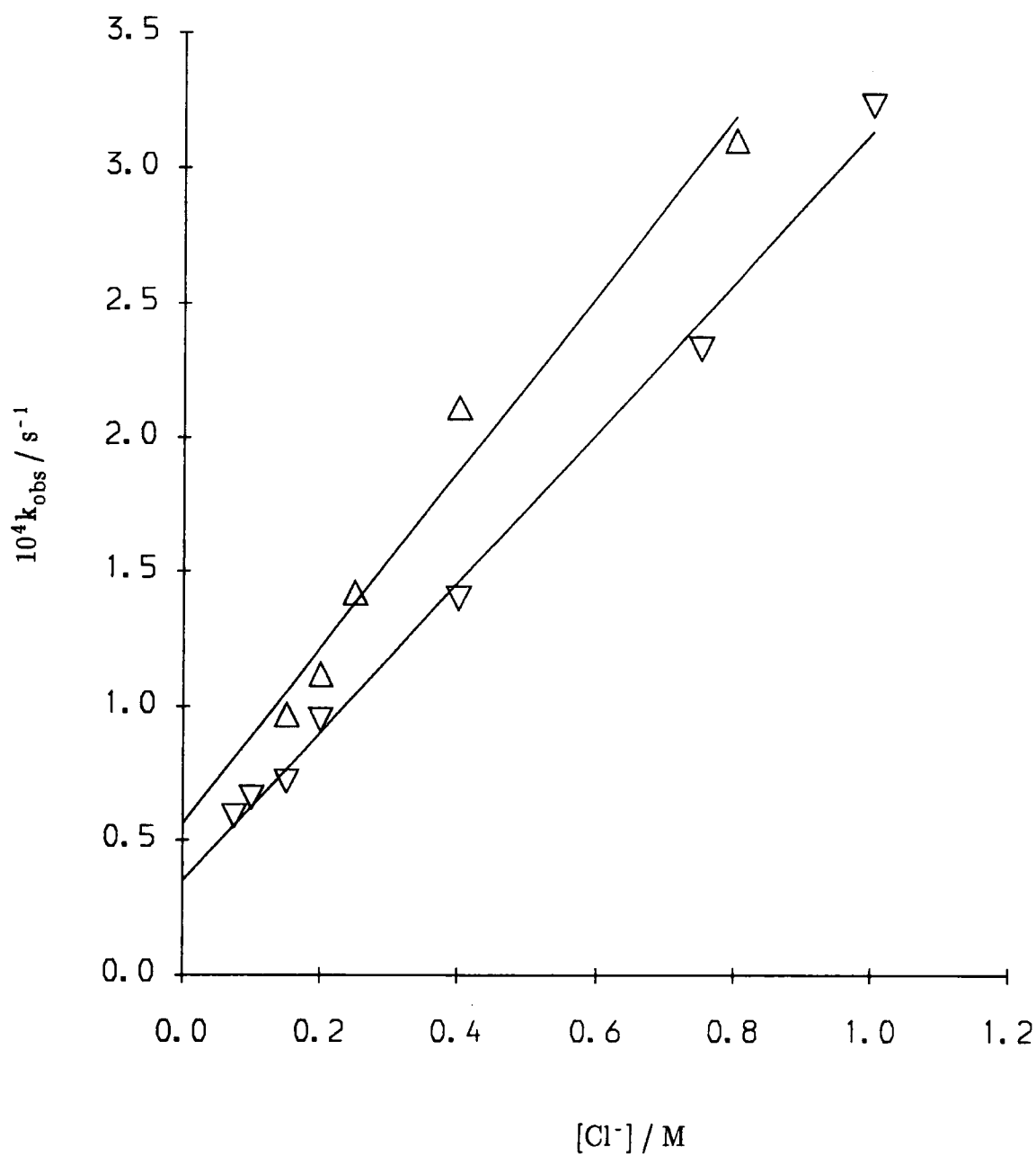
$$\left. \begin{array}{l} [\text{ECA}] = 0.25\text{M}, [\text{HNO}_2]_{\text{T}} = 2.5 \times 10^{-3}\text{M}, \text{pH} = 3.2 \\ [\text{DEM}] = 0.125\text{M}, [\text{HNO}_2]_{\text{T}} = 5.0 \times 10^{-3}\text{M}, \text{pH} = 2.8 \end{array} \right\} T = 298\text{K}$$

$[\text{Cl}^-]/\text{mol l}^{-1}$	ECA, $10^4 k_{\text{obs}}/\text{s}^{-1}$	DEM, $10^4 k_{\text{obs}}/\text{s}^{-1}$
0.075	—	0.55
0.10	—	0.66
0.15	0.97	0.72
0.20	1.12	0.95
0.25	1.42	—
0.40	2.11	1.40
0.75	—	2.33
0.80	3.10	—
1.00	—	3.23

Graph 2.13 shows the variation of k_{obs} with chloride ion concentration. The plots are linear, which corresponds to a first order reaction dependence upon $[\text{Cl}^-]$. Values of $1.40 \times 10^{12} \text{ l mol}^{-1} \text{ s}^{-1}$ and $2.34 \times 10^{13} \text{ l mol}^{-1} \text{ s}^{-1}$ for k_2^{c} were obtained, for attack of the nitrosyl chloride upon ethyl cyanoacetate and diethyl malonate respectively.

For a second order reaction in water at 298K the diffusion limit is $7.4 \times 10^9 \text{ l mol}^{-1} \text{ s}^{-1}$ i.e. 10^3 orders of magnitude smaller than the aforementioned k_2^{c} values. These large erroneous k_2^{c} values are probably due to the decomposition of nitrous acid which occurs in parallel with the nitrosation of the substrate. The chloride ion

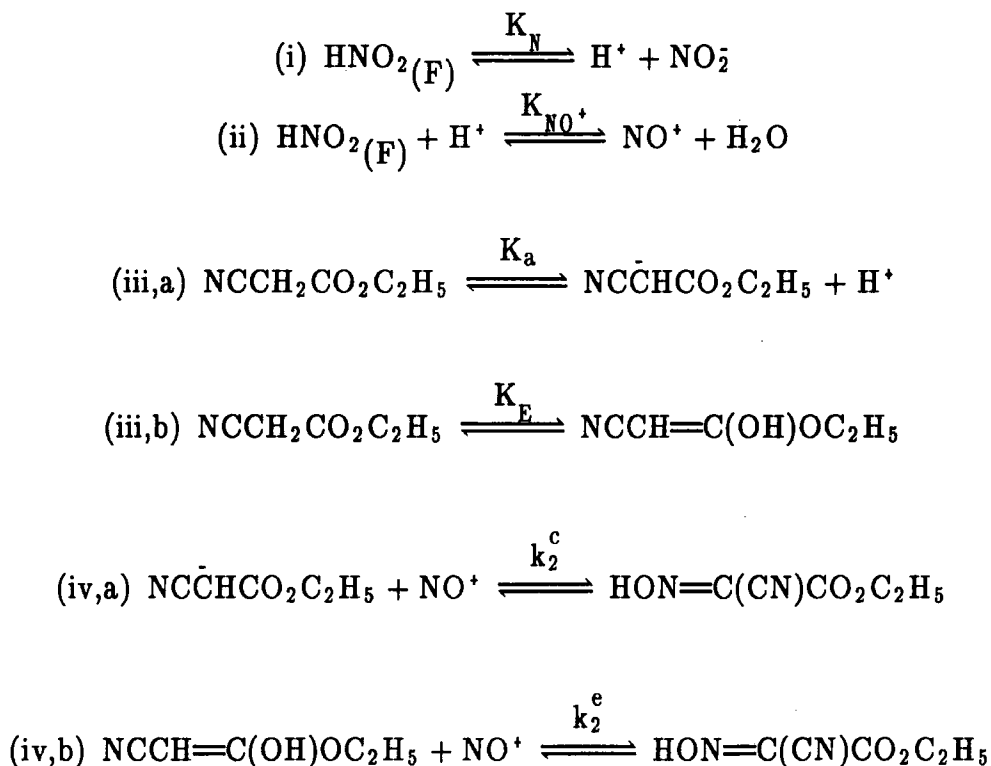
GRAPH 2.13: Chloride ion catalysed nitrosation of ethyl cyanoacetate and diethyl malonate.



▽ DEM
△ ECA

catalysis does not speed up the reaction sufficiently to make the decomposition totally negligible. To test this supposition a reaction was run, under identical conditions to the nitrosation of ethyl cyanoacetate except for the absence of ethyl cyanoacetate. The k_{obs} for this run was $1.05 \times 10^{-4} \text{ s}^{-1}$ compared with $3.10 \times 10^{-4} \text{ s}^{-1}$ when ethyl cyanoacetate was present. The k_{obs} is approximately one third of the k_{obs} when substrate was present. The decomposition of nitrous acid cannot be considered a negligible reaction. Graph 2.13 also has large positive intercepts with the ordinate axis which indicates that nitrosation is not exclusively proceeding by nitrosyl chloride, the nitrous acid is also acting as a nitrosating species.

Nitrosation, in the absence of nucleophilic catalysts, was carried out with ethyl cyanoacetate over a range of acid concentrations. Scheme 2.5 shows the possible step by step processes. Equation 2.20 is the rate equation for reaction via the carbanion and equation 2.21 is the rate equation for reaction via the enol of ethyl cyanoacetate. Both equations can be derived from scheme 2.5.



Scheme 2.5

$$\text{Rate} = \frac{k_2^c K_a K_{NO} + [ECA] [HNO_2]_T [H^+]}{K_N + [H^+]} \quad (2.20)$$

$$\text{Rate} = \frac{k_2^e K_E K_{NO} + [ECA] [HNO_2]_T [H^+]^2}{K_N + [H^+]} \quad (2.21)$$

The results of the uncatalysed (by a nucleophile) nitrosation of ethyl cyanoacetate are shown in table 2.11. Graph 2.14 shows the variation of the first order observed rate constant with acid concentration. Graph 2.15 shows the variation of the corrected observed rate constant (to allow for ionisation to nitrite ions) with acid concentration.

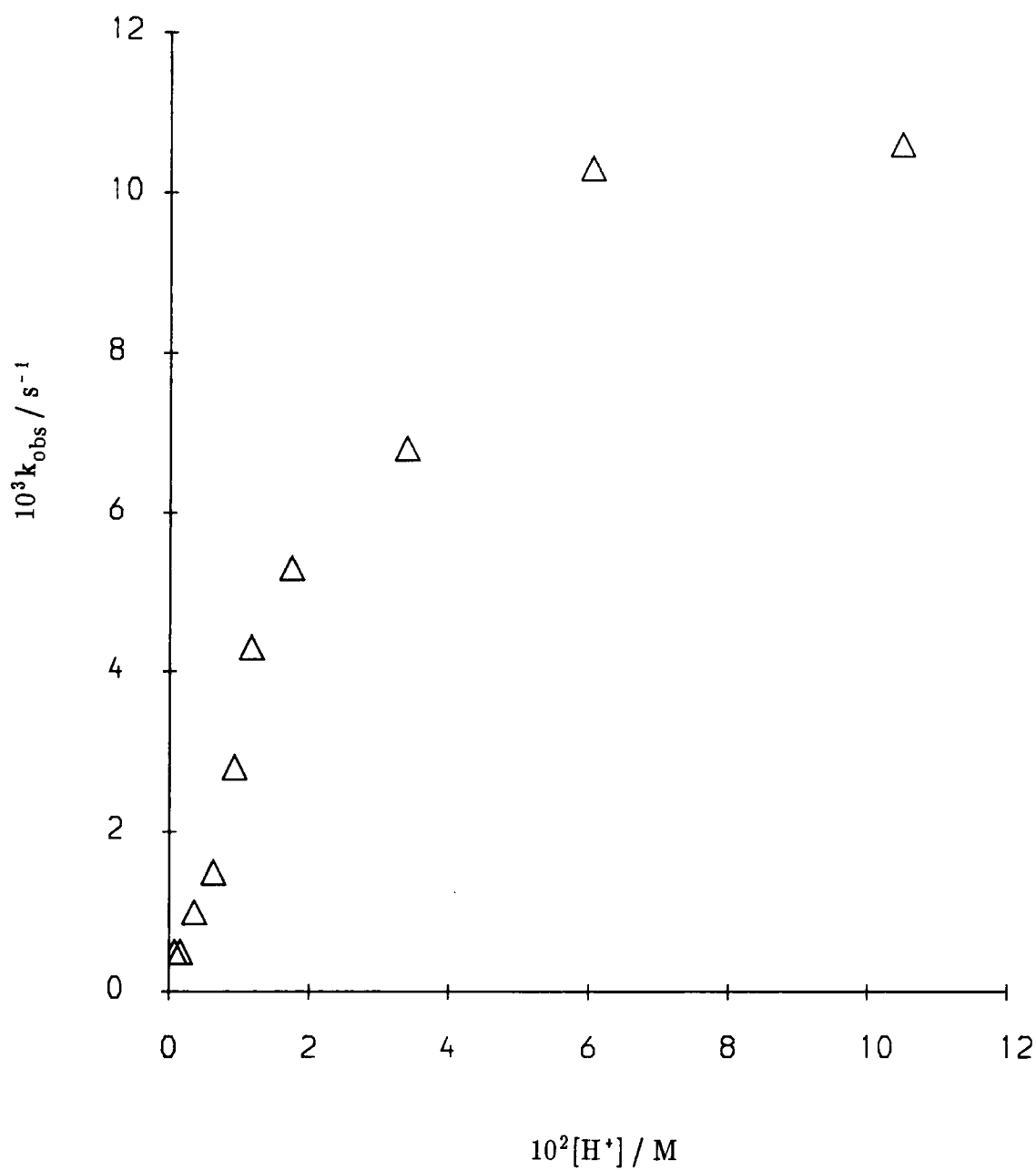
TABLE 2.11: Uncatalysed nitrosation of ethyl cyanoacetate.

$[HNO_2] = 5.0 \times 10^{-3} M$, $[ECA] = 0.247 M$, $T = 298 K$.

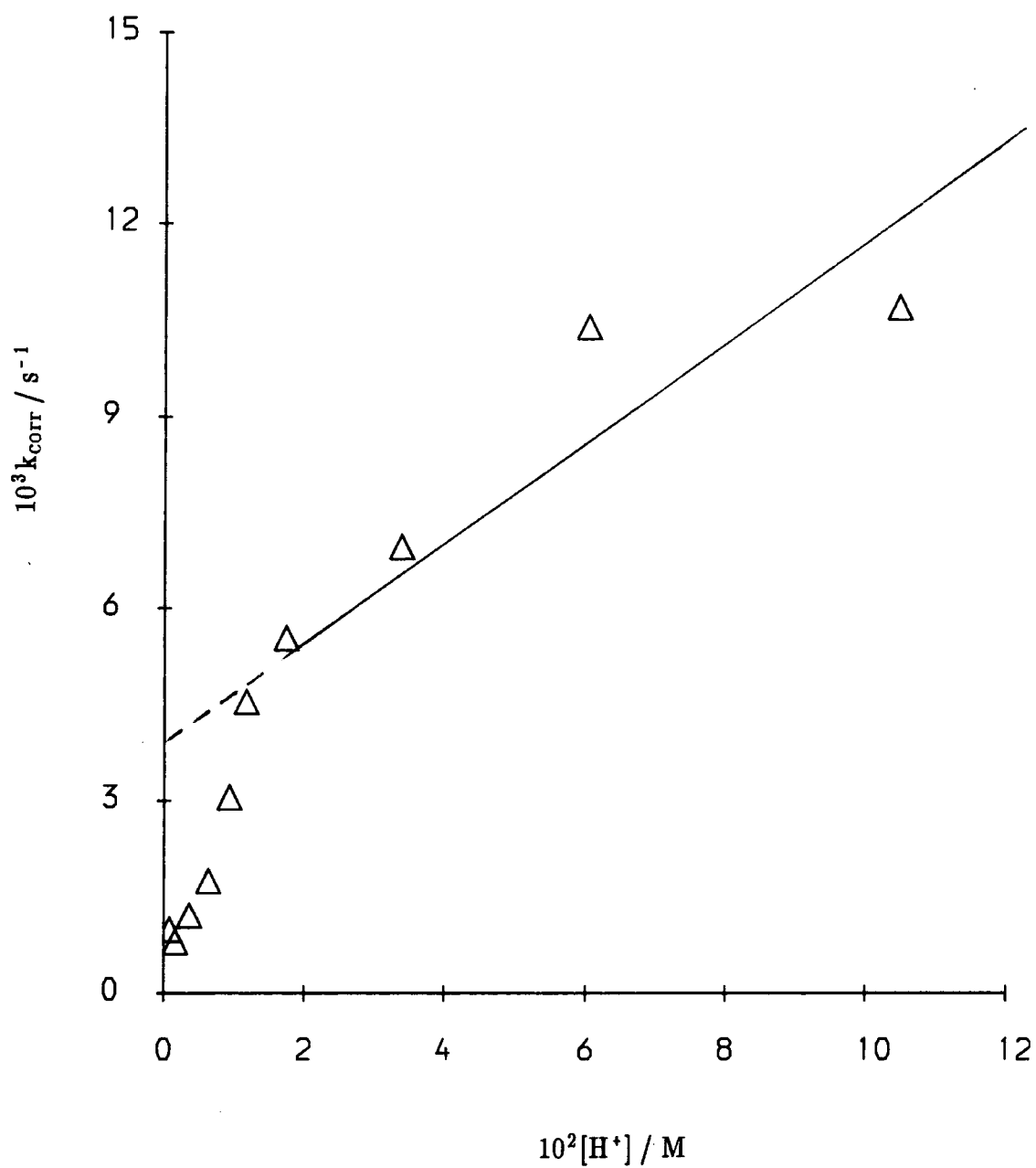
pH	$10^2 [H^+]$	$10^3 k_{obs} / s^{-1}$	$10^3 k_{corr} / s^{-1}$
0.98	10.47	10.6	10.7
1.22	6.03	10.3	10.4
1.47	3.39	6.81	6.95
1.76	1.74	5.31	5.53
1.93*	1.17	4.28	4.54
2.03	0.93	2.83	3.05
2.20	0.63	1.56	1.74
2.44	0.36	1.00	1.20
2.79	0.16	0.55	0.79
3.09	0.08	0.52	0.98

* $[ECA] = 0.495 M$, k_{obs} adjusted appropriately

GRAPH 2.14: Variation of acid concentration for the nitrosation of ethyl cyanoacetate, by nitrous acid.



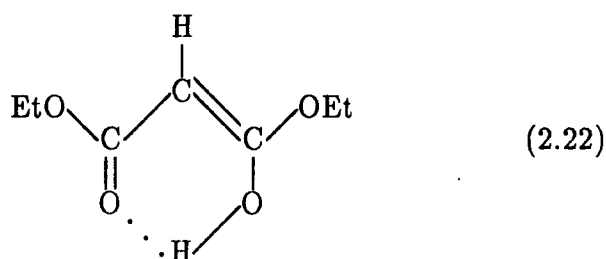
GRAPH 2.15: Variation of the corrected first order rate constant with acid concentration for the uncatalysed nitrosation of ethyl cyanoacetate.



2.3 Discussion

It is apparent from the results that over the majority of the pH range studied it is the enol that is the dominant intermediate. However at the higher pH values reaction via the carbanion intermediate is a possible pathway. This pattern of behaviour has been observed previously¹¹, in the halogenation of diethyl malonate. It is significant to note that the reactive intermediates can be differentiated between, under these reaction conditions, without isolating and characterising them.

If we assume that the reaction of the enols of ethyl cyanoacetate and diethyl malonate with nitrosyl thiocyanate is at the diffusion limit, then we can obtain values of K_E of 3.6×10^{-12} and 2.0×10^{-11} for ethyl cyanoacetate and diethyl malonate respectively, (table 2.4). The larger K_E value for diethyl malonate might be expected as it is possible that it can form a hydrogen bonded six membered ring structure, (equation 2.22), which will stabilise the enol form. This was first observed with pentane-2,4-dione¹². An intramolecular hydrogen bond, to the nitrile nitrogen, is less likely, as in the ethyl cyanoacetate case.



Also it is possible that the nitrile group which has a greater electron withdrawing capability, than the ethyl ester group, destabilises the enol double bond, favouring the keto form of the substrate. This would make the value of K_E for ethyl cyanoacetate smaller than that for diethyl malonate. These comments are made on the assumption that nitrosyl thiocyanate reacts at the diffusion limit with both substrates. This may not be the case as nitrosyl thiocyanate may not be a sufficiently reactive nitrosating species. Also the enol double bonds in each

substrate would be different. In ethyl cyanoacetate it would be more delocalised to the greater electron withdrawing ability of the nitrile group relative to the ethyl ester group. The different electron withdrawing capabilities of the two groups can be seen in their respective σ_I values, which reflect a purely inductive substituent effect. For a nitrile group¹³ $\sigma_I = +0.58$ and for an ethyl ester group¹³ $\sigma_I = +0.34$.

At the lower acid concentrations, where it has been assumed that reaction proceeds exclusively via the carbanion, k_2^c values have been obtained for bromide ion, thiocyanate ion and thiourea catalysis of the nitrosation of ethyl cyanoacetate and diethyl malonate. These values are shown in table 2.12, along with the values of k_2^c obtained for the catalysed nitrosation of malononitrile.

TABLE 2.12: Values of k_2^c for the nitrosation of malononitrile, ethyl cyanoacetate and diethyl malonate by nitrosyl bromide, nitrosyl thiocyanate and nitrosothiuronium ion.

$k_2^c / \text{l mol}^{-1} \text{s}^{-1}$	NOBr	NOSCN	$\text{NO}^+\text{SC}(\text{NH}_2)_2$
MNL †	1.1×10^{10}	4.2×10^9	5.0×10^9
MNL	7.4×10^9	7.0×10^9	—
	2.5×10^{10}	6.7×10^9	—
ECA	8.5×10^9	8.3×10^8 6.1×10^8	4.3×10^7
DEM	4.9×10^{11}	5.0×10^9 5.4×10^9	2.3×10^9

† values from ref. 1

The values of k_2^c for diethyl malonate nitrosation by all three nitrosating species are at the diffusion limit, as in the case with malononitrile. Nitrosyl bromide has been shown^{14,15} to react at the diffusion limit with other substrates, but significantly nitrosyl thiocyanate and S-nitrosothiuronium ion have only previously been shown to react at the diffusion limit with the malononitrile

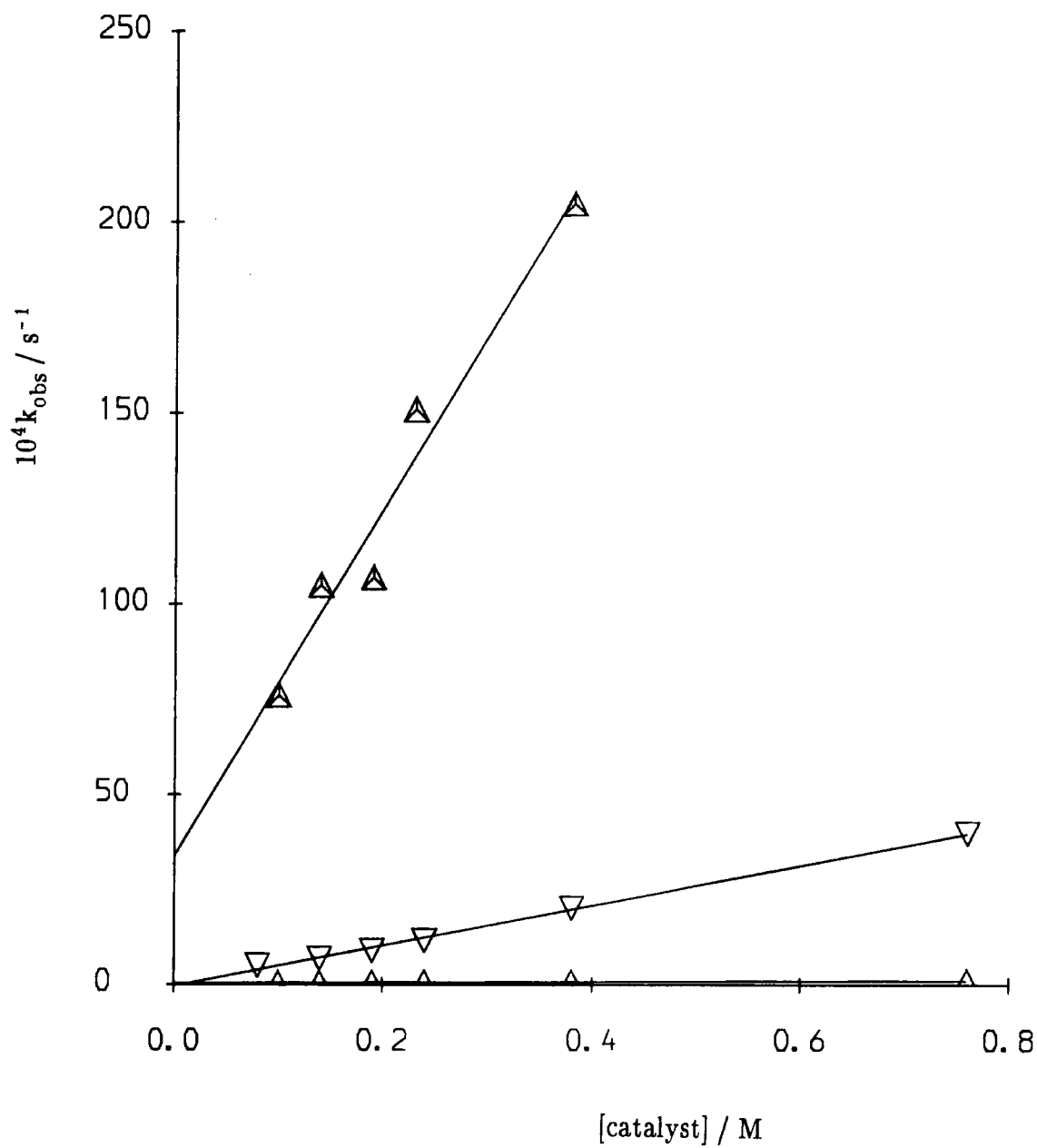
carbanion¹. The diethyl malonate carbanion appears to be as reactive as the malononitrile carbanion with respect to nitrosation, under these acidic conditions.

The rate constants for the nitrosation of ethyl cyanoacetate by the different nitrosating species are not all at the diffusion limit. Nitrosyl bromide reacts at the diffusion limit but not the other two. The three nitrosating species have the reactivity trend $\text{NOBr} > \text{NOSCN} > \text{NO}^+\text{SC}(\text{NH}_2)_2$. This trend has been shown for the nitrosation of many substrates^{14,15,17}. The catalytic effectiveness follows the trend $\text{SC}(\text{NH}_2)_2 > \text{SCN}^- > \text{Br}^-$ which can be represented by the relative gradients of k_{obs} versus [catalyst] plots, (graph 2.16), and is the reverse of the nitrosating species reactivity trend. This is because the relative magnitude of the K_{XNO} values, for each species, is the dominant factor controlling the catalytic effect of the nitrosating species.

The nitrosation of ethyl cyanoacetate, by the different nitrosating species, has conformed to the trends observed in the nitrosation of many other substrates. It appears that the ethyl cyanoacetate derived carbanion is the least reactive of the three carbanions studied in this chapter. The ethyl cyanoacetate carbanion only reacts at the diffusion limit with nitrosyl bromide, whereas the other carbanions react with all three nitrosating species at the diffusion limit. The malononitrile and diethyl malonate carbanions are the most reactive substrates, with respect to nitrosation, studied thus far.

If we consider the relative reactivities of the three carbanions, we see that ethyl cyanoacetate is the least reactive and both diethyl malonate and malononitrile carbanions react at the diffusion limit. The σ_{I} values, quoted earlier¹³, show the nitrile is a more powerful electron withdrawing species than the ethyl ester. This will have a greater 'pull' on the electron around the methylene group, effectively making it less reactive. Hence the reactivity trend $\text{DEM} > \text{ECA} > \text{MNL}$ should be observed. Only part of this is true, $\text{DEM} > \text{ECA}$. However, the greater electron withdrawing power of the nitrile group delocalises the carbanion charge, stabilising the molecule and so lowering its pK_a value. This fits with the

GRAPH 2.16: Nitrosation of ethyl cyanoacetate, in the presence of nucleophilic catalysts, bromide ion, thiocyanate ion and thiourea.



- \blacktriangle $\text{SC}(\text{NH}_2)_2$
 ∇ SCN^-
 \triangle Br^-

literature values^{8,9,10}, where $\text{pK}_a \text{ MNL} < \text{pK}_a \text{ ECA} < \text{pK}_a \text{ DEM}$. The carbanion with the smaller pK_a will be present in greater concentration under the reaction conditions used. This increased concentration could give a greater k_2^c for reaction via that carbanion. Hence a reactivity trend $\text{MNL} > \text{ECA} > \text{DEM}$ could be expected. Only the $\text{MNL} > \text{ECA}$ part is true from the experimental results obtained. Both of these effects may be in competition. This would explain why both malononitrile and diethyl malonate carbanions appear to be more reactive than the ethyl cyanoacetate carbanion.

The results for attack upon the carbanions of ethyl cyanoacetate and diethyl malonate by nitrosyl chloride have not been discussed here because of their large erroneous nature. This is mainly due to the chloride ion not being a sufficiently good catalyst for the decomposition of the nitrous acid, in acidic solution, to be negligible.

The data from graph 2.15, for the uncatalysed nitrosation of ethyl cyanoacetate, is the most difficult to interpret. At higher acid concentrations it is clear that there is a linear relationship between the corrected first order rate constant and the acid concentration. Equation 2.23 shows the proportionality of the corrected first order rate constant to reagent concentrations in the case of reaction via the ethyl cyanoacetate derived carbanion taken from equation 2.21. Equation 2.24 shows a similar relationship as equation 2.23 but for reaction via the ethyl cyanoacetate enol tautomer, taken from equation 2.22.

$$\text{Rate} \propto [\text{ECA}][\text{HNO}_2] \quad (2.23)$$

$$\text{Rate} \propto [\text{ECA}][\text{HNO}_2][\text{H}^+] \quad (2.24)$$

Only equation 2.24, reaction via the enol intermediate, corroborates the data in graph 2.15, in the higher acid concentration region. At lower acid concentration the change in nature of the k_{corr} dependence upon acid concentration is difficult to explain. If reaction were still via the enol there would be no deviation as is the case

in graphs 2.7 and 2.8, for the thiocyanate ion catalysed nitrosation of ethyl cyanoacetate and diethyl malonate. Reaction via the carbanion is independent of acid concentration and would not show the behaviour seen at low acid concentration in graph 2.15. The change in nature of the relationship occurs at an acid concentration of approximately 1.8×10^{-2} M, which is far too acidic for the effect to be due to the acid dissociation of ethyl cyanoacetate⁹ ($K_a = 1.8 \times 10^{-12}$).

As with the chloride ion catalysis the spontaneous decomposition rate of nitrous acid may not be totally negligible and at lower acid concentrations it may be more significant, accounting for the falling in the k_{corr} values at low acid concentrations. This is merely speculation and at present no clear explanation for this behaviour has been found.

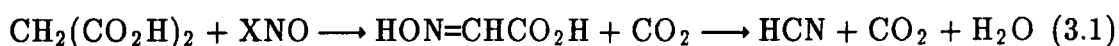
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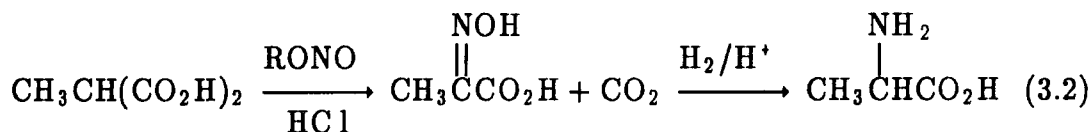
CHAPTER 3
NITROSATION OF MALONIC
AND METHYLMALONIC ACIDS

3.1 Introduction

The nitrosation of carboxylic acids has been scarcely studied and no kinetic appraisal of the reaction appears to have been made. Both malonic acid (MA) and methylmalonic acid (MMA) are known to undergo nitrosation, under certain reaction conditions. During the nitrosation of malonic acid the intermediate is thought to also undergo decarboxylation. The reaction product has not been fully characterised as it decomposes in aqueous solution at approximately 40°C¹, (equation 3.1).

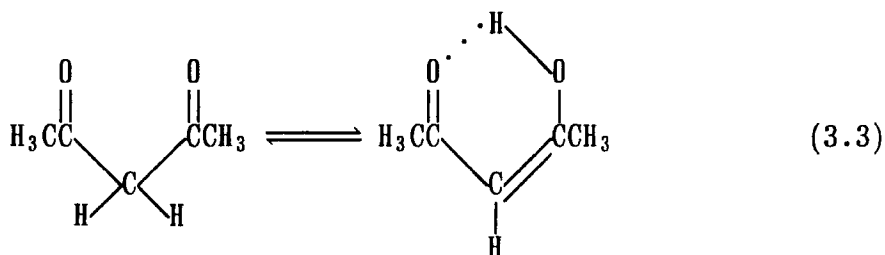


Methylmalonic acid is known to decarboxylate upon nitrosation to give α -oximinopropionic acid². The synthetic procedure is well known as the α -oximino acid is an intermediate, which after hydrogenation yields alanine³, an α -amino acid, (equation 3.2).



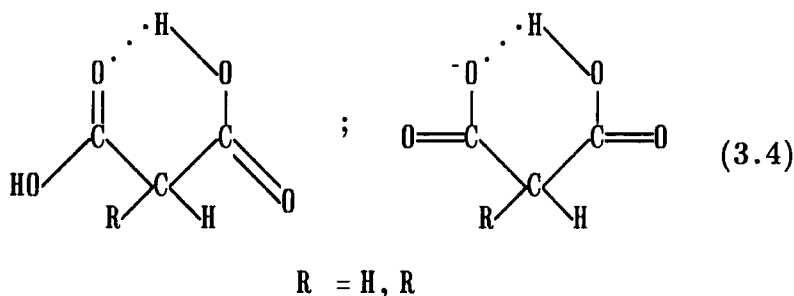
In aqueous solution the first and second dissociation constants for malonic acid^{4,5} and methylmalonic acid^{5,6} are well documented. These are for the loss of the protons from the carboxylic acid groups in the molecule. The dissociation constant for the loss of a proton from the methylene group to give the carbanion, a possible intermediate in the nitrosation of the acids, has not been determined. The other possible reaction intermediate, the enol, has been considered for some halogenation reactions^{7,8,9}, although no keto-enol equilibrium constants, K_E , have been evaluated. Involvement of enol intermediates has centred upon ketones and aldehydes but there is much current interest in carboxylic acid enols^{10,11,12}. Acid and base catalysis in enol formation is widely accepted, as is the stabilisation

of the enol in β -dicarbonyl compounds by a six membered intramolecular hydrogen bonded ring structure¹³, (equation 3.3).



Intramolecular hydrogen bonding is well known in malonic acids¹⁴ and their anions¹⁵, (equation 3.4), in aqueous solution, by formation of a six membered ring structure. This gives rise to the possibility of intramolecular acid catalysis of enol formation and has been considered, for dibasic acids, by Leopold and Haim⁸.

Intramolecular acid catalysis has been identified for some previously studied β -dicarbonyl compounds, the first identified was the intramolecular formation of the enol of pentane-2,4-dione¹⁶.



The work undertaken in this chapter was a kinetic study of the nitrosation of malonic acid and methylmalonic acid, by nitrous acid alone and also in the presence of nucleophilic catalysts; Cl^- , Br^- , SCN^- . It was carried out in aqueous acidic solution below pH 3, the aim being to try to determine some mechanistic details of the reaction.

3.2 Results

Malonic acid and methylmalonic acid concentrations were in at least a twenty fold excess over that of the nitrous acid and the reaction was followed by observing the change in absorbance due to the disappearance of nitrous acid at 370 nm.

Both malonic acid and methylmalonic acid systems were initially analysed by varying the substrate concentration, keeping the other parameters constant, (table 3.1). It was found that all of the reactions with nitrous acid presented excellent first order reaction curves, indicating a first order dependence of the reaction upon $[\text{HNO}_2]_T$. Plots of k_{obs} versus substrate concentration, (graph 3.1), for both substrates, yielded good linear plots indicating a first order reaction dependence upon the substrate concentration.

TABLE 3.1: Nitrosation of malonic acid and methylmalonic acid by nitrous acid.

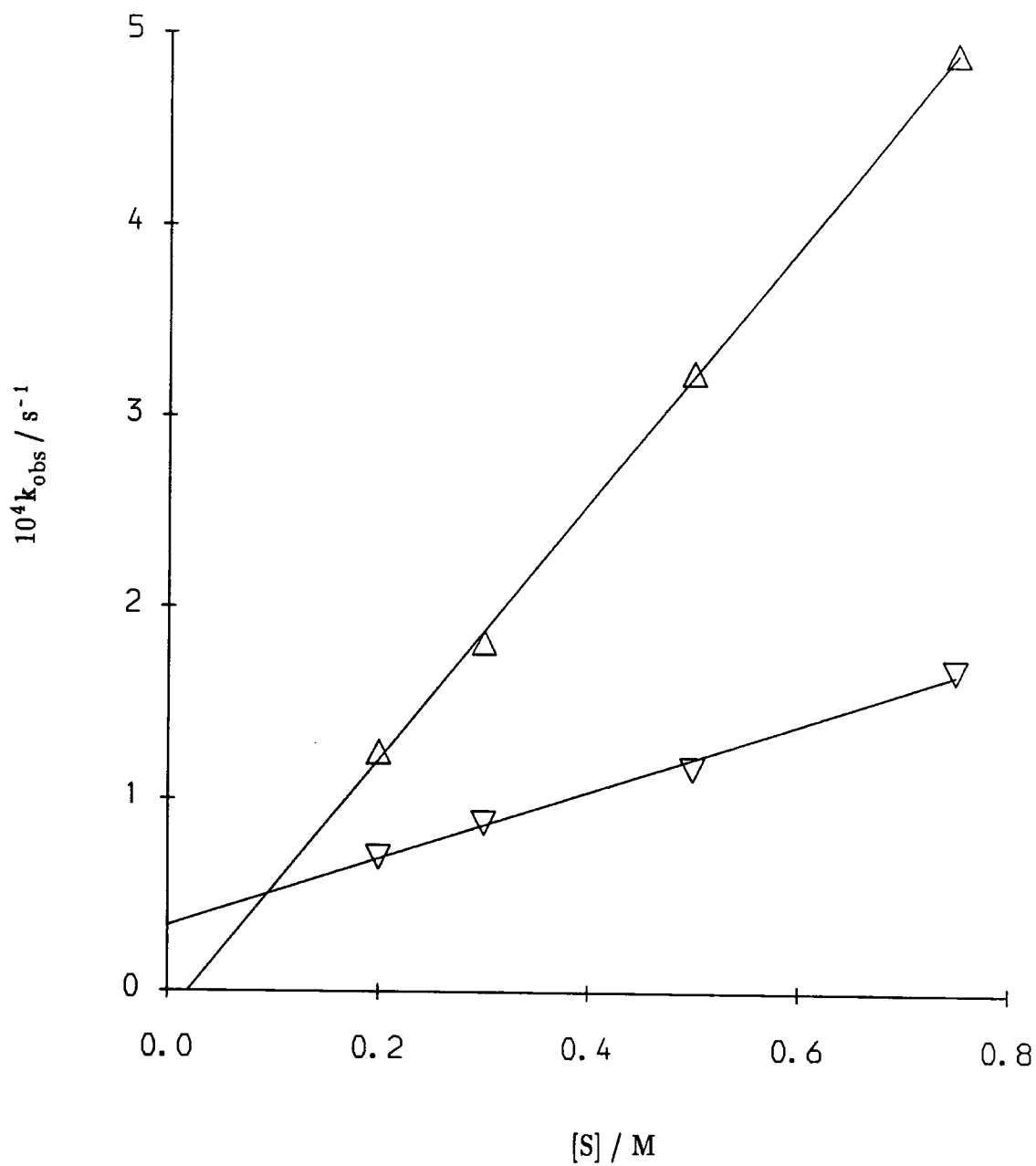
$[\text{HNO}_2]_T = 5.0 \times 10^{-3} \text{M}$, $T = 298\text{K}$, (i) MA $\text{pH} = 1.8$,

(ii) MMA $\text{pH} = 2.4$.

[S] / M	$10^4 k_{\text{obs}} / \text{s}^{-1}$	
	S = MA	S = MMA
0.20	1.25	0.70
0.30	1.82	0.88
0.50	3.24	1.17
0.75	4.90	1.68

The small positive intercept on the ordinate, for the methylmalonic acid reaction, can be attributed to either experimental error or a degree of reversibility of the reaction. Reversibility is the least likely cause as decarboxylation is known to occur upon nitrosation. For methylmalonic acid the error seems to be

GRAPH 3.1: Variation of substrate concentration in the nitrosation of malonic acid by nitrous acid.



▽ MMA
△ MA

proportionally quite large, but the reaction is quite slow and it is possible that the decomposition of nitrous acid is interfering to some extent and thus causing such a positive intercept. The greater slope of the malonic acid reaction would indicate it is a more reactive substrate to nitrosation than methylmalonic acid, as the size of slope is proportional to the rate constant for the attack of the nitrosating species upon malonic acid and methylmalonic acid.

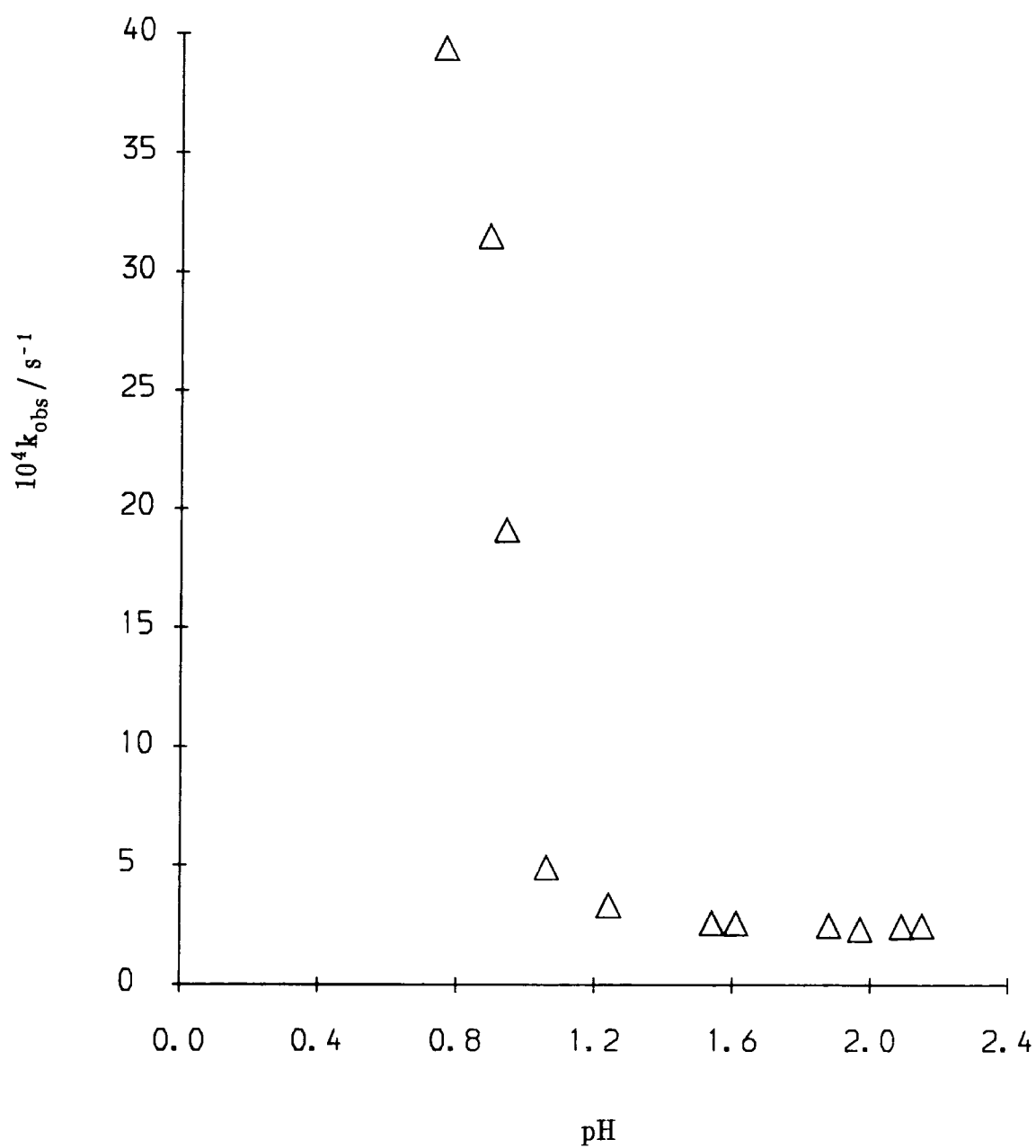
Variation of pH has been used to determine the effect of acid concentration upon the reaction. Results are presented in tables 3.2 and 3.3 and also in graphs 3.2, 3.3, 3.4 and 3.5.

TABLE 3.2: Nitrosation of malonic acid by nitrous acid.

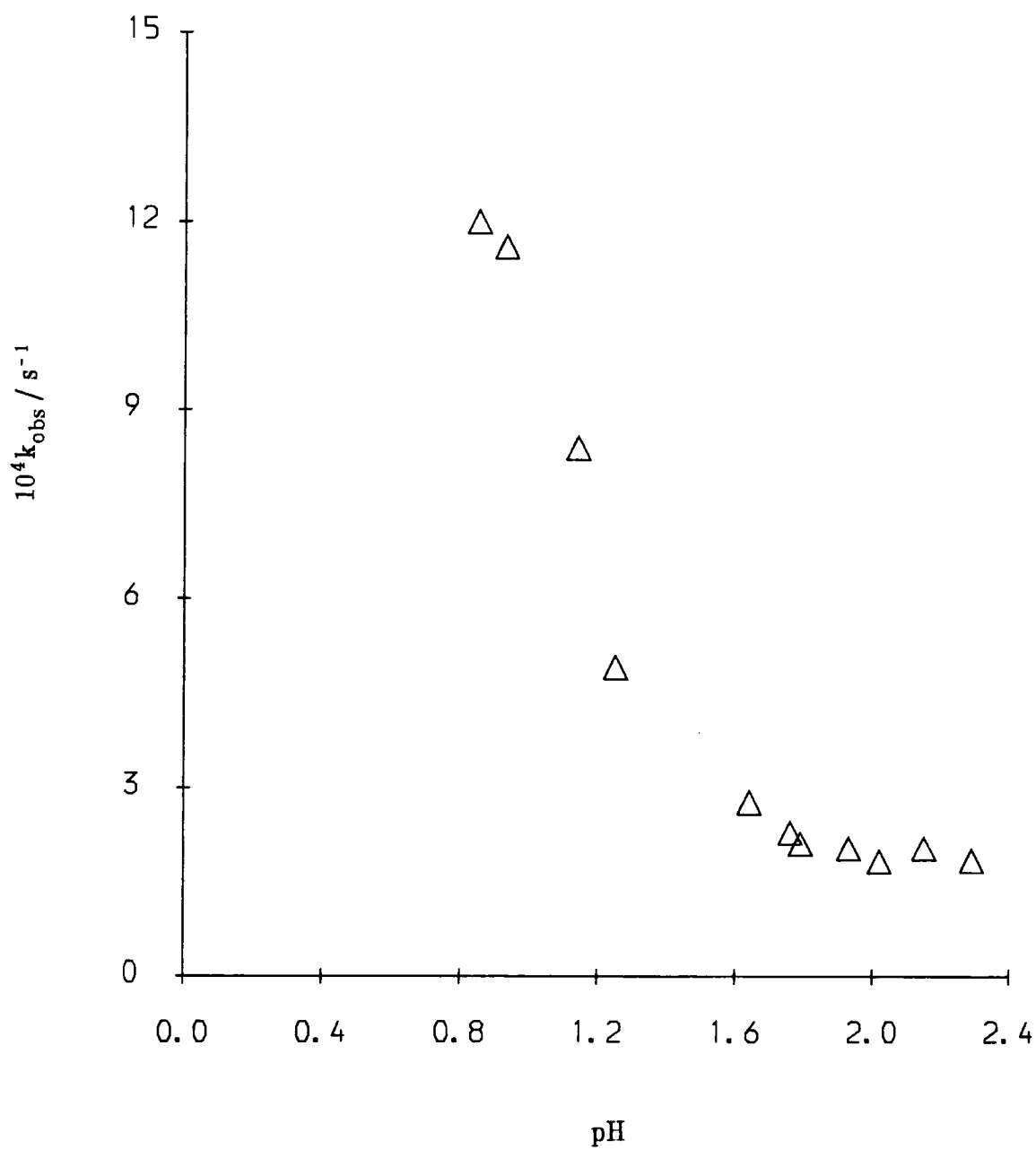
$$[\text{MA}] = 0.30\text{M}, [\text{HNO}_2]_{\text{T}} = 5.0 \times 10^{-3}\text{M}.$$

pH	$10^2 [\text{H}^+] / \text{M}$	$10^4 k_{\text{obs}} / \text{s}^{-1}$
0.76	17.4	39.4
0.89	12.9	31.5
0.94	11.5	19.1
1.06	8.7	4.91
1.24	5.8	3.32
1.54	2.9	2.58
1.61	2.5	2.57
1.88	1.3	2.48
1.97	1.1	2.32
2.09	0.8	2.44
2.15	0.7	2.47

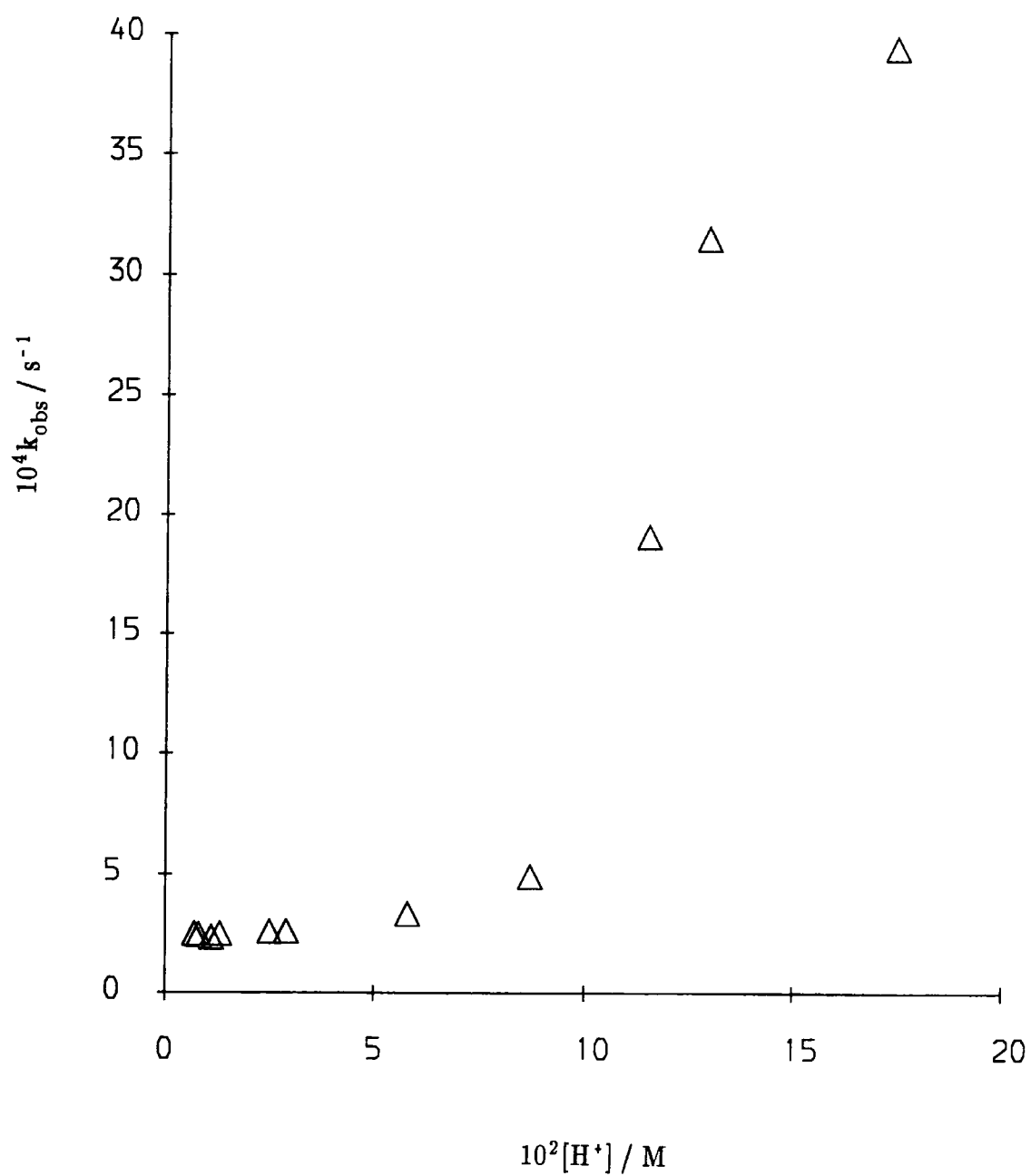
GRAPH 3.2: Nitrosation of malonic acid , by nitrous acid, at various pH.



GRAPH 3.3: Nitrosation of methylmalonic acid , by nitrous acid, at various pH.



GRAPH 3.4: Nitrosation of malonic acid, by nitrous acid, at various acid concentrations.



GRAPH 3.5: Nitrosation of methylmalonic acid, by nitrous acid, at various acid concentrations.

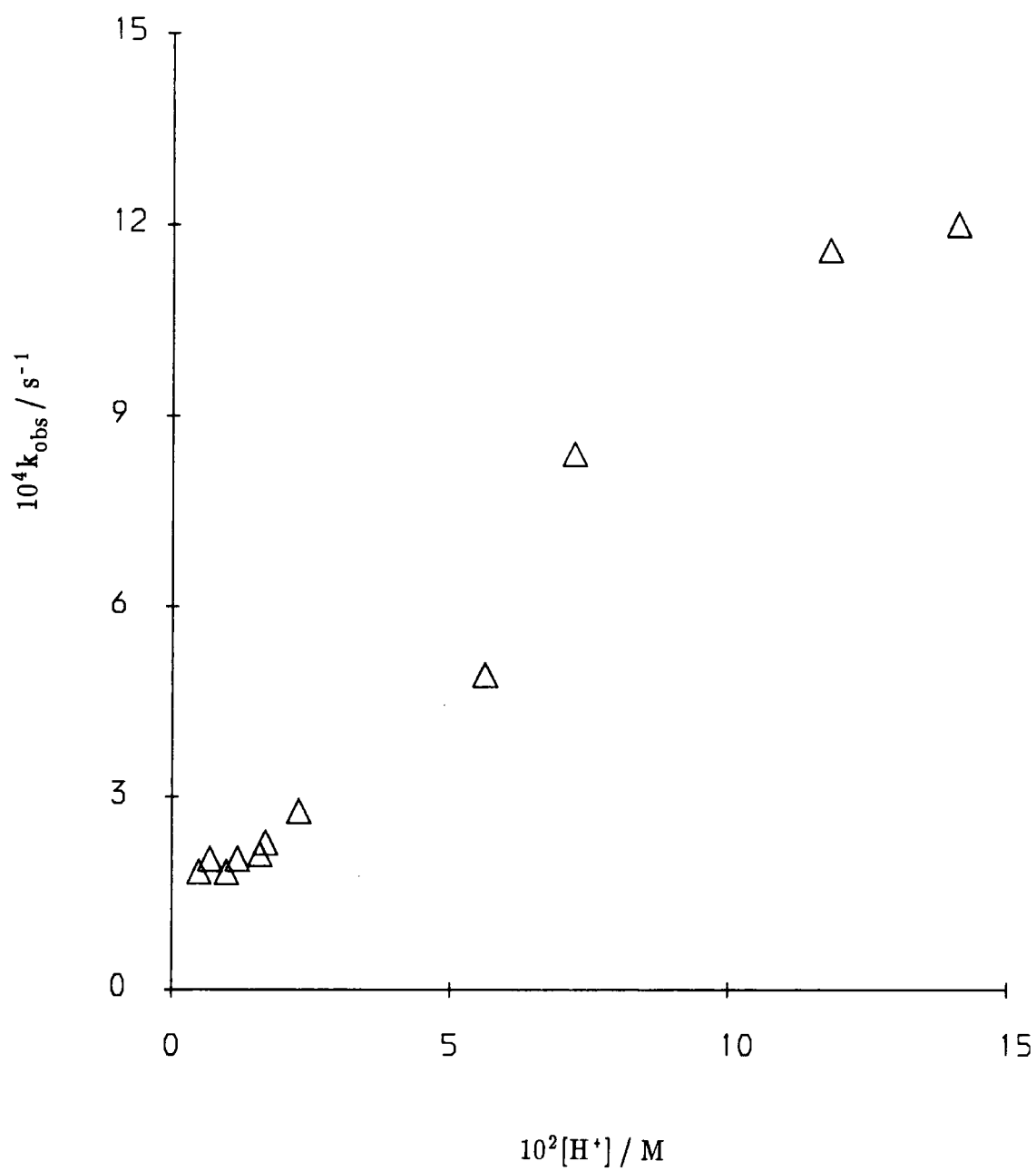
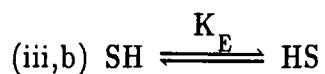
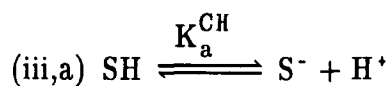
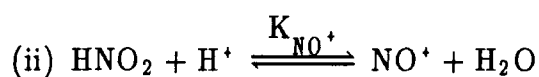


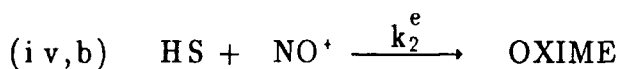
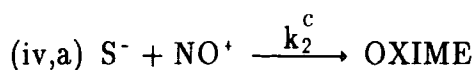
TABLE 3.3: Nitrosation of methylmalonic acid by nitrous acid.

$$[\text{MMA}] = 0.30\text{M}, [\text{HNO}_2]_{\text{T}} = 5.0 \times 10^{-3}\text{M}.$$

pH	$10^2 [\text{H}^+] / \text{M}$	$10^4 k_{\text{obs}} / \text{s}^{-1}$
0.85	14.1	12.0
0.93	11.8	11.6
1.14	7.2	8.40
1.25	5.6	4.92
1.64	2.3	2.78
1.76	1.7	2.29
1.79	1.6	2.11
1.93	1.2	2.04
2.02	1.0	1.83
2.15	0.7	2.04
2.29	0.5	1.84

The results can be rationalised by considering the step by step processes for both carbanion and enol intermediate routes, scheme 3.1.





Scheme 3.1

Now K_N is the dissociation constant for nitrous acid¹⁷ (7.1×10^{-4}), K_{NO^+} is the equilibrium constant for the formation of the nitrosonium ion, K_a^{CH} is the dissociation constant for the loss of a proton from the carbon of the methylene group of malonic acid or methylmalonic acid, K_E is the keto-enol equilibrium constant and finally k_2^c and k_2^e are the second order rate constants for the attack of the nitrosonium ion upon the carbanion and enol intermediates respectively.

As the measured points on graph 3.2 and 3.3, for malonic acid and methylmalonic acid respectively, are at or below pH 2.1, then the value for acid concentration for all of these points is going to be substantially larger than K_N ($[H^+] \gg K_N$), the dissociation constant for nitrous acid. Effectively in deriving a rate equation from scheme 3.1 step (i) can be ignored. Hence the derived rate equations, for reaction via an enol or carbanion intermediates, are given in equations 3.5 and 3.6 respectively.

$$Rate = k_2^e K_E K_{NO^+} [SH][HNO_2]_T [H^+] \quad (3.5)$$

$$Rate = k_2^c K_a^{CH} K_{NO^+} [SH][HNO_2]_T \quad (3.6)$$

The reactions all gave first order curves, showing a first order reaction dependence upon $[HNO_2]_T$. Thus we can use $rate = k_{obs}[HNO_2]_T$ and this can be substituted into equations 3.5 and 3.6 to give rate constant equations, (equations 3.7 and 3.8).

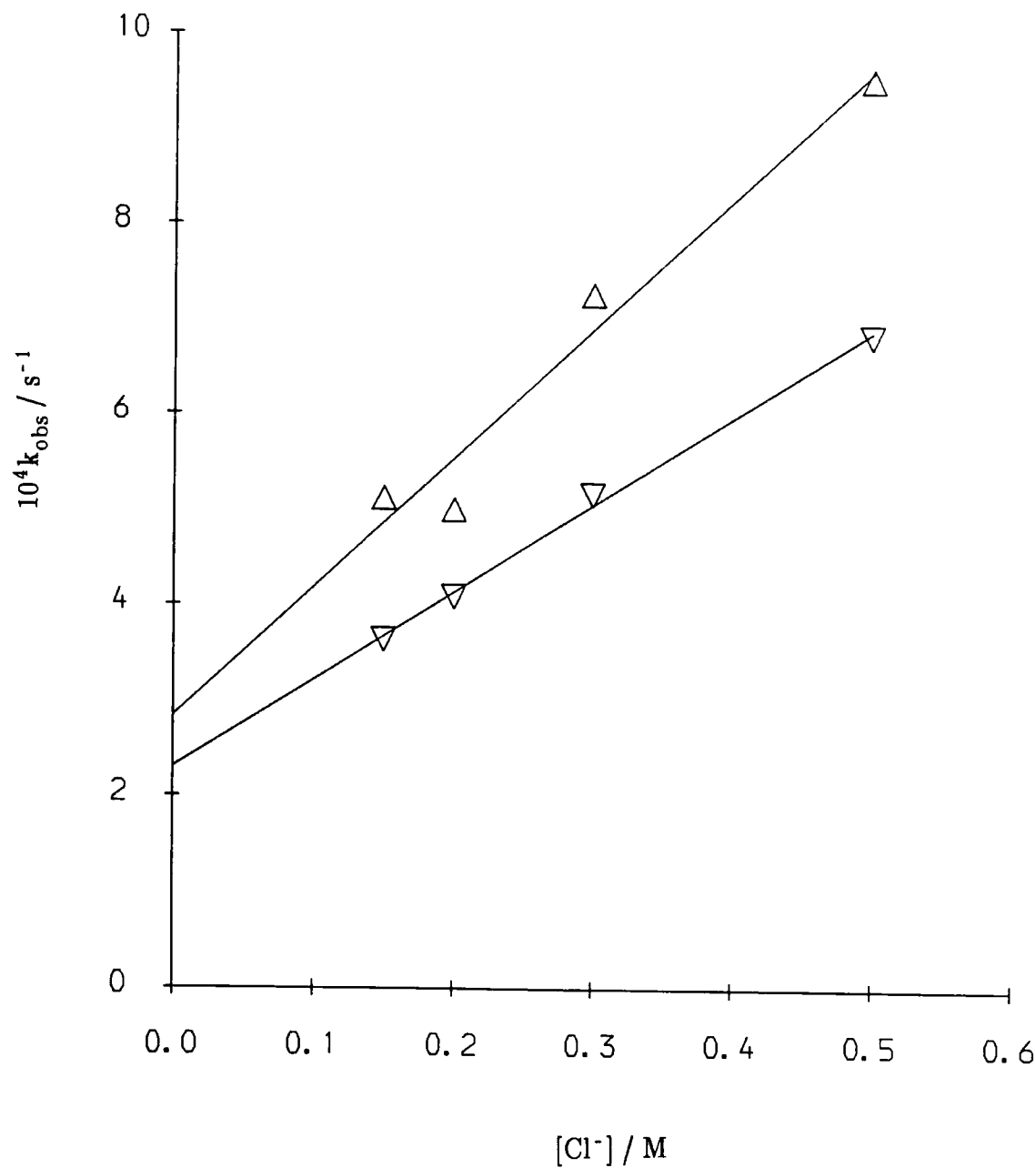
$$k_{\text{obs}} = k_2^e K_E K_{\text{NO}^+} [\text{SH}] [\text{H}^+] \quad (3.7)$$

$$k_{\text{obs}} = k_2^c K_a^{\text{CH}} K_{\text{NO}^+} [\text{SH}] \quad (3.8)$$

Reaction via the enol intermediate would give a linear increase in k_{obs} with increase of $[\text{H}^+]$, (equation 3.7). This is a first order reaction dependence upon acid concentration. Carbanion intermediate involvement would be independent of acid concentration, (equation 3.8). Graph 3.4 and 3.5 represent the variation of k_{obs} with change in $[\text{H}^+]$. At low acid concentration k_{obs} is independent of $[\text{H}^+]$, behaviour compatible with equation 3.8, this corresponds to reaction proceeding via the derived carbanion intermediate. At higher $[\text{H}^+]$ the dependence of k_{obs} upon $[\text{H}^+]$ alters to first order, which is the behaviour indicated by equation 3.7, and represents reaction via the enol intermediate. As the acidity of the reaction solution is increased there is a change in dominant reaction intermediate from carbanion to enol.

Reactions of a similar nature were performed in the presence of chloride ion as a catalyst. These were carried out at an acid concentration where the dominant reaction intermediate is the carbanion, this was at pH 1.31 for malonic acid and pH 1.64 for methylmalonic acid. The results are shown below in table 3.4 and graph 3.6.

GRAPH 3.6: Chloride ion catalysed nitrosation of malonic acid and methylmalonic acid.



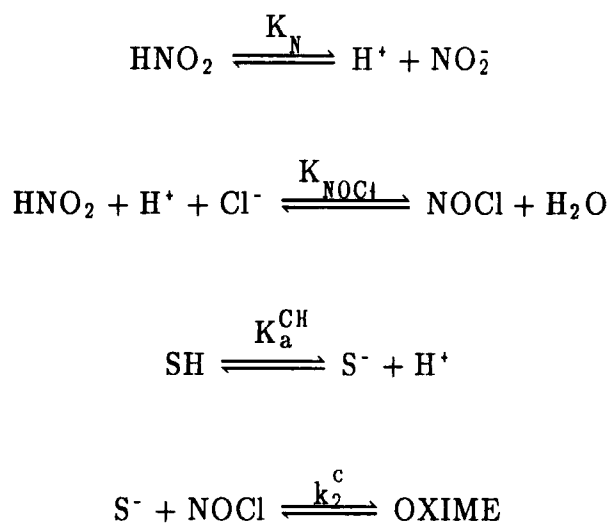
∇ MMA at pH 1.64
 Δ MA at pH 1.31

TABLE 3.4: Attack of malonic acid and methylmalonic acid, at fixed acid concentrations, by nitrosyl chloride.

$[MA], [MMA] = 0.30M, [HNO_2]_T = 5.0 \times 10^{-3}M, T = 298K.$

$[Cl^-] / M$	$10^4 k_{obs} / s^{-1}$	
	MA	MMA
0.15	5.12	3.64
0.20	5.75	4.09
0.30	7.26	5.16
0.50	9.52	6.83

As can be seen in graph 3.6 there is a linear relationship between k_{obs} and $[Cl^-]$, which is predicted by the rate equation, (equation 3.9), derived from the proposed stepwise scheme for the reaction involving a carbanion intermediate, (scheme 3.2).



Scheme 3.2

$$Rate = k_2^c K_a^{CH} K_{NOCl} [SH][HNO_2]_T [Cl^-] \quad (3.9)$$

A value for $k_2^c K_a^{CH}$ can be obtained for both substrates, (equation 3.10), from the slopes of the k_{obs} versus $[Cl^-]$ plots, (graph 3.6).

$$\text{Rate} = k_{obs} [HNO_2]_T,$$

substituted in equation 3.9 then taking slope of k_{obs} versus $[Cl^-]$ plots gives

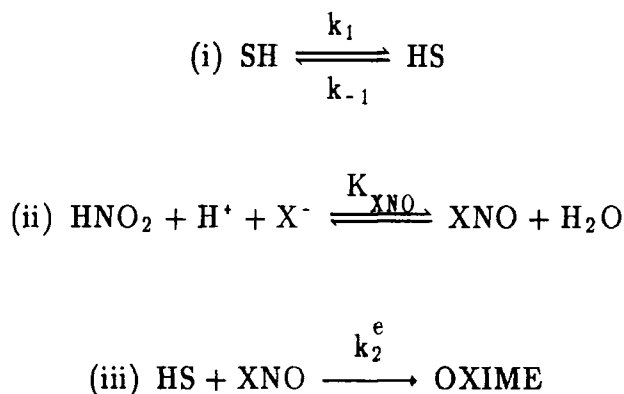
$$\text{Slope} = k_2^c K_a^{CH} K_{NOCl} [SH] \quad (3.10)$$

Values of $k_2^c K_a^{CH}$ for malonic acid and methylmalonic acid are 3.82 s^{-1} and 2.77 s^{-1} respectively, calculated from equation 3.10. If the assumption is made that nitrosyl chloride reacts with both carbanions at the diffusion limit, which is certainly the case for the carbanion derived from malononitrile¹⁸ and several other substrates¹⁹, then we obtain values of 9.3 and 9.4 for the pK_a^{CH} values of malonic acid and methylmalonic acid, respectively, acting as carbon acids. These are not unreasonable values considering the literature values of $pK_a = 11.39$ for malononitrile²⁰ and $pK_a = 12.90$ for diethyl malonate²¹, which are similar structures in as much as they contain an active methylene group with two electron withdrawing groups attached.

Bromide ion catalysis was examined next with the intention of examining if a trend in catalytic effectiveness of different nucleophiles existed. However the early experiments, using variation of bromide ion concentration, did not fit the first order reaction kinetics, seen for chloride ion catalysis or nitrosation by nitrous acid alone. The absorbance time plots were no longer exponential in character. The deviation was such that the reaction profile appeared to be a combination of first and zero order behaviour. Equation 3.11 can be used to help explain the reason for this deviation.



All of the previously discussed work falls into one category, that is when the rate of step (3) is very much slower than the rate of step (2), therefore step (3) is totally rate determining. There is another limiting case, when the rate of step (2) is much slower than the rate of step (3), making step (1) (intermediate formation) rate determining. Under these conditions the absorbance time plots would be linear, i.e. zero order behaviour. The initial bromide ion catalysed nitrosation results do not fall at either extreme limit but somewhere in between when neither step (1) nor step (3) is fully rate determining. The reaction kinetics obtained are mixed zero and first order. The intermediate in this case is probably the enol since increasing the acidity increases the rate of the zero order component of the reaction, i.e. the step is acid catalysed. A stepwise process for the reaction is proposed, scheme 3.3. It is worth pointing out, at this time, that in scheme 3.3 no consideration is taken of the detailed form of acid or base catalysis, this will be dealt with in section 3.3.



Scheme 3.3

The enol is represented by HS in scheme 3.3. The overall rate equation from this scheme was derived as follows. The rate of formation of product is equivalent to the rate of reaction, (equation 3.12).



$$\text{Rate} = \frac{d[\text{PRODUCT}]}{d t} \quad (3.12)$$

Also from (iii) of scheme 3.3 we have equation 3.13,

$$\frac{d[\text{PRODUCT}]}{d t} = k_2^e [\text{ENOL}][\text{XNO}] \quad (3.13)$$

$[\text{XNO}]$ can be substituted by $K_{\text{XNO}}[\text{HNO}_2]_T[\text{H}^+][\text{X}^-]$ from (ii) in scheme 3.3.

Considering the rate of enol formation, (equation 3.14).

$$\frac{d[\text{ENOL}]}{d t} = k_1 [\text{MA}] - (k_{-1} [\text{ENOL}] + k_2^e [\text{ENOL}][\text{XNO}]) \quad (3.14)$$

By the Steady State Hypothesis $\frac{d[\text{ENOL}]}{d t} = 0$, hence equation 3.14 can be rearranged, (equation 3.15).

$$[\text{ENOL}] = \frac{k_1 [\text{MA}]}{k_{-1} + k_2^e [\text{XNO}]} \quad (3.15)$$

Substitutions in equation 3.13 give the overall rate expression, (equation 3.16).

$$\text{Rate} = \frac{k_1 k_2^e K_{\text{XNO}} [\text{MA}][\text{HNO}_2]_T[\text{H}^+][\text{X}^-]}{k_{-1} + k_2^e K_{\text{XNO}} [\text{HNO}_2]_T[\text{H}^+][\text{X}^-]} \quad (3.16)$$

Equation 3.16 is the quantitative representation of the situation discussed around equation 3.11. If the nitrosation is the rate determining step then $k_{-1} \gg k_2^e K_{\text{XNO}} [\text{HNO}_2]_T[\text{H}^+][\text{X}^-]$ and equation 3.16 will simplify, (equation 3.17).

$$\text{Rate} = K_E k_2^e K_{\text{XNO}} [\text{HNO}_2]_T [\text{H}^+] [\text{X}^-] \quad (3.17)$$

$$\text{where } K_E = \frac{k_1}{k_{-1}}$$

$$\text{Rate} = k_1 [\text{MA}] \quad (3.18)$$

The other limiting case is when enolisation is rate determining and follows from the inequality $k_2^e K_{\text{XNO}} [\text{HNO}_2]_T [\text{H}^+] [\text{X}^-] \gg k_{-1}$ and the overall rate equation, (equation 3.16), will simplify, (equation 3.18). One limit is first order, (equation 3.17), and the other zero order, (equation 3.18), with respect to nitrous acid concentration. Between limiting cases equation 3.16 is valid. Inversion of equation 3.16 gives an equation of the form shown in equation 3.19,

$$\frac{1}{\text{Rate}} = \frac{p + q(a - x)}{r(a - x)} \quad (3.19)$$

where $(a - x) = [\text{HNO}_2]$, $p = k_{-1}$, $q = k_2^e K_{\text{XNO}} [\text{X}^-] [\text{H}^+]$,
 $r = k_1 k_2^e K_{\text{XNO}} [\text{MA}] [\text{X}^-] [\text{H}^+]$ which simplifies to equation 3.20.

$$\frac{1}{\text{Rate}} = \frac{p}{r} \cdot \frac{1}{(a - x)} + \frac{q}{r} \quad (3.20)$$

$$\text{and } \frac{p}{r} = \frac{k_{-1}}{k_1 k_2^e K_{\text{XNO}} [\text{MA}] [\text{X}^-] [\text{H}^+]}, \quad \frac{q}{r} = \frac{1}{k_1 [\text{MA}]}$$

If the rate can be measured, then plotting $(\text{Rate})^{-1}$, the slope of tangents to points on the reaction curve, against $(a - x)^{-1}$, the absorbance due to nitrous acid at points on the reaction curve, should give a straight line with a slope $\frac{p}{r}$ and intercept $\frac{q}{r}$. From the intercept it is possible to calculate k_1 , the overall first order enolisation rate constant. Some calculations were performed with a method derived by Dubois *et al*²², previously used with some success in calculations from

nitrosation of ketones²³ where neither the enolisation nor nitrosation were rate limiting. These calculations were unsuccessful in this work and results not used.

Bromide ion catalysed nitrosation of methylmalonic acid results are shown below in table 3.5. The k_1 values listed are calculated from the intercept value obtained experimentally used in conjunction with the intercept term from equation 3.20, or directly from the slope of linear absorbance time plots.

TABLE 3.5: Bromide ion catalysed nitrosation of methylmalonic acid.

$$[\text{HNO}_2]_{\text{T}} = 5.0 \times 10^{-3}\text{M}, \text{ T} = 298\text{K}.$$

[HClO ₄] = 6.46 x 10 ⁻² M, [MMA] = 0.30M	
[Br ⁻] / M	10 ⁴ k ₁ / s ⁻¹
0.15	2.20 ^a
0.20	2.18 ^a
0.30	2.07 ^a
0.50	2.72 ^a
[HClO ₄] = 1.33M, [MMA] = 0.30M	
[Br ⁻] / M	10 ⁴ k ₁ / s ⁻¹
0.15	2.09 ^a 1.35 ^b
0.20	2.13 ^a 1.64 ^b
0.30	2.98 ^a 1.92 ^b
0.50	2.59 ^a 2.14 ^b
[H ₂ SO ₄] = 1.00M, [MMA] = 0.28M	
[Br ⁻] / M	10 ⁴ k ₁ / s ⁻¹
0.50	2.25 ^a

a – Calculated from intercept in equation 3.20

b – Calculated directly from slope of absorbance plots

Of the k_1 values obtained by the two different methods the most reliable values of k_1 are obtained when the reaction is fully zero order, i.e. the enolisation is rate limiting. This occurs with high catalyst concentration and high acidity. Table 3.6 shows the enolisation rate constant for methylmalonic acid reaction to be reasonably constant at a variety of high acid concentrations.

TABLE 3.6: Nitrosation of methylmalonic acid by nitrosyl bromide, at high acidity.

$[\text{MMA}] = 0.30\text{M}$, $[\text{Br}^-] = 0.50\text{M}$, $[\text{HNO}_2]_{\text{T}} = 5.0 \times 10^{-3}\text{M}$, $T = 298\text{K}$.

$[\text{HClO}_4] / \text{M}$	$10^4 k_1 / \text{s}^{-1}$
1.33	2.14
1.36	1.84
1.46	1.91
1.69	2.13
1.96	2.14

Unlike methylmalonic acid, malonic acid nitrosation by nitrosyl bromide even at high acidity cannot be made to give fully zero order behaviour. The results obtained experimentally appeared to be of mixed zero and first order throughout and so the k_1 values in table 3.7 are all calculated from the intercept of plots of $(\text{rate})^{-1}$ against $(a - x)^{-1}$.

TABLE 3.7: Bromide ion catalysed nitrosation of malonic acid.

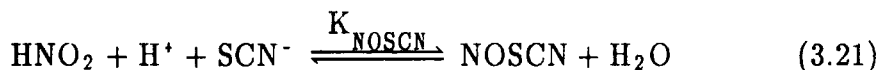
$$[\text{HNO}_2]_{\text{T}} = 5.0 \times 10^{-3} \text{M}, T = 298\text{K}.$$

$[\text{HClO}_4] = 6.46 \times 10^{-2} \text{M}, [\text{MA}] = 0.30 \text{M}$	
$[\text{Br}^-] / \text{M}$	$10^4 k_1 / \text{s}^{-1}$
0.15	—
0.20	0.87
0.30	1.09
0.50	2.58
$[\text{HClO}_4] = 1.33 \text{M}, [\text{MA}] = 0.30 \text{M}$	
$[\text{Br}^-] / \text{M}$	$10^4 k_1 / \text{s}^{-1}$
0.15	1.12
0.20	2.50
0.30	2.84
0.50	4.43
$[\text{HClO}_4] = 1.63 \text{M}, [\text{MA}] = 0.30 \text{M}$	
$[\text{Br}^-] / \text{M}$	$10^4 k_1 / \text{s}^{-1}$
0.30	3.45
0.50	3.84

The values for k_1 of malonic acid appear to be more varied. Analysis could not yield exclusively zero order reaction profiles. That meant calculations could only be performed by means of the double reciprocal plots, (equation 3.20). The very nature of these plots gives a very large inherent error in any values obtained. As rate limiting enolisation could not be obtained another nitrosating species, nitrosyl thiocyanate, was used. Nitrosyl thiocyanate is a less reactive nitrosating species than nitrosyl bromide but it is present in much larger concentrations which accounts for the increase in the rate of the reaction.

The use of thiocyanate ion as the nucleophilic catalyst was unsatisfactory.

This can be explained because of the magnitude of $K_{\text{NOSCN}} = 30^{24}$. If we consider the equilibrium for nitrosyl thiocyanate formation, (equation 3.21), then we obtain an expression for K_{NOSCN} , (equation 3.22).



$$K_{\text{NOSCN}} = \frac{[\text{NOSCN}]}{[\text{HNO}_2]_{\text{T}} [\text{H}^+] [\text{SCN}^-]} \quad (3.22)$$

In a typical reaction $[\text{H}^+] \approx 1.0 \text{ M}$, $[\text{SCN}^-] = 0.2 \text{ M}$. So the value for $\frac{[\text{NOSCN}]}{[\text{HNO}_2]_{\text{T}}}$ is 6. A substantial fraction of nitrous acid is converted into nitrosyl thiocyanate at these relatively high thiocyanate ion and high acid concentrations. Nitrosyl thiocyanate (which is pink in colour at low concentrations) is quite unstable and decomposes in a complex kinetic reaction. This decomposition affected the absorbance time plots such that the kinetic studies did not exclusively follow the nitrosation of the substrates. Clear results for the nitrosation of malonic acid and methylmalonic acid by nitrosyl thiocyanate could not be obtained.

The use of thiourea as the catalyst gave no workable results, for the nitrosation of malonic acid and methylmalonic acid. A similar explanation as to the impracticalities found with nitrosyl thiocyanate is the reason for the inability to use thiourea as a nucleophilic catalyst in the nitrosation reactions.

3.3 Discussion

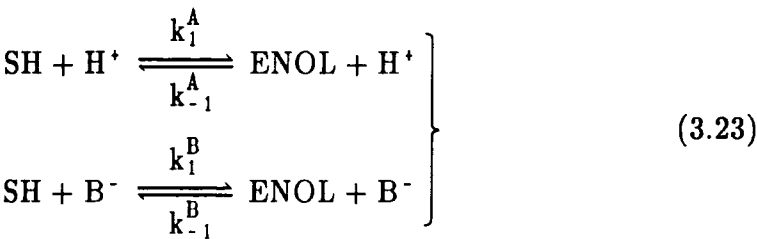
The reactions of malonic acid and methylmalonic acid proceeding via their enol tautomer in nitrosation at high acidities is not an unrealistic idea. Bafna and coworkers^{7,25,26,27}, as long ago as the 1950's, discussed the possibility of iodination via the enol. More recently values for the enolisation rate constant have been cited^{8,9}, in the halogenation of malonic acid and methylmalonic acid. These values are compared with those determined in this chapter, (table 3.8).

TABLE 3.8: Values of the enolisation rate constant, k_1 , for malonic acid and methylmalonic acid.

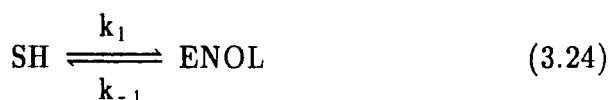
Reaction studied	k_1 / s^{-1}
¹ H nmr of isotope exchange	MA, 1.066×10^{-3} (Ref.28) MMA, 5.7×10^{-5} (Ref.28,29)
Bromination	MA, 2.4×10^{-3} (Ref.8)
Nitrosation	MA, 4.75×10^{-3} to 8.7×10^{-5} ^a MMA, $2.13 (\pm 0.38) \times 10^{-4}$ ^b

a – this work, range of values obtained
b – this work, mean of values obtained

These values are in broad reasonable agreement, although the values for k_1 of malonic acid in this work cover a wide range. The rate constant k_1 is the overall enolisation rate constant, without specifying acid or base catalysis, (equation 3.23).



Now the overall enolisation rate constant, k_1 , can be seen in equation 3.24.



We know that

$$K_E = \frac{[\text{ENOL}]_T}{[\text{SH}]_T},$$

where K_E is the keto-enol equilibrium constant, $[\text{ENOL}]_T$ is the total enol concentration and $[\text{SH}]_T$ is the total concentration of malonic acid or methylmalonic acid. Strictly $K_E = [\text{ENOL}]/[\text{SH}]_{\text{Free}}$ but for very small K_E values $[\text{SH}]_{\text{Free}} \simeq [\text{SH}]_T$. We also know that $[\text{ENOL}]_T = [\text{ENOL}]_A + [\text{ENOL}]_B$, where $[\text{ENOL}]_A$ and $[\text{ENOL}]_B$ are the concentrations of enol from the acid (A) and base (B) catalysed processes respectively, although it is possible that there are other routes to the intermediate enol formation. These other pathways will be discussed in chapter 4. Classically³⁰ enolisation is thought of as an acid and base catalysed process. We now have another expression for K_E , (equation 3.25).

$$K_E = \frac{[\text{ENOL}]_A + [\text{ENOL}]_B}{[\text{SH}]_T} \quad (3.25)$$

If we consider the rate equation for acid catalysed enolisation, (equation 3.26), within the overall picture of nitrosation of malonic acid and methylmalonic acid, scheme 3.3.

$$\begin{aligned} \frac{d([\text{ENOL}]_A)}{dt} &= k_1^A [\text{SH}][\text{H}^+] - (k_{-1}^A [\text{ENOL}]_A [\text{H}^+] + k_2 [\text{ENOL}]_A [\text{XNO}]) \quad (3.26) \\ &= 0, \text{ by the Steady State Hypothesis.} \end{aligned}$$

We obtain an expression for $[\text{ENOL}]_A$, (equation 3.27), and similarly for the base catalysed enolisation, (equation 3.28).

$$[\text{ENOL}]_A = \frac{k_1^A [\text{SH}] [\text{H}^+]}{k_{-1}^A [\text{H}^+] + k_2 [\text{XNO}]} \quad (3.27)$$

$$[\text{ENOL}]_B = \frac{k_1^B [\text{SH}] [\text{B}^-]}{k_{-1}^B [\text{B}^-] + k_2 [\text{XNO}]} \quad (3.28)$$

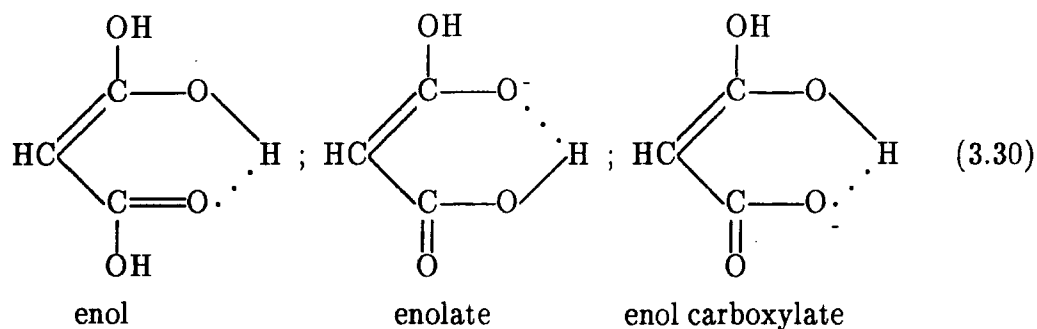
When considering the overall rate equation, (equation 3.16), there is simplification, when the enolisation is rate limiting, to equation 3.18, again shown below.

$$\text{Rate} = k_1 [\text{SH}] \quad (3.18)$$

However using the substitution of equations 3.27 and 3.28 in equation 3.16, there is a new simplified rate equation for rate limiting enolisation, (equation 3.29).

$$\text{Rate} = (k_1^A [\text{H}^+] + k_1^B [\text{B}^-]) [\text{SH}] \quad (3.29)$$

Hence k_1 represents both acid and base catalysed (and possibly a linear combination of other) mechanisms. It has been proposed⁹ that the base involved is the carboxylate monoanion of the substrates, malonic acid and methylmalonic acid. Not only that but also that at higher pH the reactive intermediate is in fact the enolate, which is a resonance structure of the carbanion. The enol carboxylate has been proposed as another reaction intermediate at higher pH values. It is interesting to note that all of these possible intermediates can form an intramolecular hydrogen bond, stabilising the enol, enolate and enol carboxylate structures, (equation 3.30).



The values of the overall enolisation rate constant, k_1 , have been shown to be independent of the acid concentration, for nitrosation of methylmalonic acid by nitrosyl bromide, (table 3.6). This independence of k_1 upon acid concentration lends weight to the possibility of an intramolecular acid catalysed route to enol formation. The possibility of an intramolecular route is reasonable as it has been seen previously for some enolisation reactions³¹.

Another possibility is the loss of a methylene proton, from the unprotonated substrate as an initial step. This has been shown to occur in the bromination³² and nitrosation²³ of 1,3-dichloroacetone. Here the enolisation rate constant is independent of the acid concentration and it is believed that the proton loss from the unprotonated ketone is due to the increased acidity of the proton on account of the presence of the chlorine atoms in the molecule, which make the proton sufficiently acidic to leave the molecule.

It is possible therefore that the two, electron withdrawing, carboxylic acid groups of malonic acid and methylmalonic acid have made the methylene protons sufficiently acidic to be lost from the acid. This would then display an independence of the enolisation rate constant upon acid concentration. It is not possible from this work to differentiate between the intramolecular acid catalysis or this proton loss pathway.

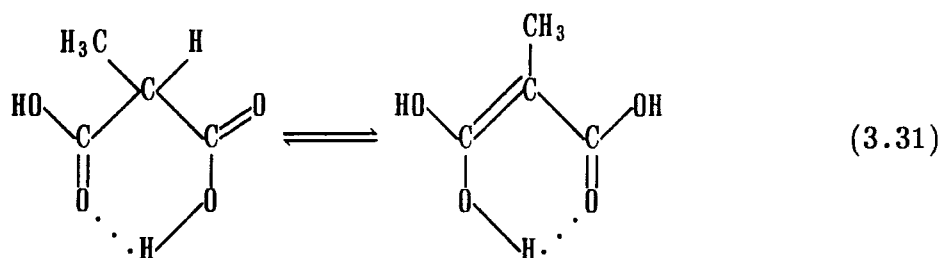
It is clear, however, that working with mixed zero and first order reaction plots makes further analysis difficult. Ideally working at either extreme (totally zero or first order) would be the most beneficial course of action.

Some ideas of different reaction intermediates for the nitrosation of malonic acid and methylmalonic acid have been mentioned and the dominance of these

intermediates is affected by the variation of the acid concentration of the reaction solution. Clearly if the reaction conditions can be adjusted to give rate limiting enolisation more information can be accrued to validate proposed mechanisms.

Nitrosation does not appear to be a sufficiently effective process (with the nitrosating species used) to effect rate limiting enolisation with malonic acid. However, it is almost reached for methylmalonic acid. Halogenation was considered to be a more profitable line of investigation as it is a more effective electrophilic process than nitrosation and some work had already been performed with these substrates in this field; this work is reported in chapters 4, 5 and 6.

We can however discuss the effect of the difference in structure of malonic acid and methylmalonic acid upon the size of the enolisation rate constant. The values in table 3.8 show that k_1 (or k_e) for malonic acid to be of the order of 10 greater than k_e for methylmalonic acid. This could be due to the relative energies of the transition states of each intermediate, leading to enol formation.. The energy of the transition state for malonic acid reaction being lower than that for the methylmalonic acid transition state, hence a larger enolisation rate constant is obtained for malonic acid. Both malonic acid and methyl-malonic acid enol tautomers can be formed by an intramolecular acid catalysed process involving a six membered intermediate ring structures. The methyl group of methylmalonic acid makes the formation of the intramolecular hydrogen bonded ring less favourable by altering the configuration of the methylmalonic acid molecule which increases the energy of this transition state with respect to the malonic acid transition state, which in turn can be seen experimentally by the decrease in magnitude of k_e between malonic acid and methylmalonic acid. The intramolecular acid catalysis can be seen in equation 3.31.



Effects upon k_e and K_E , the keto-enol equilibrium constant, have also been seen when other alkyl groups have been introduced at the α position of β -dicarbonyl compounds³³. The keto-enol equilibrium constant is affected more clearly by these structural effects than the enolisation rate constant. The stability of keto and enol forms is affected by the changes in structure. A further investigation of the effect of different α -substituents is also reported in chapters 5 and 6, by considering the halogenation of ethyl ethylmalonic acid (EtMA) and phenylmalonic acid (PhMA) as well as malonic acid and methylmalonic acid.

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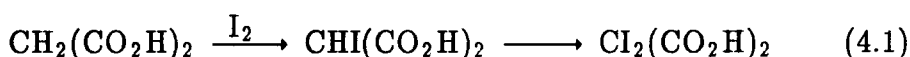
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CHAPTER 4

IODINATION OF MALONIC ACID

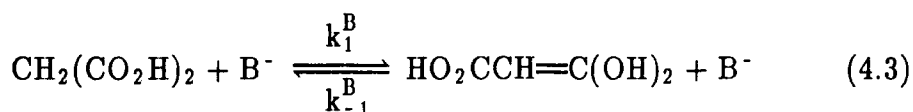
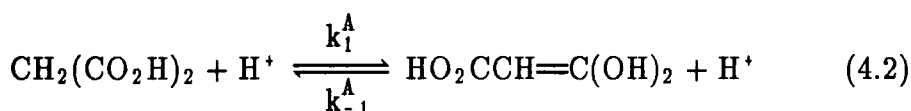
4.1 Introduction

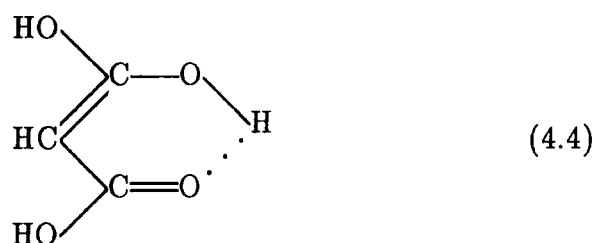
In 1912 Meyer¹ performed a kinetic study of the bromination of malonic acid (MA) and he concluded the reaction involved rate limiting enolisation. The iodination of malonic acid was first discussed in 1938². Synthetically the iodination of malonic acid is known to yield both the mono- and di-iodomalonic acids^{2,3,4}, (equation 4.1).



The second iodination step can be prevented by carrying out the reaction in acidic solution, when the moniodomalonic acid is the major reaction product. This is an important factor for kinetic studies if interference by the second iodination step is to be avoided. It has been shown⁴ that iodination of malonic acid can yield iodoform as a reaction product, under certain conditions, by decarboxylation during the first or second iodination steps.

Several Indian authors^{5 - 9} have studied the kinetics of the iodination of malonic acid, with conflicting results. Much more recently the iodine-malonic acid reaction was again studied¹⁰. The mechanism of the reaction is complex due to a variety of equilibria formed in solution. Reaction via the enol can be both acid and base catalysed, (equation 4.2 and 4.3). It is likely that the enol tautomer is stabilised by the formation of an intramolecular hydrogen bonded six membered ring, (equation 4.4).





This stabilised intramolecular hydrogen bonded ring structure is known for other β -dicarbonyl compounds¹¹. Intramolecular hydrogen bonding is also known for malonic acid¹² and its monoanion¹³ in aqueous solution, indicating that this intramolecular hydrogen bonded structure may be possible for the carboxylic acid enol.

The base, in mildly acidic solution, involved in the base catalysed enolisation, is most probably the malonic acid monocarboxylate. At very high acid concentrations the quantity of this base present would be low, and at the same time the acid catalysed pathway would be enhanced. It is possible for the acid catalysed enolisation to become predominant with the base catalysed pathway negligible. It is also possible that an intramolecular acid catalysed process is involved in enol formation (mentioned previously in section 3.3). This route would be independent of the variation in acid concentration.

Another consideration is the iodination of the carboxylate, which can also enolise to give the enol carboxylate species. This is another reaction which is dependent upon solution acidity, as is the proton loss from the enol to give the enolate or carbanion (both are resonance structures). This is another possible reaction intermediate to be considered.

In solution the nature of the iodinating species must be taken into consideration¹⁴. Iodine alone in solution will predominate because the triiodide, (equation 4.5), would only be present in very small quantities, as there is very little iodide present.



However the addition of excess iodide would make the less effective electrophile, the triiodide ion, I_3^- .

The work in this chapter was undertaken to try to obtain values of k_1 , the enolisation rate constant, to tie in with the proposed involvement of the enol tautomer in the nitrosation of malonic acid, from chapter 3, and to try and identify by which routes the reactive enol intermediate is formed.

4.2 Results

Iodination of malonic acid was performed in aqueous acidic solution, by iodine alone, at the maximum concentration solubility would allow, and also with added sodium iodide. The reactions were followed at 459 nm for reaction with molecular iodine, where the molar extinction coefficient, ϵ , is $697 \text{ l mol}^{-1} \text{ cm}^{-1}$, and at 353 nm for reaction with triiodide ion, the extinction coefficient, ϵ , is $2.6 \times 10^4 \text{ l mol}^{-1} \text{ cm}^{-1}$, due to the triiodide (as ϵ for iodine at 353 nm is only $18 \text{ l mol}^{-1} \text{ cm}^{-1}$). The disappearance of absorbance due to the halogenating species in both cases was monitored.

The concentration of iodine was varied for fixed malonic acid concentration at two different acidities, table 4.1.

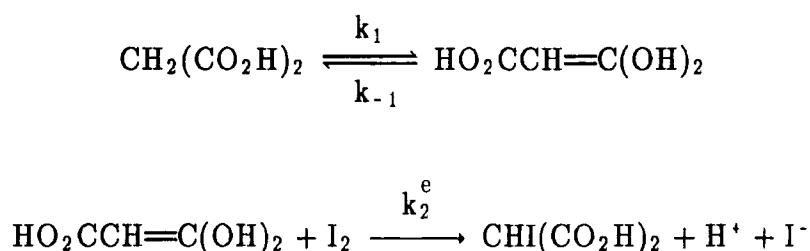
TABLE 4.1: Iodination of malonic acid by iodine.

$[\text{MA}] = 0.10\text{M}$, $T = 298\text{K}$.

$10^4 [\text{I}_2] / \text{M}$	$10^4 k_{\text{obs}} / \text{mol l}^{-1} \text{s}^{-1}, \text{in H}_2\text{O}$	$10^4 k_{\text{obs}} / \text{mol l}^{-1} \text{s}^{-1}$ with $\text{HClO}_4, [\text{HClO}_4] = 0.5\text{M}$
6.01	3.44	2.46
4.00	2.75	2.34
2.50	2.44	1.99
1.00	1.54	1.14

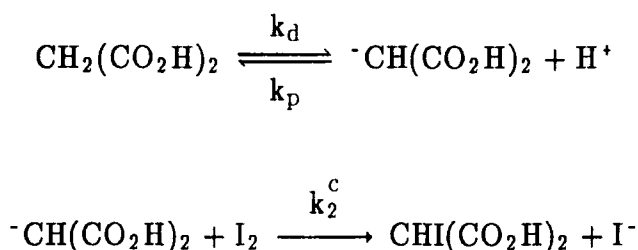
All of the above observed rate constants are zero order constants, taken from the slopes of linear voltage time plots (voltage from stopped-flow spectrophotometry is equivalent to absorbance used in conventional u.v./visible spectrophotometry). These plots are linear in nature suggesting the independence of the reaction upon iodine concentration. However upon changing the initial concentration of iodine, k_{obs} also changes to some extent. Consideration of the proposed schemes for this reaction can explain this deviation.

Scheme 4.1 shows the mechanism for reaction via the enol leading to the rate equation, (equation 4.6), where k_1 is the enolisation rate constant, k_2^e is the second order rate constant for the iodine attack upon the enol, k_{-1} is the overall ketonisation rate constant. Similarly reaction via the carbanion (enolate) is considered in scheme 4.2 leading to another rate equation, (equation 4.7), where k_d is the rate constant for the loss of a proton from the methylene of malonic acid, k_p is the rate constant for the protonation of this site and k_2^c is the second order rate constant for the attack of the iodine upon the carbanion.



Scheme 4.1

$$\text{Rate} = \frac{k_1 k_2^e [\text{MA}][\text{I}_2]}{k_{-1} + k_2^e [\text{I}_2]} \quad (4.6)$$



Scheme 4.2

$$\text{Rate} = \frac{k_d k_2^c [\text{MA}][\text{I}_2]}{k_p [\text{H}^+] + k_2^c [\text{I}_2]} \quad (4.7)$$

For zero order reaction conditions we are considering both rate equations,

(equations 4.6 and 4.7), at one extreme limiting form, i.e. when $k_2[I_2] \gg k_{-1}$ (or $k_p[H^+]$) and the overall rate equations can simplify to the forms shown in equations 4.8 and 4.9 for enol and carbanion intermediate involvement respectively.

$$\text{Rate} = k_1[MA] \quad (4.8)$$

$$\text{Rate} = k_d[MA] \quad (4.9)$$

For a zero order reaction $\text{Rate} = k_{\text{obs}}$, so the values in table 4.1 should be independent of $[I_2]$. The small change with changing iodine concentration may arise because the inequality $k_2[I_2] \gg k_{-1}$ (or $k_p[H^+]$) may not be completely valid. As the iodine concentration is decreased a first order component of the reaction increases, effectively decreasing the slope of the linear plot. Also as the acid concentration is increased the inequality is no longer valid. This is obvious for reaction via the carbanion where the inequality is $k_2^c[I_2] \gg k_p[H^+]$. For reaction via the enol the inequality is $k_2^e[I_2] \gg k_{-1}$, but k_{-1} is the ketonisation rate constant which can contain both acid and base catalysed components, similar to those of k_1 as described in section 3.3. Hence with increased acid concentration the value of k_{-1} will also increase.

The following work was performed with the iodine concentration at the maximum solubility would allow¹⁷, in an attempt to obtain truly zero order reaction kinetics. The concentration of the acid was varied as was the substrate concentration, tables 4.2 and 4.3.

TABLE 4.2: Iodination of malonic acid by iodine in different concentration acidic solutions.

$[MA] = 0.10M$, $[I_2] = 5.24 \times 10^{-4}M$ for $[HClO_4] = 0 - 0.100M$,
and $[I_2] = 6.01 \times 10^{-4}M$ for $[HClO_4] = 0.100 - 2.000M$.

$[HClO_4] / M$	$10^4 k_{obs} / mol\ l^{-1} s^{-1}$
0	2.73 / 2.54
0.010	2.75
0.020	2.63
0.025	2.79
0.037	2.69
0.050	2.70 / 2.49
0.075	2.27
0.100	2.17 / 2.54
0.200	2.74
0.500	2.60
1.000	1.91
2.000	1.40

GRAPH 4.1: Iodination of malonic acid by molecular iodine.

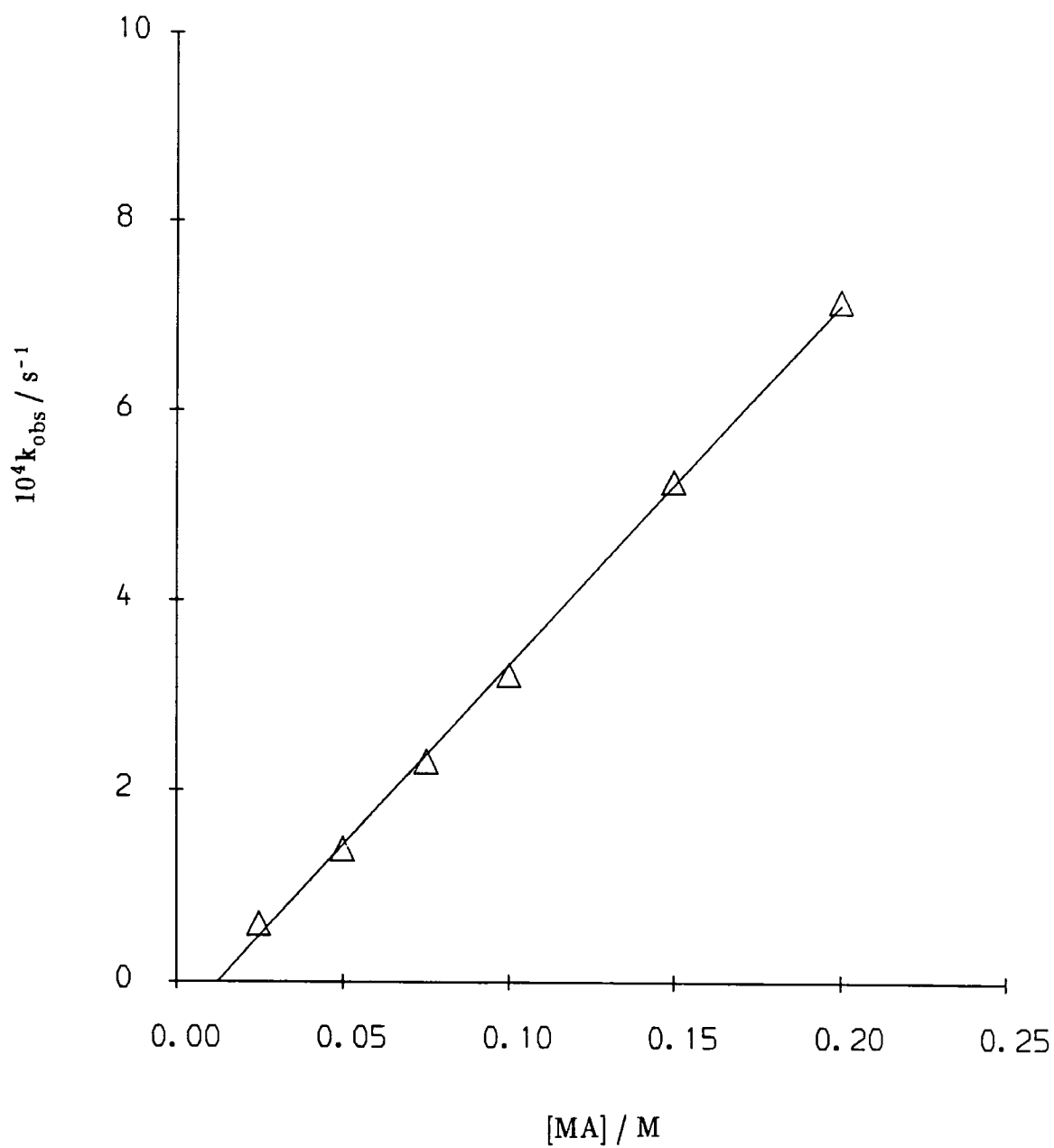


TABLE 4.3: Iodination of malonic acid by iodine, with variation of malonic acid concentration.

$$[I_2] = 5 \cdot 24 \times 10^{-4} \text{ M}, T = 298 \text{ K}.$$

$[MA] / \text{M}$	$10^4 k_{\text{obs}} / \text{mol l}^{-1} \text{s}^{-1}$
0.025	0.61
0.050	1.39
0.075	2.31
0.100	3.22
0.150	5.27
0.200	7.17

These results show clearly a first order dependence upon $[MA]$, represented by the straight line obtained in the plot of k_{obs} versus $[MA]$, (graph 4.1), as expected, and an independence of $[H^+]$ up to approximately 0.075M. These results cannot be used to draw the distinction between the enol or carbanion mechanisms. The reduction in zero order observed rate constants, at high acid concentration, can be explained in both cases. It is necessary therefore to look at the other limiting condition, where first order reaction kinetics is to be expected. At this extreme the inequalities in the denominators of equations 4.6 and 4.7 are $k_{-1} \gg k_2^e[I_2]$ and $k_p[H^+] \gg k_2^c[I_2]$ respectively. The resulting rate equations are equation 4.10 for enol intermediate and equation 4.11 for the carbanion.

$$\text{Rate} = \frac{k_1}{k_{-1}} k_2^e [MA][I_2] \quad (4.10)$$

$$\text{Rate} = \frac{k_d}{k_p} \frac{k_2^c [MA][I_2]}{[H^+]} \quad (4.11)$$

The enol rate equation has no direct dependence upon acid concentration but the carbanion case has a reciprocal relationship with acid concentration. Hence if the first order reaction conditions can be achieved the reaction intermediate can be identified.

The minimum iodine concentration that could be used, within the constraints of the stopped-flow spectrophotometer, was $1.0 \times 10^{-4} \text{M}$. At higher acidities the curves are almost totally first order but as the pH increases so does the zero order character which effectively increases the first order k_{obs} . Table 4.4 does in fact display this effect. Overall however it can be said that the first order observed rate constant is reasonably independent of acid concentration.

TABLE 4.4: Iodination of malonic acid at low iodine concentrations.

$[\text{MA}] = 0.05 \text{M}$, $[\text{I}_2] = 1.0 \times 10^{-4} \text{M}$, $T = 298 \text{K}$.

$[\text{HClO}_4] / \text{M}$	$k_{\text{obs}} / \text{s}^{-1}$
0	2.10
0.10	1.48
0.25	1.42
0.50	1.44
0.75	1.35

It was felt that the reduction in iodine concentration was not sufficient to gain totally first order curves hence the nature of the iodinating species was altered.

Sodium iodide was added into solutions. Now the effective halogenating species was the triiodide, I_3^- , (equation 4.12), a weaker electrophile than molecular iodine.



The overall rate equations, (equation 4.6 and 4.7), will change to account for this change in iodinating species, (equation 4.13 and 4.14),

$$\text{Rate} = \frac{k_1 k_2^e K_{I_3^-} [MA] [I_2] [I^-]}{k_{-1} + k_2^e K_{I_3^-} [I_2] [I^-]} \quad (4.13)$$

$$\text{Rate} = \frac{k_d k_2^c K_{I_3^-} [MA] [I_2] [I^-]}{k_p [H^+] + k_2^c K_{I_3^-} [I_2] [I^-]} \quad (4.14)$$

using the substitution $K_{I_3^-} = [I_3^-] / [I_2][I^-]$, and where $K_{I_3^-}$ has been found¹⁷ to be 714 l mol^{-1} .

Iodination of malonic acid by triiodide was performed firstly by variation of acid concentration and then at a fixed acid concentration but varying the iodine concentration. This work is represented in tables 4.5 and 4.6.

If the reaction intermediate was the carbanion one would expect a decrease in k_{obs} , (equation 4.11), the first order observed rate constant, this is clearly not the case, table 4.5. Reaction via the enol intermediate, (equation 4.10), predicts no change in k_{obs} with increased acid concentration. This is what is seen in table 4.5 at least up to 0.20 M perchloric acid. At very high acid concentration a substantial increase in k_{obs} is seen. This is due to the oxidation of the excess iodide ions present. At these high acid concentrations the change in voltage observed is greatly affected by the oxidation, causing an increase in the observed first order rate constant value. This effect was further studied by carrying out two identical iodinations with the same conditions except that in one (case a) the iodine/iodide solution only comes into contact with the acidic solution upon mixing in the stopped-flow and in the other (case b) the iodine/iodide solution is made up at the appropriate acidity. In the second case the oxidation had longer to proceed and should give a larger k_{obs} value. This is the what is seen in table 4.5 for the highest acid concentration values.

TABLE 4.5: Variation of the acid concentration in the iodination of malonic acid by triiodide ion.

$$[\text{MA}] = 0.10\text{M}, [\text{I}_2] = 2.5 \times 10^{-5}\text{M}, [\text{NaI}] = 5.0 \times 10^{-3}\text{M}, T = 298\text{K}$$

$[\text{HClO}_4] / \text{M}$	$k_{\text{obs}} / \text{s}^{-1}$	
	a	b
0	1.06	—
0.02	0.98	—
0.05	0.90	—
0.075	0.94	—
0.10	0.93	0.97
0.15	1.04	—
0.20	1.10	1.12
0.50	1.60	1.64
1.00	3.16	2.75
2.00	7.75	11.55

a – HClO_4 only present in one stopped-flow solution.

b – HClO_4 present in both stopped-flow solutions.

TABLE 4.6: Iodination of malonic acid by triiodide ion at a fixed acid concentration.

$$[\text{MA}] = 0.30\text{M}, [\text{NaI}] = 5.0 \times 10^{-3}\text{M}, T = 298\text{K}.$$

$10^5 [\text{I}_2] / \text{M}$	$k_{\text{obs}} / \text{s}^{-1}$
5.00	1.05
3.75	1.02
2.50	1.13
1.25	1.20

Table 4.6 shows that at lower pH the observed rate constant is independent of iodine concentration. Equation 4.15 represents the rate equation for first order reaction plots for reaction via the enol. Substitution, in equation 4.15, of the expression $\text{rate} = k_{\text{obs}}[\text{I}_2]$, (equation 4.16), shows that k_{obs} should be independent of iodine concentration.

$$\text{Rate} = \frac{k_1}{k_{-1}} k_2^e K_{\text{I}_3^-} [\text{MA}][\text{I}_2][\text{I}^-] \quad (4.15)$$

$$k_{\text{obs}} = \frac{k_1}{k_{-1}} k_2^e K_{\text{I}_3^-} [\text{MA}][\text{I}^-] \quad (4.16)$$

4.3 Discussion

Within the acid concentration range used the iodination of malonic acid occurs via the enol. At high iodine concentration the reaction rate is independent of the iodine concentration and the rate limiting step is the enolisation. At lower iodine concentrations or in the presence of added iodide ions (where the effective iodinating species is the triiodide ion) the reaction of the enol is rate limiting. Reaction via the carbanion (or enolate) can not be totally ruled out at higher pH values and may even become dominant, as is the case for the nitrosation of diethyl malonate and ethyl cyanoacetate (chapter 2) and the halogenation of diethyl malonate^{18,19,20}.

Simplification of the overall rate equation for the reaction via the enol, equation 4.6, and below, for the zero order reaction limit

$$\text{Rate} = \frac{k_1 k_2^e [\text{MA}] [\text{I}_2]}{k_{-1} + k_2^e [\text{I}_2]}$$

and substitution of $\text{rate} = k_{\text{obs}}$ gives equation 4.17.

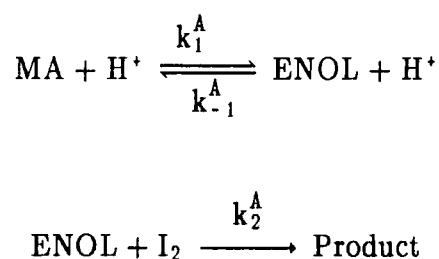
$$\text{Rate} = k_1 [\text{MA}] \quad (4.17)$$

The enolisation rate constant, k_1 , can be obtained directly from equation 4.17. From table 4.1, from reactions at highest iodine concentration and lowest acid concentration we get the closest to fully zero order behaviour. Hence the mean k_{obs} for the iodination of malonic acid in water gave $k_1 = 3.44 (\pm 0.06) \times 10^{-3} \text{ s}^{-1}$. The data in table 4.2 when plotted as k_{obs} versus $[\text{MA}]$, (graph 4.1), gave a straight line, indicative of a first order reaction dependence upon the concentration of malonic acid. Also the slope of this plot gives the value of k_1 to be $3.80 (\pm 0.01) \times 10^{-3} \text{ s}^{-1}$. At low acidity, $[\text{HClO}_4] < 0.075\text{M}$, the mean of the values of k_{obs} in table 4.3 give a mean k_1 value of $2.69 (\pm 0.08) \times 10^{-3} \text{ s}^{-1}$. These

values are in reasonable agreement with each other and also with the enolisation rate constants found by Leopold and Haim¹⁰, in their malonic acid iodination reactions, and also those values observed by Hansen and Ruoff²¹, in their isotope exchange experiments ($k_1 = 1.066 (\pm 0.003) \times 10^{-3} \text{ s}^{-1}$).

The enolisation rate constant, k_1 , should be considered as comprising several parts, each for different enolisation pathways:

(i) Acid catalysed enol formation. The stepped process is in scheme 4.3 and equation 4.18 shows the rate equation derived from that.



Scheme 4.3

$$\text{Rate} = \frac{k_1^A k_2^A [\text{MA}] [\text{H}^+] [\text{I}_2]}{k_{-1}^A [\text{H}^+] + k_2^A [\text{I}_2]} \quad (4.18)$$

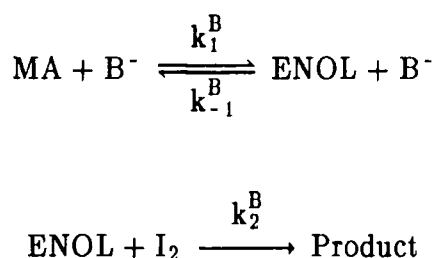
Equation 4.18 can be simplified to give two limiting cases, when enolisation is rate limiting, $k_2^A [\text{I}_2] \gg k_{-1}^A [\text{H}^+]$ (zero order reaction kinetics are obtained, (equation 4.19)), and when iodination is rate limiting, $k_{-1}^A [\text{H}^+] \gg k_2^A [\text{I}_2]$ (first order reaction kinetics are obtained, (equation 4.20)).

$$\text{Rate} = k_1^A [\text{MA}] [\text{H}^+] \quad (4.19)$$

$$\text{Rate} = K_E k_2^A [\text{MA}] [\text{I}_2] \quad (4.20)$$

$$K_E \left[= \frac{k_1^A}{k_{-1}^A} \right] \text{ is the keto-enol equilibrium constant.}$$

(ii) Base catalysed enol formation. The base present in solution is the malonic acid monocarboxylate ion. The reaction scheme, (scheme 4.4), leads to a derived rate equation, (equation 4.21), which can be simplified by the same principles as in the acid catalysed case for rate limiting enolisation, (equation 4.22), and rate limiting iodination, (equation 4.23).



Scheme 4.4

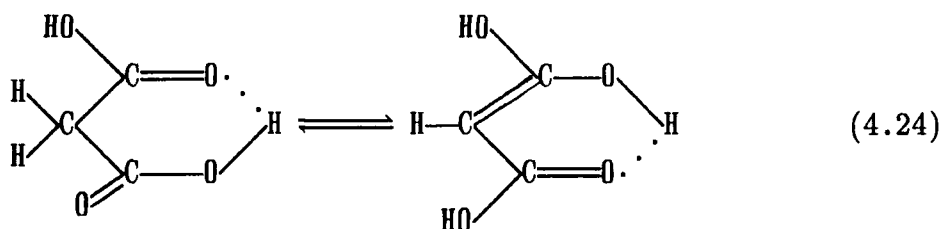
$$\text{Rate} = \frac{k_1^{\text{B}} k_2^{\text{B}} K_a [\text{MA}]^2 [\text{I}_2]}{k_{-1}^{\text{B}} K_a [\text{MA}] + k_2^{\text{B}} [\text{H}^+] [\text{I}_2]} \quad (4.21)$$

$$\text{when } [\text{B}^-] = [\text{MA}^-] = K_a [\text{MA}] / [\text{H}^+].$$

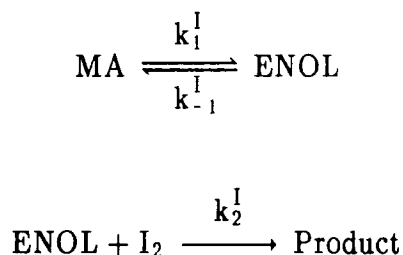
$$\text{Rate} = \frac{K_a k_1^{\text{B}} [\text{MA}]^2}{[\text{H}^+]} \quad (4.22)$$

$$\text{Rate} = K_E k_2^{\text{B}} [\text{MA}] [\text{I}_2] \quad (4.23)$$

(iii) Intramolecular enolisation. This involves a proton transfer within the six membered hydrogen bonded ring and a [1,5] proton shift, (equation 4.24).



The processes of the iodination reaction are shown in scheme 4.5 and the rate equation from this is equation 4.25. As previously this can be separated into two extremes, rate limiting enolisation, (equation 4.26), and rate limiting iodination, (equation 4.27).



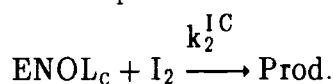
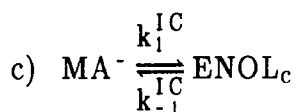
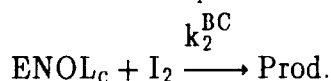
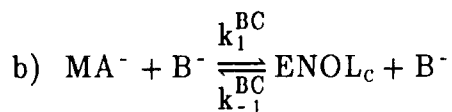
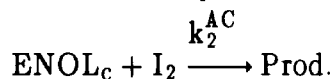
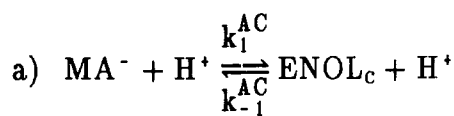
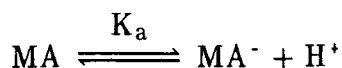
Scheme 4.5

$$\text{Rate} = \frac{k_1^I k_2^I [\text{MA}][\text{I}_2]}{k_{-1}^I + k_2^I [\text{I}_2]} \quad (4.25)$$

$$\text{Rate} = k_1^I [\text{MA}] \quad (4.26)$$

$$\text{Rate} = K_E k_2^I [\text{MA}][\text{I}_2] \quad (4.27)$$

(iv) Enol carboxylate formation. The malonic acid carboxylate need not only be present to serve as a catalyst in the base catalysed pathway, but it too can undergo enolisation by the same three processes as the malonic acid; acid catalysed, base catalysed and intramolecular. Scheme 4.6 shows these possible reaction pathways.



Scheme 4.6

Where ENOL_c is the enol carboxylate intermediate. The acid catalysed pathway (4.6(a)) gives an overall rate equation, (equation 4.28), which can be simplified in the same manner as for the acid catalysed enol formation, (equations 4.29 and 4.30).

$$\text{Rate} = \frac{k_1^{\text{AC}} k_2^{\text{AC}} K_a [\text{MA}] [\text{I}_2]}{k_1^{\text{AC}} [\text{H}^+] + k_2^{\text{AC}} [\text{I}_2]} \quad (4.28)$$

$$\text{Rate} = k_1^{\text{AC}} K_a [\text{MA}] \quad (4.29)$$

$$\text{Rate} = \frac{K_E k_2^{\text{AC}} K_a [\text{MA}] [\text{I}_2]}{[\text{H}^+]} \quad (4.30)$$

Similar treatments can be given to the base catalysed (4.6(b)) and

intramolecular (4.6(c)) enol carboxylate reaction pathways, (equations 4.31 to 4.36).

$$\text{Rate} = \frac{k_1^{\text{BC}} k_2^{\text{BC}} (K_a)^2 [\text{MA}]^2 [\text{I}_2]}{k_1^{\text{BC}} K_a [\text{MA}] [\text{H}^+] + k_2^{\text{BC}} [\text{I}_2] [\text{H}^+]^2} \quad (4.31)$$

For the base catalysed route, simplifying to,

$$\text{Rate} = \frac{k_1^{\text{BC}} (K_a)^2 [\text{MA}]^2}{[\text{H}^+]^2} \quad (4.32)$$

for rate limiting enolisation and

$$\text{Rate} = \frac{K_E K_a k_2^{\text{BC}} [\text{MA}] [\text{I}_2]}{[\text{H}^+]} \quad (4.33)$$

for rate limiting iodination.

$$\text{Rate} = \frac{k_1^{\text{IC}} K_a k_2^{\text{IC}} [\text{MA}] [\text{I}_2]}{[\text{H}^+] (k_1^{\text{IC}} + k_2^{\text{IC}} [\text{I}_2])} \quad (4.34)$$

For the intramolecular route, giving

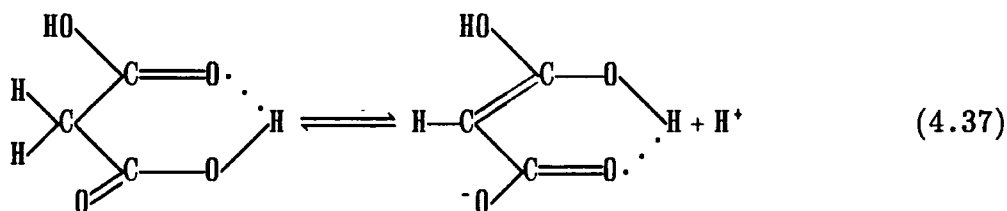
$$\text{Rate} = \frac{k_1^{\text{IC}} K_a [\text{MA}]}{[\text{H}^+]} \quad (4.35)$$

for rate limiting enolisation and

$$\text{Rate} = \frac{K_E k_2^{\text{IC}} K_a [\text{MA}] [\text{I}_2]}{[\text{H}^+]} \quad (4.36)$$

for rate limiting iodination, upon simplification.

(v) Enol carboxylate directly from malonic acid. This is very similar to the situation, (equation 4.24), of malonic acids intramolecular enol formation but with proton loss as well as a [1,5] proton shift, (equation 4.37).



This mechanism would yield a rate equation, (equation 4.38), which would simplify to rate equations for the rate limiting enolisation, (equation 4.39), and iodination, (equation 4.40).

$$\text{Rate} = \frac{k_1^{\text{IC}'} k_2^{\text{IC}'} [\text{MA}] [\text{I}_2]}{k_{-1}^{\text{IC}'} [\text{H}^+] + k_2^{\text{IC}'} [\text{I}_2]} \quad (4.38)$$

$$\text{Rate} = k_1^{\text{IC}'} [\text{MA}] \quad (4.39)$$

$$\text{Rate} = \frac{K_E k_2^{\text{IC}'} [\text{MA}] [\text{I}_2]}{[\text{H}^+]} \quad (4.40)$$

Each different possible reaction pathway has a relationship between the acid concentration and zero or first order observed rate constants. Using the relationships $\text{rate} = k_{\text{obs}}$, for the zero order case, and $\text{rate} = k_{\text{obs}} [\text{I}_2]$, for the first order case, the relationships are shown in table 4.7.

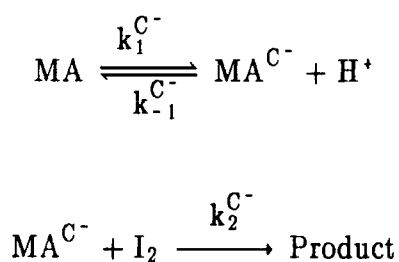
TABLE 4.7: Relationships between k_{obs} and $[\text{H}^+]$ for enol and enol carboxylate formation.

	Rate determining enolisation	Rate determining iodination
1. Acid catalysed enol formation	$k_{\text{obs}} = k_1^{\text{A}} [\text{MA}] [\text{H}^+]$	$k_{\text{obs}} = K_{\text{E}} k_2^{\text{A}} [\text{MA}]$
2. Base catalysed enol formation	$k_{\text{obs}} = \frac{k_1^{\text{B}} K_{\text{a}} [\text{MA}]}{[\text{H}^+]}$	$k_{\text{obs}} = K_{\text{E}} k_2^{\text{B}} [\text{MA}]$
3. Intramolecular enol formation	$k_{\text{obs}} = k_1^{\text{I}} [\text{MA}]$	$k_{\text{obs}} = K_{\text{E}} k_2^{\text{I}} [\text{MA}]$
4. Acid catalysed enol _c formation	$k_{\text{obs}} = k_1^{\text{AC}} K_{\text{a}} [\text{MA}]$	$k_{\text{obs}} = \frac{K_{\text{E}} K_{\text{a}} k_2^{\text{AC}} [\text{MA}]}{[\text{H}^+]}$
5. Base catalysed enol _c formation	$k_{\text{obs}} = \frac{k_1^{\text{BC}} (K_{\text{a}})^2 [\text{MA}]^2}{[\text{H}^+]^2}$	$k_{\text{obs}} = \frac{K_{\text{E}} K_{\text{a}} k_2^{\text{BC}} [\text{MA}]}{[\text{H}^+]}$
6. Intramolecular enol _c formation	$k_{\text{obs}} = \frac{k_1^{\text{IC}} K_{\text{a}} [\text{MA}]}{[\text{H}^+]}$	$k_{\text{obs}} = \frac{K_{\text{E}} K_{\text{a}} k_2^{\text{IC}} [\text{MA}]}{[\text{H}^+]}$
7. Enol _c formed directly from MA	$k_{\text{obs}} = k_1^{\text{IC}'} [\text{MA}]$	$k_{\text{obs}} = \frac{K_{\text{E}} k_2^{\text{IC}'} [\text{MA}]}{[\text{H}^+]}$

Graph 4.1 shows the first order relationship between malonic acid concentration and the measured zero order observed rate constant. Using table 4.7, only (5), the base catalysed enol carboxylate formation pathway does not fit this linear relationship, as this mechanism requires a second order substrate dependence, $k_{\text{obs}} \propto [\text{MA}]^2$. Therefore this pathway can be ruled out under these reaction conditions. Both the limiting zero and first order measured rate constants are independent of acid concentration, (tables 4.3, 4.4 and 4.5). At very high acid concentration the dependences upon acid concentration have already been explained as the loss of the zero order limiting conditions and the oxidation of iodide for the zero and first order cases respectively.

Of all the possible pathways involving enol or enol carboxylate formation there is only one which is consistent with the experimental results, and that is the mechanism involving intramolecular enol formation. Under the experimental conditions used the mechanism that dominates, therefore, involves an intramolecular acid catalysed mechanism of enol formation followed by iodination of the enol, and either step can be made rate limiting. Upon increasing the pH it is possible that other pathways may become more prominent, (chapter 6).

From table 4.7 it is perhaps worthy of note that each pathway has a different combination of k_{obs} – acid concentration dependences except for (4) and (7), the acid catalysed enol carboxylate formation and enol carboxylate formation directly from malonic acid. The mechanism for reaction via the carbanion, (scheme 4.7), and derived rate equation, (equation 4.41), also yield the same k_{obs} – acid concentration dependences as (4) and (7), hence if the dominant mechanism fitted these criteria this study would not be able to distinguish between these three possible reaction pathways.



Scheme 4.7

$$\text{Rate} = \frac{k_1^{\text{C}^-} k_2^{\text{C}^-} [\text{MA}] [\text{I}_2]}{k_1^{\text{C}^-} [\text{H}^+] + k_2^{\text{C}^-} [\text{I}_2]} \quad (4.41)$$

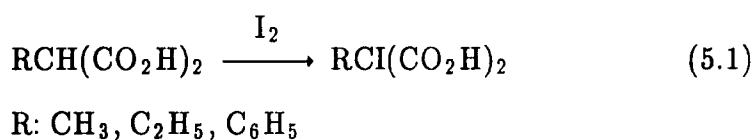
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CHAPTER 5
IODINATION OF METHYLMALONIC ACID,
ETHYLMALONIC ACID AND PHENYLMALONIC ACID

5.1 Introduction

Methylmalonic acid (MMA), ethylmalonic acid (EtMA) and phenylmalonic acid (PhMA) are all known to yield the corresponding iodoacids, (equation 5.1), upon iodination.



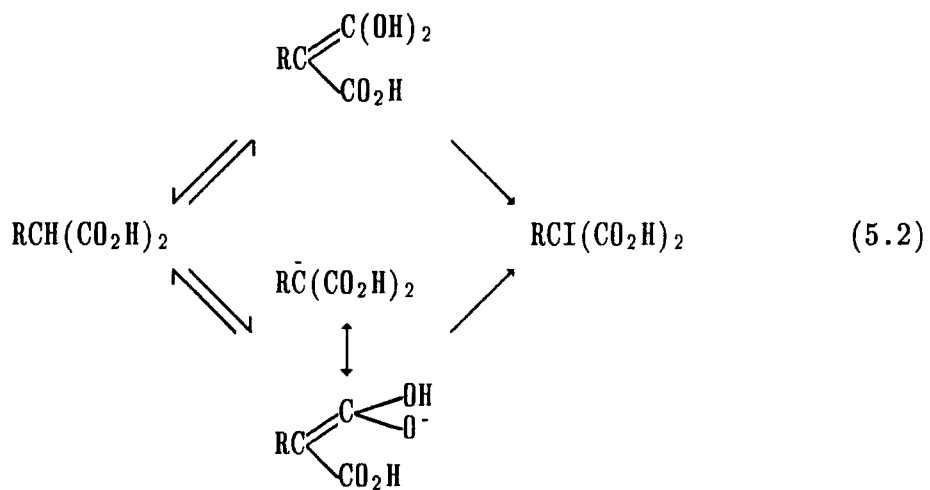
Unlike malonic acid there is no possibility of the diiodo product¹ as the second proton on the methylene group has been replaced by an alkyl or aryl group. In aqueous solution the effects of the different groups is only small as far as the first and second dissociation constants are concerned. The pK₁ and pK₂ values for all four dibasic acids are displayed in table 5.1.

TABLE 5.1: pK₁ and pK₂ values for malonic acid², methylmalonic acid³, ethylmalonic acid⁴ and phenylmalonic acid³.

Acid	pK ₁	pK ₂
MA ²	2.85	5.70
MMA ³	2.96	5.83
EtMA ⁴	2.99	5.83
PhMA ³	2.52	5.59

The purpose of the work discussed in this chapter is to compare the effects of the additional methyl-, ethyl- and phenyl- groups in the dibasic acids, upon their reactivity with respect to iodination. Further it is hoped to identify the reaction intermediate, either as the carbanion (or enolate) or the enol, (equation 5.2). If the

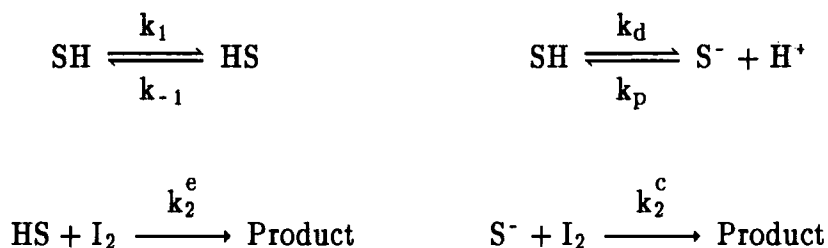
intermediate is the enol then further clarification is needed as to which pathway to its formation is preferred under the reaction conditions used.



5.2 Results

All iodination reactions in this chapter were followed at 459 nm where the molar extinction coefficient, ϵ , of molecular iodine, is $697 \text{ mol l}^{-1} \text{ cm}^{-1}$. The absorbance at this wavelength is due totally to the iodine in solution and the disappearance of voltage with time is due to the reaction of iodine with the substrates. In the case of methylmalonic acid some of the results stated are from the work that was carried out by Peter Ratcliffe, in his final year undergraduate project.

Scheme 5.1 represents the possible step by step process for reaction via either the enol or carbanion.



SH: MMA, EtMA, PhMA. HS: Enol tautomer

Scheme 5.1

Here k_1 and k_{-1} are the enolisation and ketonisation rate constants, k_d and k_p are the rate constants for the deprotonation and protonation of the substituted methylene in each substrate, k_2^e and k_2^c are the rate constants for the attack of the iodine upon the enol or carbanion (enolate) intermediates respectively. These alternative mechanisms give corresponding overall rate equations, (equations 5.3 and 5.6), which can both be simplified to limiting zero and first order cases, (equations 5.4 and 5.5, and equations 5.7 and 5.8).

$$\text{Rate} = \frac{k_1 k_2^e [\text{SH}][\text{I}_2]}{k_{-1} + k_2^e [\text{I}_2]} \quad (5.3)$$

$$\text{Zero order limit:} \quad \text{Rate} = k_1[\text{SH}] \quad (5.4)$$

$$\text{First order limit:} \quad \text{Rate} = K_E k_2^e[\text{SH}][\text{I}_2] \quad (5.5)$$

$$\text{Rate} = \frac{k_d k_2^c[\text{SH}][\text{I}_2]}{k_p[\text{H}^+] + k_2^c[\text{I}_2]} \quad (5.6)$$

$$\text{Zero order limit:} \quad \text{Rate} = k_d[\text{SH}] \quad (5.7)$$

$$\text{First order limit:} \quad \text{Rate} = \frac{K_a k_2^c[\text{SH}][\text{I}_2]}{[\text{H}^+]} \quad (5.8)$$

K_E is the keto-enol equilibrium constant for the substrate and K_a is the dissociation constant for loss of proton, by the substrate, at carbon. Under these conditions, for all four substrates, absorbance time plots are linear confirming the zero order dependence.

The results for the dependence of the zero order rate constant with variation of acid concentration are shown in table 5.2 and 5.3, for methylmalonic acid, ethylmalonic acid and phenylmalonic acid. These show an independence of the zero order rate constant upon the acidity, within experimental error.

TABLE 5.2: Iodination of methylmalonic acid by molecular iodine.

1. This work

2. From final year project of P.Ratcliffe

$[\text{HClO}_4]/\text{M}$	1. $[\text{MMA}] = 0.10\text{M}$, $[\text{I}_2] = 5.24 \times 10^{-4}\text{M}$ $10^5 k_{\text{obs}}/\text{mol l}^{-1}\text{s}^{-1}$	2. $[\text{MMA}] = 5.25 \times 10^{-3}\text{M}$, $[\text{I}_2] = 6.01 \times 10^{-4}\text{M}$ $10^7 k_{\text{obs}}/\text{mol l}^{-1}\text{s}^{-1}$
0	2.37	—
0.010	2.14	—
0.025	2.02	—
0.050	1.72	9.56
0.075	—	9.23
0.100	1.83	8.57
0.125	—	9.44
0.150	—	9.61
0.200	1.73	8.38
0.250	—	9.77
0.300	—	8.85
0.400	—	9.07
0.500	1.57	9.25
0.750	—	9.57
1.000	1.48	7.75
1.250	—	7.59
1.500	—	7.78
2.000	1.27	7.62

TABLE 5.3: Iodination of ethylmalonic acid and phenylmalonic acid by molecular iodine.

$$[\text{EtMA}] = [\text{PhMA}] = 0.050\text{M}, [\text{I}_2] = 5.24 \times 10^{-4}\text{M}, T = 298\text{K}.$$

$[\text{HClO}_4]/\text{M}$	EtMA $10^6 k_{\text{obs}}/\text{mol l}^{-1}\text{s}^{-1}$	PhMA $10^4 k_{\text{obs}}/\text{mol l}^{-1}\text{s}^{-1}$
0	9.83	1.62
0.010	5.11	1.52
0.025	4.69	1.57
0.050	4.41	1.59
0.100	4.26	1.49
0.200	3.91	1.45
0.500	4.09	1.23
1.000	3.87	0.88
1.500	3.37	0.64
2.000	3.25	0.50

In all cases however there is something of a tendency for k_{obs} to decrease with acidity at high acidities greater than 1M. The explanation for this, as suggested for malonic acid, is that we are no longer looking at a pure zero order dependence but there is the incursion of a first order component.

Table 5.4 contains the data for the fully first order rate constant, for the three substrates, and its dependence upon acid concentration. To gain first order rate constants the concentration of iodine used had to be sufficiently low, here $1.0 \times 10^{-4}\text{M}$ was just sufficient. Lower concentrations were not possible because of the limitations of the apparatus used.

With all three substrates the first order rate constant is independent of acid concentration. All of these results are consistent with reaction via the enol intermediate, where enolisation is catalysed by an intramolecular proton transfer.

TABLE 5.4: First order rate constants for the iodination of methylmalonic acid, ethylmalonic acid and phenylmalonic acid.

$[MMA] = [EtMA] = [PhMA] = 0.050M, [I_2] = 1.00 \times 10^{-4}M, T = 298K.$

$[HClO_4] / M$	k_{obs} / s^{-1}		
	MMA	EtMA	PhMA
0	0.33	0.13	5.83
0.10	0.34	0.13	5.26
0.25	0.31	0.12	5.51
0.50	0.27	0.12	5.66
0.75	0.27	0.11	5.28

Methylmalonic acid iodination was also carried out without added acid at different iodine concentrations. Again the observed rate constant decreases with decreasing iodine concentration resulting from the loss of the zero order limiting condition, (table 5.5). The best zero order behaviour was followed when the concentration of iodine was at the maximum value which its solubility would allow⁵.

TABLE 5.5: Iodination of methylmalonic acid as a function of iodine concentration, without added acid.

$[MMA] = 0.10M, T = 298K.$

$10^4 [I_2] / M$	$10^5 k_{obs} / mol\ l^{-1} s^{-1}$
5.24	2.26
4.00	2.09
3.00	2.05
2.00	1.91

A value of $8.40 \times 10^{-7} \text{ mol l}^{-1} \text{ s}^{-1}$, for the zero order observed rate constant, was found by P. Ratcliffe for iodination of methylmalonic acid under the following conditions, $[\text{MMA}] = 5.25 \times 10^{-3} \text{ M}$ and $[\text{I}_2] = 6.01 \times 10^{-4} \text{ M}$, when good zero order behaviour was found.

Variation of substrate concentration is reported in table 5.6 for the iodination of ethylmalonic acid and phenylmalonic acid at high iodine concentration, when zero order kinetics prevail. In both cases, as expected, there is a first order dependence upon substrate concentration, which is represented by the linear plots of k_{obs} versus substrate concentration in graphs 5.1 and 5.2. Values of k_1 , the enolisation rate constant, obtained from these results are shown in table 5.7.

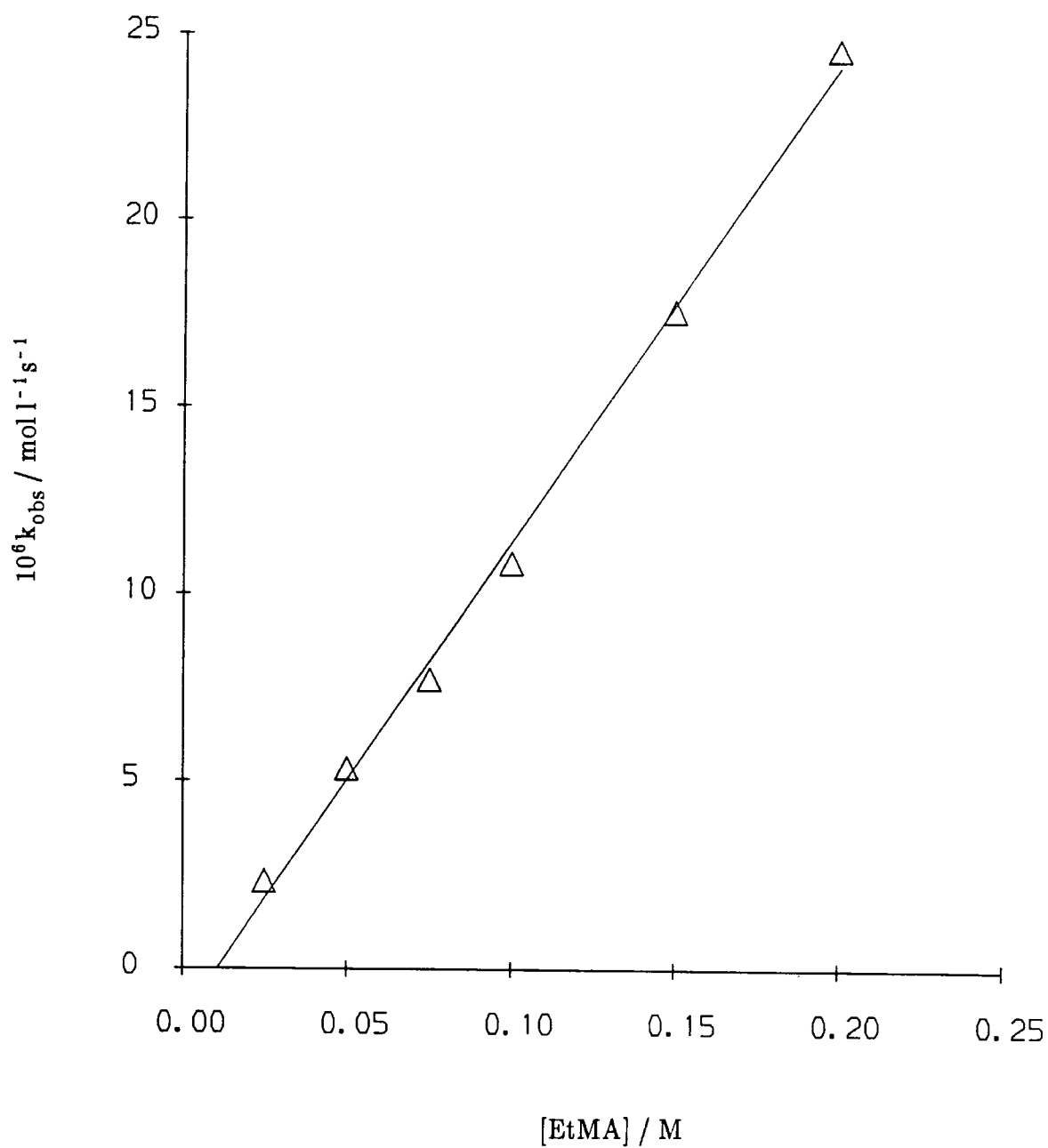
TABLE 5.6: Iodination of ethylmalonic acid and phenylmalonic acid, with variation of substrate concentration.

$$[\text{I}_2] = 5.24 \times 10^{-4} \text{ M}, T = 298 \text{ K}.$$

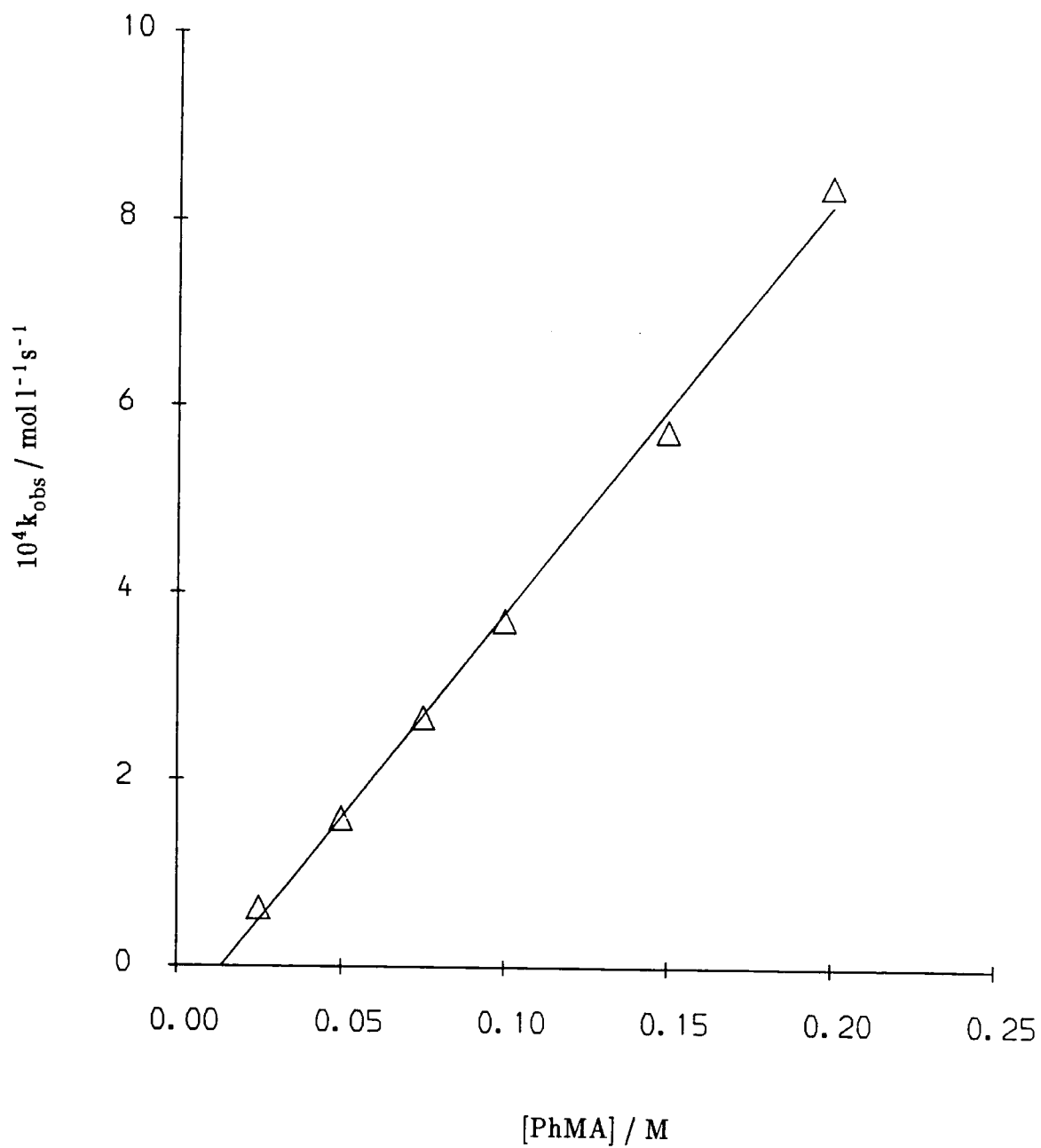
$[\text{EtMA}] \text{ and } [\text{PhMA}] / \text{ M}$	$10^6 k_{\text{obs}} / \text{ mol l}^{-1} \text{ s}^{-1}$	$10^4 k_{\text{obs}} / \text{ mol l}^{-1} \text{ s}^{-1}$
0.025	2.34	0.63
0.050	5.34	1.59
0.075	7.72	2.67
0.100	10.84	3.71
0.150	17.59	5.75
0.200	24.60	8.38

The major problem encountered in both this and the previous chapter is maintaining either pure zero or pure first order limiting reaction conditions, as variation of either iodine or acid concentrations affects the inequalities derived from the terms in the denominator of the rate equation, (equation 5.3).

GRAPH 5.1: Iodination of ethylmalonic acid by molecular iodine.



GRAPH 5.2: Iodination of phenylmalonic acid by molecular iodine.



5.3 Discussion

The evidence indicates that, under the reaction conditions employed, the iodination of methylmalonic acid, ethylmalonic acid and phenylmalonic acid proceeds via the enol tautomer. The enolisation rate constant, k_1 , for each substrate can be calculated from the zero order k_{obs} , (equation 5.9).

$$\text{Rate} = k_1[\text{SH}] = k_{\text{obs}}, \quad \text{for the zero order limit}$$

SH: MMA, EtMA, PhMA

$$k_1 = \frac{k_{\text{obs}}}{[\text{SH}]} \quad (5.9)$$

Table 5.7 contains all of the calculated k_1 values.

TABLE 5.7: Enolisation rate constants for methylmalonic, ethylmalonic and phenylmalonic acids, derived from the iodination experiments.

	MMA	EtMA	PhMA
$10^4 k_1 / \text{s}^{-1}$	1.91 (± 0.26) ^a		
	1.75 (± 0.09) ^b	1.04 (± 0.42) ^a	29.9 (± 2.6) ^a
	2.26 (± 0.03) ^c	1.27 (± 0.02) ^c	43.9 (± 0.2) ^c
	1.6 ^b		

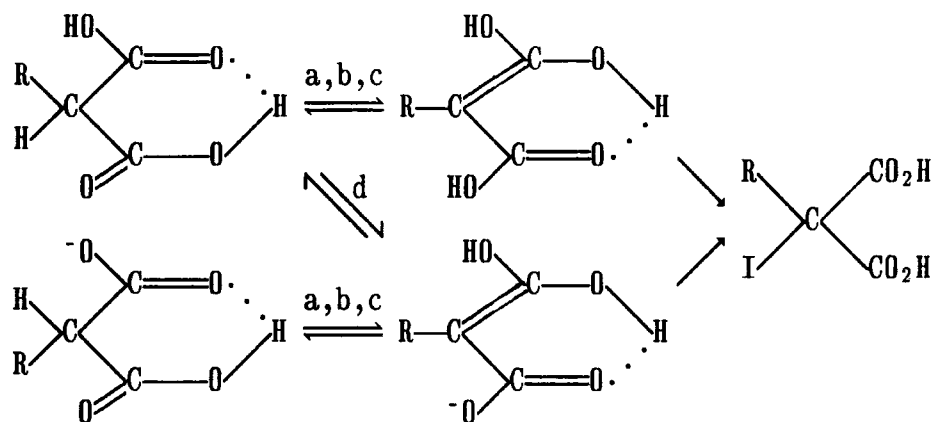
a – mean of all values from variation of $[\text{HClO}_4]$, below 1.0M

b – from final year project of P. Ratcliffe

c – slopes from k_{obs} versus $[\text{SH}]$ plots

As with malonic acid the enol intermediate can be formed, in principle, from several separate reaction pathways. Those previously discussed (chapter 4), are all also possibilities for methylmalonic acid, ethylmalonic acid and phenylmalonic acid

i.e., acid or base catalysed enol formation, enol formation via an intramolecular process, the formation of an enol carboxylate directly from the alkylmalonic acid, acid or base catalysed formation of an enol carboxylate (from the monoanion of the acid), or an intramolecular process similar to that for enol formation from acid, (scheme 5.2).



R: CH_3 , C_2H_5 , C_6H_5

a – acid catalysed equilibria

b – base catalysed equilibria

c – intramolecular equilibria

d – intramolecular rearrangement with proton loss

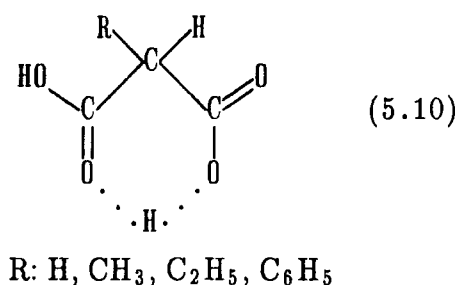
Scheme 5.2

As before the rate equations for each pathway can be simplified to two limiting cases, where the enolisation is rate limiting (zero order) and where iodination is rate limiting (first order). The dependence of k_{obs} on acid concentration in each case is shown in table 5.8.

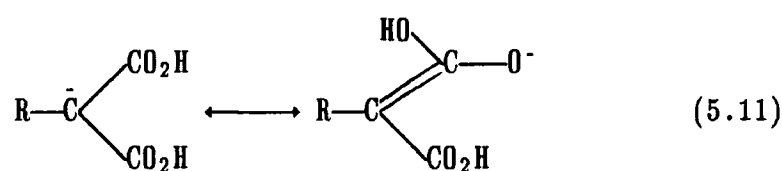
TABLE 5.8: Proportionalities of zero and first order k_{obs} with acid concentration.

Pathway	Zero order k_{obs}	First order k_{obs}
Acid catalysed enol formation	$k_{\text{obs}} \propto [\text{H}^+]$	k_{obs} independent of $[\text{H}^+]$
Base catalysed enol formation	$k_{\text{obs}} \propto \frac{1}{[\text{H}^+]}$	k_{obs} independent of $[\text{H}^+]$
Intramolecular enol formation	k_{obs} independent of $[\text{H}^+]$	k_{obs} independent of $[\text{H}^+]$
Enol _c formation from acid	k_{obs} independent of $[\text{H}^+]$	$k_{\text{obs}} \propto \frac{1}{[\text{H}^+]}$
Acid catalysed enol _c formation	k_{obs} independent of $[\text{H}^+]$	$k_{\text{obs}} \propto \frac{1}{[\text{H}^+]}$
Base catalysed enol _c formation	$k_{\text{obs}} \propto \frac{1}{[\text{H}^+]^2}$	$k_{\text{obs}} \propto \frac{1}{[\text{H}^+]}$
Intramolecular enol _c formation	$k_{\text{obs}} \propto \frac{1}{[\text{H}^+]}$	$k_{\text{obs}} \propto \frac{1}{[\text{H}^+]}$

Experimental results show that k_{obs} (both zero and first order) are independent of the acid concentration. The only pathway to correspond to these conditions is that involving an intramolecular mechanism. This is the same result that was found for malonic acid, chapter 4. The intramolecular acid catalysis pathway would appear to involve a transition state containing a six membered ring structure, (equation 5.10), which is similar to other transition state ring structures, postulated in other work^{7,8,9,10}.

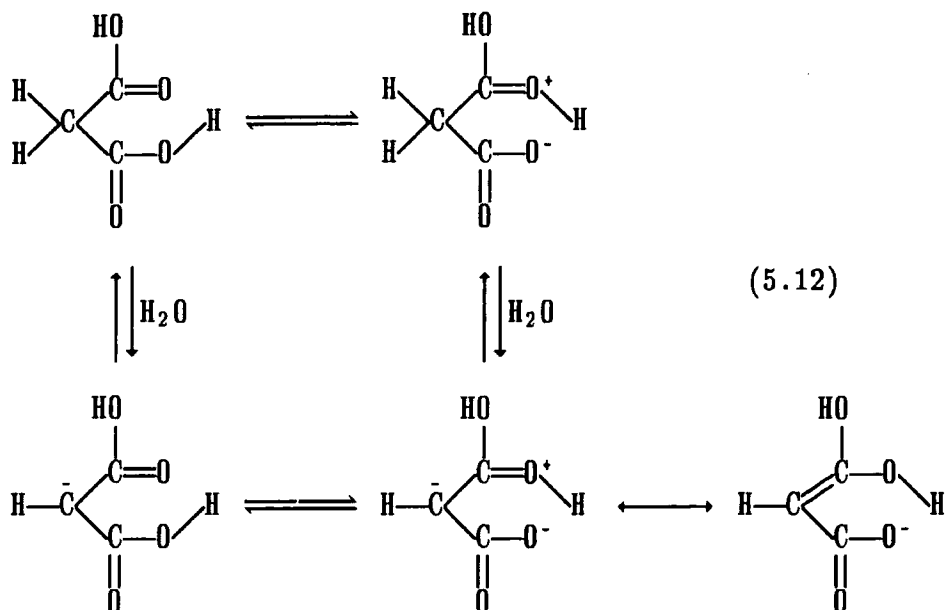


As the acidity of the reaction mixture is reduced it is possible that one or more of the alternative pathways will become more dominant, a situation found by Furrow, with methylmalonic acid⁸, and other authors^{9,10,11} with other substrates. The usual trend being reaction via enol changing to reaction via enolate at higher pH. Furrow found that as the pH increased the reactive intermediate changed from the enol to the enol carboxylate and then at even higher pH to reaction via the enolate, which is a resonance structure of the carbanion, (equation 5.11).



In this work the pH has not been increased sufficiently for a change in reaction intermediate to be observed. A discussion of the effect of the structure of the substrate upon the relative magnitudes of k_1 for the four dibasic acids will be discussed in chapter 6.

The kinetic results obtained in this study indicate that at high acid concentration the enolisation of malonic and the alkylmalonic acids proceeds by a mechanism independent of acid concentration. It has been described that this mechanism involves an intramolecular proton transfer between the carboxylic acid groups followed by the loss of a methylene proton either intramolecularly to the carboxylate of the intermediate or to a water molecule, acting as a base, producing the enol and enol carboxylate respectively. It is more probable that the water molecule, acting as a base, would remove the methylene proton. This can take place either before or after the intramolecular proton transfer, (equation 5.12). This mechanism is also independent of the acid concentration and so would also fit the kinetic data. The results obtained can not differentiate between the different possible intramolecular mechanisms.



Although the carboxylate group is a stronger base than water the removal of the methylene proton, by the carboxylate, involves a four membered ring structure in the transition state, which would be highly unfavourable. This will make the reaction with water, acting as a base, more likely, in the pH independent enol formation. The effect of the methyl, ethyl or phenyl groups upon the enolisation rate constant may not be fully explained by considerations of their effect upon the geometry of the molecule and the influence of this upon the intramolecular proton transfer. The effect of these substituents upon the proton transfer to water would also affect the magnitude of the enolisation rate constants.

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CHAPTER 6
BROMINATION OF MALONIC, METHYLMALONIC,
ETHYLMALONIC AND PHENYLMALONIC ACIDS

6.1 Introduction

Bromination of a wide range of substrates, in aqueous solution, has been as widely studied^{1,2,3} as iodination. The equilibria formed involving bromine in aqueous solution alone, or with added bromide ions, have been documented^{4,5,6} and hence reaction conditions can be controlled to give the required electrophilic species, in solution. Bromination of simple carbonyl compounds has been shown^{7,8,9} to proceed via the enol tautomer or under more basic conditions the enolate ion, which is a resonance structure of the carbanion.

More specifically the bromination of malonic acid and the methyl, ethyl and phenyl substituted malonic acids has been studied for about seventy years^{10,11}. The involvement of the enol tautomer was proposed even in that early work. Further work discussed^{12,13,14,15} these bromination reactions as zero order with respect to the bromine, at high bromine concentrations. This is conducive with reaction involving rate limiting enol formation, followed by the reaction of the enol with the bromine. Malonic acid was also suggested as an autocatalyst to the reaction. These conclusions were drawn in parallel to the work carried out in the iodination^{16,17} of malonic acid, methylmalonic acid and ethylmalonic acid. Unlike the iodination of malonic acid and alkylmalonic acids, the bromination has not been as widely reported because the reactivity of iodine is important in oscillating reactions^{18,19}, which have received substantial recent interest.

The reaction products, of the bromination, are all the monobromo acids, (equation 6.1), even with malonic acid itself where the use of acidic solution prevents the formation of the dibromo product.



R: H, CH₃, C₂H₅, C₆H₅

This work is designed to try and further elucidate the pathways to enol

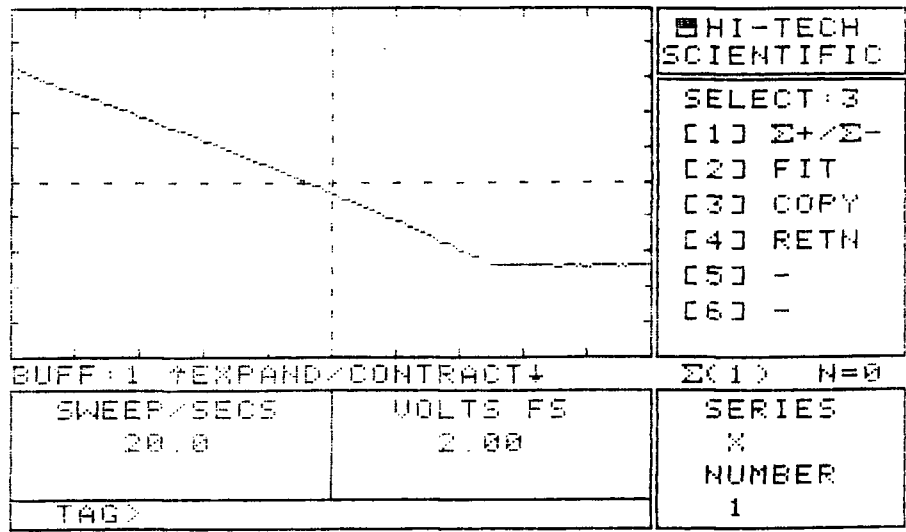
formation involved in the halogenation reactions by performing the brominations over a wider pH range. Simultaneously to confirm k_1 , the enolisation rate constants, for each acid, were measured at high acidity, which should show an independence upon the halogenating or nitrosating species²⁰.

6.2 Results

All brominations were carried out in aqueous acidic solution at 25°C, by following the disappearance of the absorbance (or voltage) at 393 nm which is due exclusively to the bromine molecule. The extinction coefficient, at this wavelength, was found to be $\epsilon = 128.39 \text{ l mol}^{-1} \text{ cm}^{-1}$. Due to the greater solubility of bromine⁵, in water, than iodine²¹, and also its greater reactivity, saturated bromine solutions were not necessary.

Initially each substrate was brominated in water alone, where excellent zero order reaction kinetics were observed, (graph 6.1).

GRAPH 6.1: Voltage time plot for the bromination of phenylmalonic acid.



The zero order rate equation, (equation 6.2), is one limiting case for the overall rate equation, (equation 6.3). The other limiting case, (equation 6.4), yields totally first order reaction kinetics. These equations are derived in the same manner discussed for the iodination of these substrates.

$$\text{Rate} = k_1 [\text{SH}] \quad (6.2)$$

$$\text{Rate} = \frac{k_1 k_2^e [\text{SH}] [\text{Br}_2]}{k_{-1} + k_2 [\text{Br}_2]} \quad (6.3)$$

$$\text{Rate} = K_e k_2^e [\text{SH}] [\text{Br}_2] \quad (6.4)$$

Both extremes are reached from the inequalities possible in the denominator of equation 6.3. When $k_{-1} \gg k_2 [\text{Br}_2]$ bromination is the rate determining step, (equation 6.4), and would be demonstrated by first order reaction curves under the conditions used. An increase in bromine concentration and/or decrease in acid concentration will affect the inequality. When the inequality is no longer valid, reaction kinetics should be mixed zero and first order. The other extreme is when bromine concentration is sufficiently high and the acid concentration is sufficiently low, such that totally zero order conditions are achieved, (equation 6.2), when $k_2 [\text{Br}_2] \gg k_{-1}$. The ketonisation rate constant is k_{-1} which may contain an acid concentration term if the process is acid catalysed.

These initial results for bromination are displayed in table 6.1. The k_1 , enolisation rate constants, values come directly from substitution of $\text{rate} = k_{\text{obs}}$ into equation 6.2, (equation 6.5).

$$\text{Rate} = k_{\text{obs}} = k_1 [\text{SH}] \quad (6.6)$$

Each substrate was then examined over a range of perchloric acid concentrations, (tables 6.2 to 6.5), the pH of each solution was carefully measured so the effect of the substrate upon acidity can be considered, especially at low perchloric acid concentration where the substrate contribution to the acidity is no longer negligible. Sodium hydroxide was added to solutions to obtain some of the higher pH values used.

TABLE 6.1: Bromination of malonic acid, methylmalonic acid, ethylmalonic acid and phenylmalonic acid, in distilled water.

$$[\text{SH}] = 5.0 \times 10^{-2} \text{M}, [\text{Br}_2] = 2.5 \times 10^{-3} \text{M}, T = 298\text{K}.$$

SH	$k_{\text{obs}} / \text{mol l}^{-1} \text{s}^{-1}$	k_1 / s^{-1}
MA	2.44×10^{-4}	$4.88 (\pm 0.12) \times 10^{-3}$
MMA	1.48×10^{-5}	$2.96 (\pm 0.04) \times 10^{-4}$
EtMA	6.40×10^{-6}	$1.28 (\pm 0.01) \times 10^{-4}$
PhMA	2.41×10^{-4}	$4.82 (\pm 0.12) \times 10^{-3}$

TABLE 6.2: Bromination of malonic acid at various pH values.

$$[\text{MA}] = 0.050\text{M}, [\text{Br}_2] = 2.5 \times 10^{-3} \text{M}, T = 298\text{K}.$$

$[\text{HClO}_4] / \text{M}$	pH	$10^4 k_{\text{obs}} / \text{mol l}^{-1} \text{s}^{-1}$
—	3.78	$0.79 (\pm 0.11)$
—	3.20	$1.45 (\pm 0.04)$
—	2.79	$1.93 (\pm 0.06)$
—	2.51	$2.30 (\pm 0.11)$
—	2.10	$2.46 (\pm 0.06)$
0.01	1.74	$2.44 (\pm 0.02)$
0.025	1.41	$2.35 (\pm 0.01)$
0.05	1.19	$2.26 (\pm 0.06)$
0.10	0.87	$2.29 (\pm 0.08)$
0.25	0.56	$2.23 (\pm 0.16)$
0.50	0.31	$2.33 (\pm 0.02)$
1.00	0	$2.21 (\pm 0.16)$
2.00	-0.3	$1.75 (\pm 0.05)$

TABLE 6.3: Bromination of methylmalonic acid at various pH values.

$[\text{MMA}] = 0.050\text{M}$, $[\text{Br}_2] = 2.5 \times 10^{-3}\text{M}$, $T = 298\text{K}$.

$[\text{HClO}_4] / \text{M}$	pH	$10^5 k_{\text{obs}} / \text{mol l}^{-1} \text{s}^{-1}$
—	3.93	0.65 (± 0.01)
—	3.44	1.12 (± 0.01)
—	3.07	1.35 (± 0.01)
—	2.73	1.48
—	2.00	2.27 (± 0.09)
0.01	1.52	2.00 (± 0.02)
0.025	1.27	1.96 (± 0.05)
0.05	0.98	1.89 (± 0.05)
0.10	0.66	1.94 (± 0.05)
0.25	0.38	1.83 (± 0.03)
0.50	0.21	1.77 (± 0.03)
1.00	0	1.71 (± 0.03)
2.00	-0.3	1.64 (± 0.03)

TABLE 6.4: Bromination of ethylmalonic acid at various pH values.

$[\text{EtMA}] = 0.050\text{M}$, $[\text{Br}_2] = 2.5 \times 10^{-3}\text{M}$, $T = 298\text{K}$.

$[\text{HClO}_4] / \text{M}$	pH	$10^6 k_{\text{obs}} / \text{mol l}^{-1} \text{s}^{-1}$
—	4.04	2.33 (± 0.17)
—	3.31	4.13 (± 0.11)
—	2.99	5.48 (± 0.08)
—	2.65	6.84 (± 0.09)
—	2.10	6.40 (± 0.08)
0.01	1.87	6.43 (± 0.08)
0.025	1.50	6.71 (± 0.07)
0.05	1.26	6.76 (± 0.08)
0.10	0.99	7.06 (± 0.13)
0.25	0.62	6.58 (± 0.07)
0.50	0.33	6.60 (± 0.12)
1.00	0	6.27 (± 0.13)
2.00	-0.3	5.69 (± 0.14)

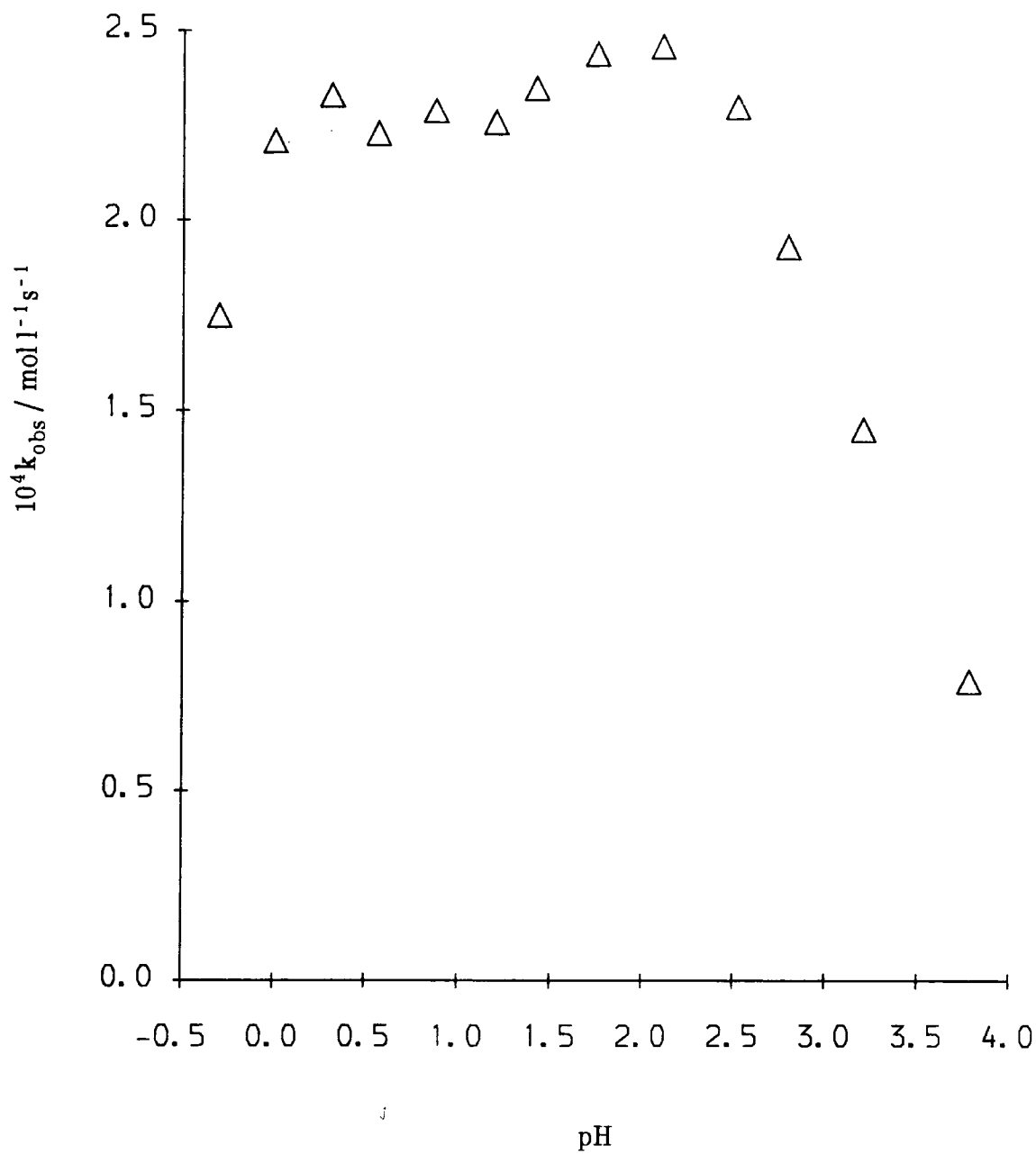
TABLE 6.5: Bromination of phenylmalonic acid at various pH values.

$$[\text{PhMA}] = 0.050\text{M}, [\text{Br}_2] = 2.5 \times 10^{-3}\text{M}, T = 298\text{K}.$$

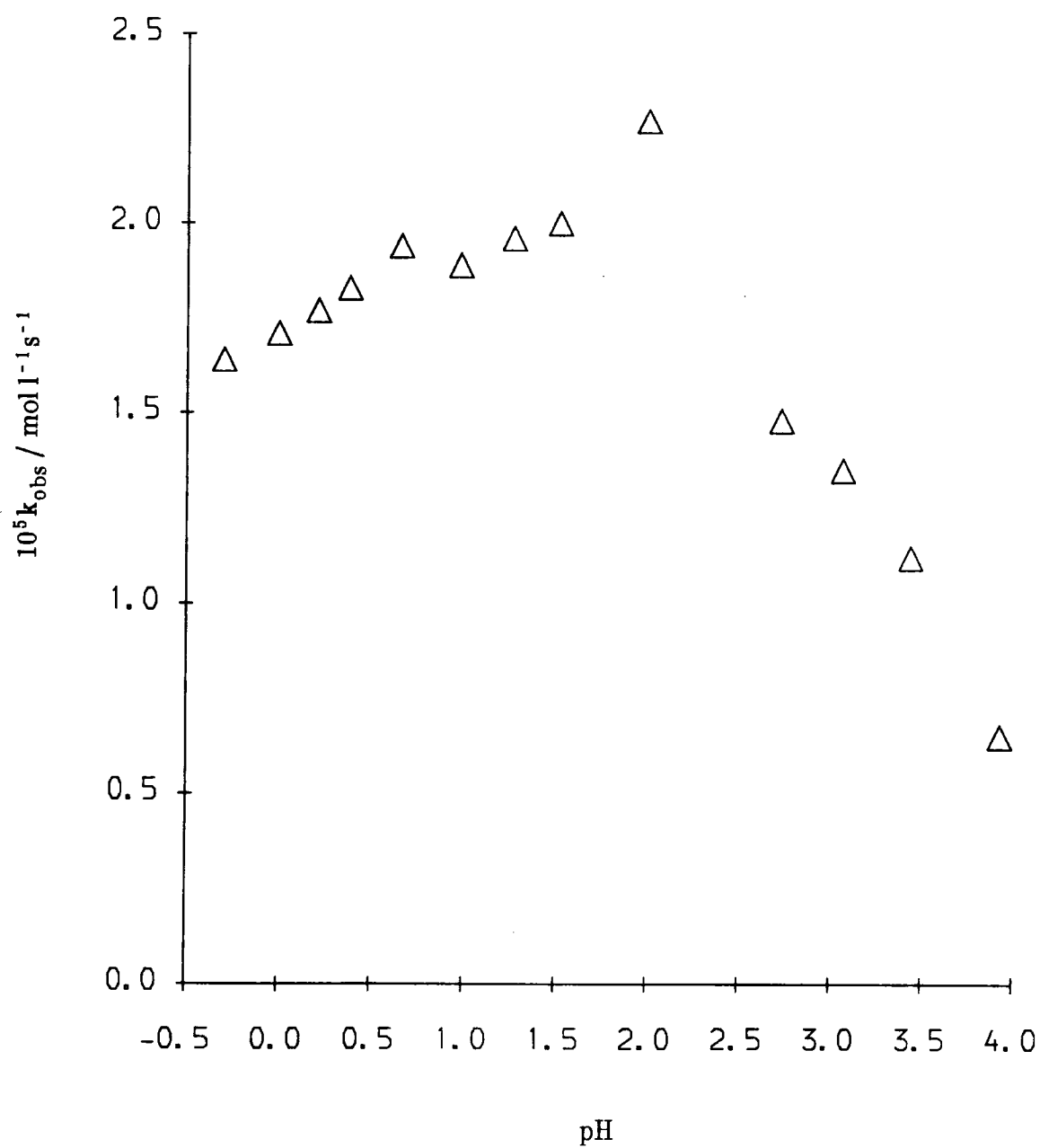
$[\text{HClO}_4] / \text{M}$	pH	$10^4 k_{\text{obs}} / \text{mol l}^{-1} \text{s}^{-1}$
—	3.54	0.54 (± 0.03)
—	2.85	1.25 (± 0.01)
—	2.48	1.75 (± 0.09)
—	2.21	2.02 (± 0.02)
—	1.74	2.50 (± 0.09)
0.01	1.65	2.50 (± 0.12)
0.025	1.56	2.54 (± 0.06)
0.05	1.27	2.53 (± 0.05)
0.10	0.95	2.47 (± 0.06)
0.25	0.56	2.51 (± 0.09)
0.50	0.28	2.41 (± 0.07)
1.00	0	2.27 (± 0.02)
2.00	-0.3	1.86 (± 0.04)

The variation of k_{obs} with respect to pH has also been plotted, (graphs 6.2 to 6.5). Each acid displays a change in the nature of the relationship between k_{obs} and the pH of the solution as the pH of the solution increases beyond a certain point. To see if the substrate itself has a catalytic role in the mechanism, the dependence of k_{obs} upon substrate concentration was established at pH 1.4 and pH 3.2, (table 6.6). At pH 1.4 k_{obs} is unaffected by small pH variation, whereas at pH 3.2 k_{obs} decreases with increasing pH. These reactions were carried out with malonic acid.

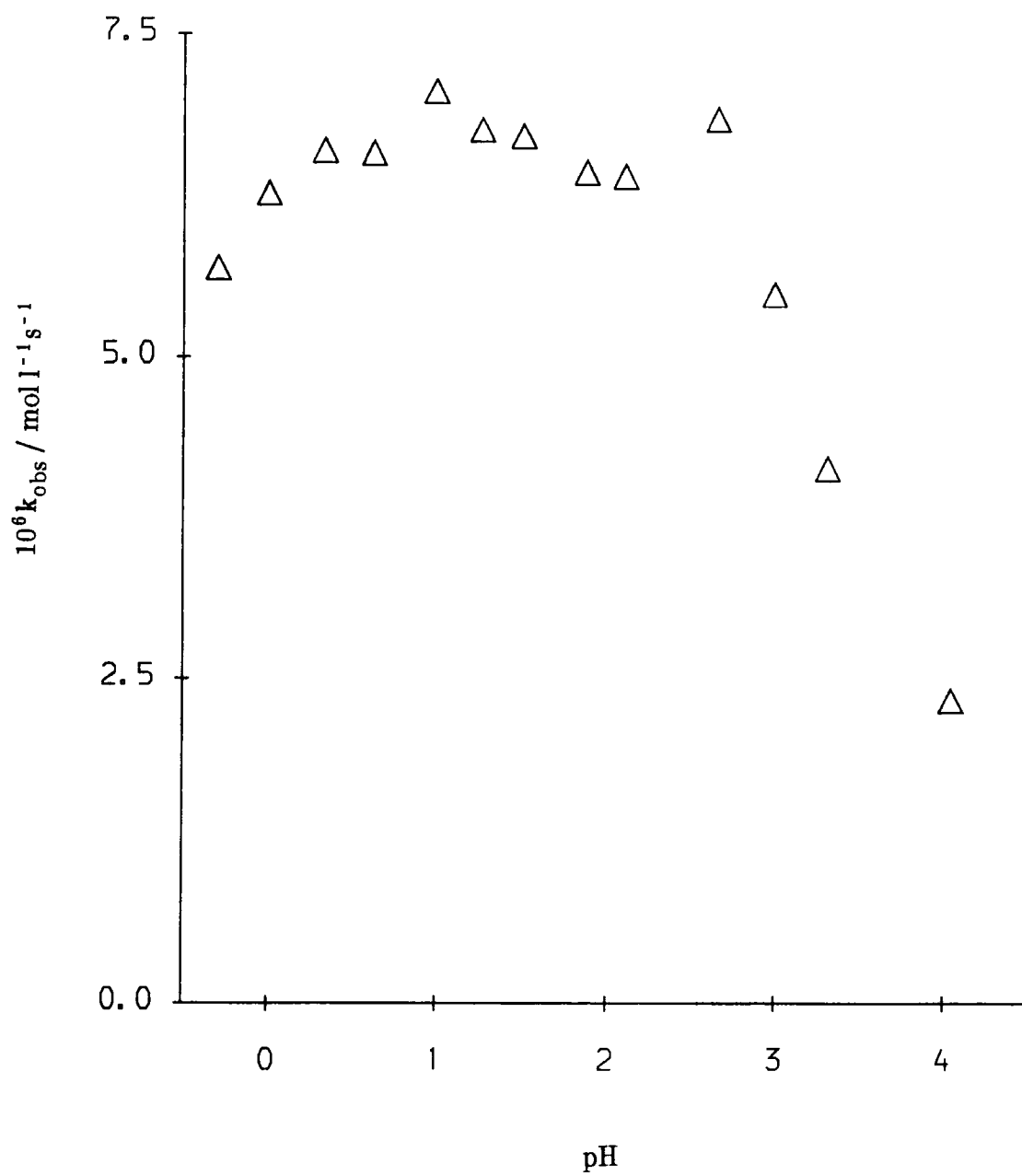
GRAPH 6.2: Variation of k_{obs} with pH for the bromination of malonic acid.



GRAPH 6.3: Variation of k_{obs} with pH for the bromination of methylmalonic acid.



GRAPH 6.4: Variation of k_{obs} with pH for the bromination of ethylmalonic acid.



GRAPH 6.5: Variation of k_{obs} with pH for the bromination of phenylmalonic acid.

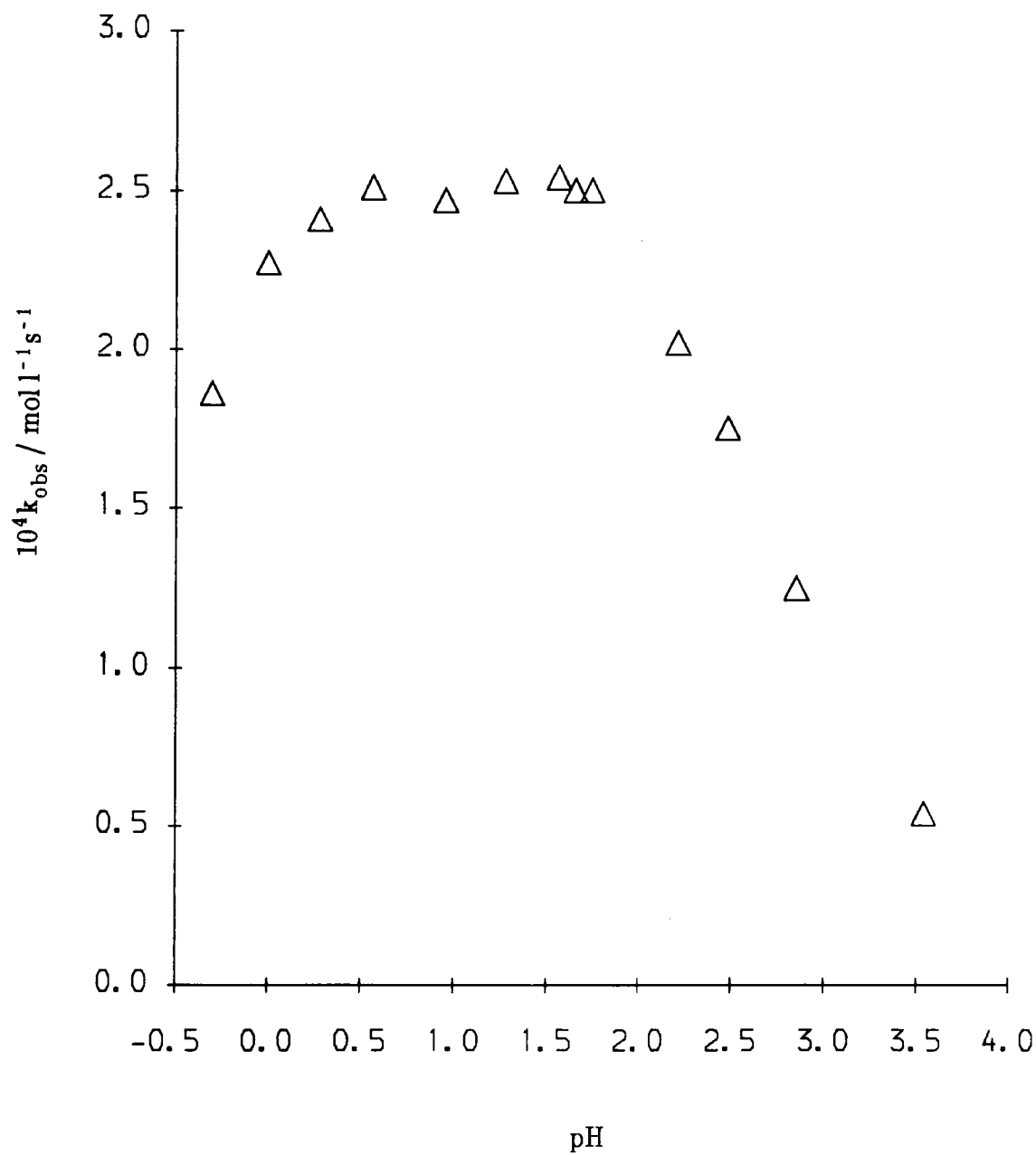


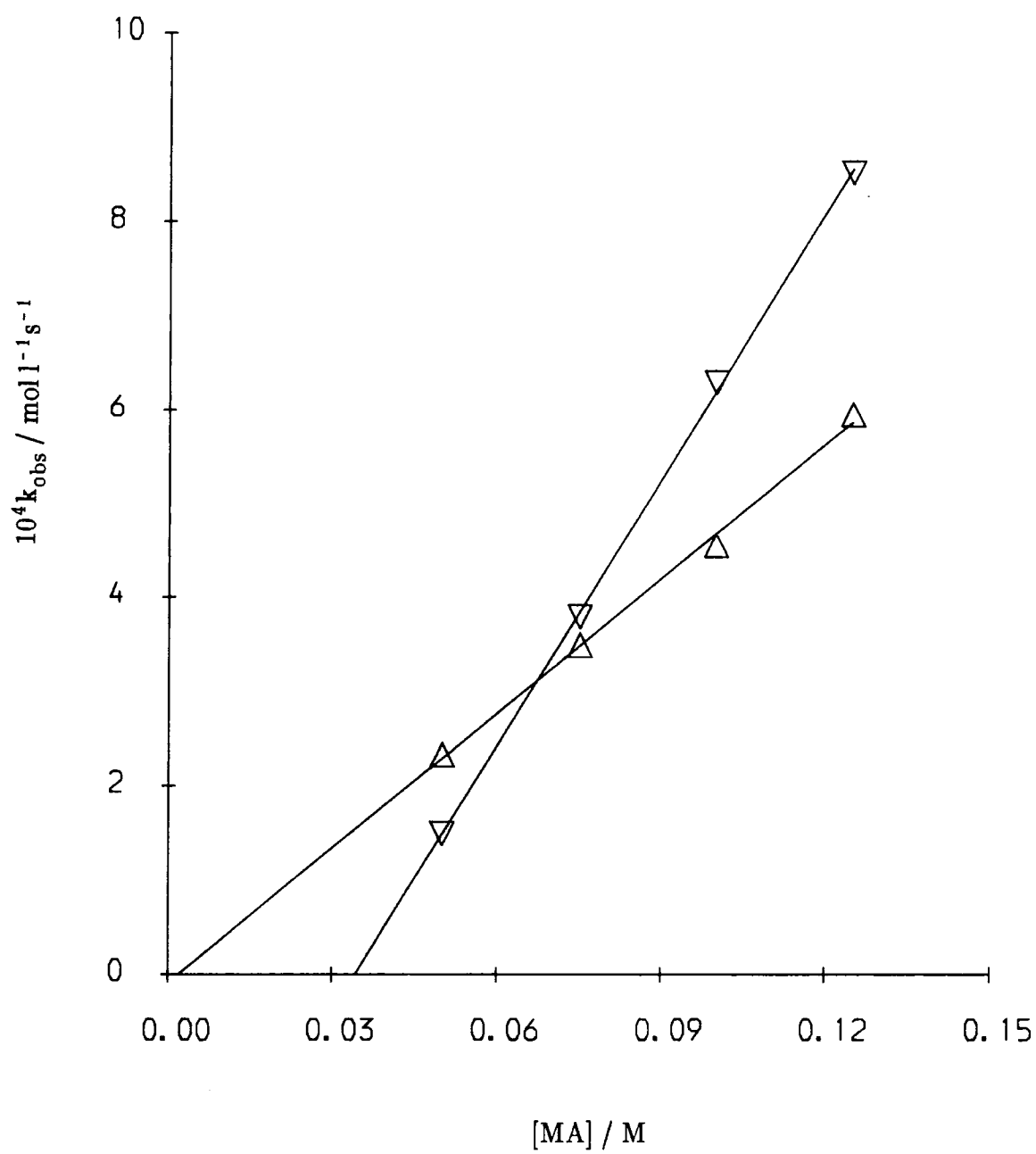
TABLE 6.6: Bromination of malonic acid at pH 1.4 and pH 3.2.

$$[\text{Br}_2] = 2.5 \times 10^{-3} \text{ M}, T = 298\text{K}.$$

[MA] / M	$10^4 k_{\text{obs}} / \text{mol l}^{-1} \text{s}^{-1}$	
	pH 1.4	pH 3.2
0.050	2.33 (± 0.13)	1.49 (± 0.07)
0.075	3.49 (± 0.12)	3.79 (± 0.08)
0.100	4.55 (± 0.16)	6.29 (± 0.19)
0.125	5.95 (± 0.25)	8.52 (± 0.28)

Plots of k_{obs} versus malonic acid concentration, (graph 6.6), for both pH values give good linear plots, indicating a first order dependence upon substrate concentration. At pH 3.2 however there is an exceptionally large negative intercept which is not possible as the plot should pass through the origin. It is possible however that at low substrate concentration, at the higher of the two pH values, the dependence upon substrate concentration is no longer first order. The plot for reaction at pH 1.4 does go through the origin, maintaining a first order dependence of the reaction upon the substrate concentration throughout.

GRAPH 6.6: Bromination of malonic acid at pH 1.4 and pH 3.2.



▽ pH 3.2
△ pH 1.4

6.3 Discussion

In order to account for the behavioural patterns observed in the results, (section 6.2), the various possible reaction pathways need to be considered. These are identical to those outlined for iodination except that bromine is now the halogenating species. Both zero and first order limiting cases were found experimentally in the iodination. Bromination, with molecular bromine, only involves one of these limiting cases and that is the rate limiting enolisation, with zero order reaction kinetics.

The different reaction pathways to enol formation and their rate equations are shown in table 6.8 along with the limiting expressions for the observed rate when enolisation is rate limiting.

Graphs 6.2 to 6.5 all have a region at lower pH values, between pH 0.5 and pH 2.0, where the observed rate constant is independent of the acid concentration. This is the same trend as was found for the iodination of all four acid substrates, discussed in chapters four and five. For iodination the results indicated enol formation which is intramolecularly acid catalysed, and either enol formation or enol reaction, with iodine, can be rate limiting, depending upon the reaction conditions. Again for bromination this pathway fits the results except that since bromine is more reactive than iodine it was not possible to achieve the inequality, in the rate equation denominator, which results in the rate limiting bromination of the enol.

At lower acid concentrations there is a change in the relationship between the zero order observed rate constant and the acid concentration. For each substrate this alteration in acid dependence occurs as the pH, of the reaction solution, increases towards the first pKa value, for the loss of a proton from oxygen. At these higher pH values the substrate is increasingly more in the carboxylate form.

TABLE 6.8: Rate and rate constant equations for the mechanisms of MA, MMA, EtMA and PhMA bromination.

Pathway	Rate equation	Rate limiting enolisation
(A) Acid catalysed enol formation	$\text{Rate} = \frac{k_1^A k_2^A [\text{SH}] [\text{H}^+] [\text{Br}_2]}{k_{-1}^A [\text{H}^+] + k_2^A [\text{Br}_2]}$	$k_{\text{obs}} = k_1^A [\text{SH}] [\text{H}^+]$
(B) Base catalysed enol formation	$\text{Rate} = \frac{k_1^B k_2^B K_a [\text{SH}]^2 [\text{Br}_2]}{k_{-1}^B K_a [\text{SH}] + k_2^B [\text{H}^+] [\text{Br}_2]}$	$k_{\text{obs}} = \frac{k_1^B K_a [\text{SH}]^2}{[\text{H}^+]}$
(I) Intramolecular enol formation	$\text{Rate} = \frac{k_1^I k_2^I [\text{SH}] [\text{Br}_2]}{k_{-1}^I + k_2^I [\text{Br}_2]}$	$k_{\text{obs}} = k_1^I [\text{SH}]$
(IC') Enol _c formed from substrate	$\text{Rate} = \frac{k_1^{\text{IC}'} k_2^{\text{IC}'} [\text{SH}] [\text{Br}_2]}{k_{-1}^{\text{IC}'} [\text{H}^+] + k_2^{\text{IC}'} [\text{Br}_2]}$	$k_{\text{obs}} = k_1^{\text{IC}'} [\text{SH}]$
(AC) Acid catalysed enol _c formation	$\text{Rate} = \frac{k_1^{\text{AC}} k_2^{\text{AC}} K_a [\text{SH}] [\text{Br}_2]}{k_{-1}^{\text{AC}} [\text{H}^+] + k_2^{\text{AC}} [\text{Br}_2]}$	$k_{\text{obs}} = k_1^{\text{AC}} K_a [\text{SH}]$
(BC) Base catalysed enol _c formation	$\text{Rate} = \frac{k_1^{\text{BC}} k_2^{\text{BC}} (K_a)^2 [\text{SH}]^2 [\text{Br}_2]}{k_{-1}^{\text{BC}} K_a [\text{SH}] [\text{H}^+] + k_2^{\text{BC}} [\text{Br}_2] [\text{H}^+]^2}$	$k_{\text{obs}} = \frac{k_1^{\text{BC}} (K_a)^2 [\text{SH}]^2}{[\text{H}^+]^2}$
(IC) Intramolecular enol _c formation	$\text{Rate} = \frac{k_1^{\text{IC}} k_2^{\text{IC}} K_a [\text{SH}] [\text{Br}_2]}{[\text{H}^+] (k_{-1}^{\text{IC}} + k_2^{\text{IC}} [\text{Br}_2])}$	$k_{\text{obs}} = \frac{k_1^{\text{IC}} K_a [\text{SH}]}{[\text{H}^+]}$

Graph 6.6 shows the relationship between k_{obs} and substrate concentration, in the case of malonic acid, at pH 1.4 and pH 3.2. At these different pH values if reaction exclusively involved intramolecular acid catalysis then these slopes should be the same. This is not what is seen. At pH 3.2 the gradient is greater than that for reaction at pH 1.4, (graph 6.6). Another pathway is possibly involved. In the pH range 2.0 to 4.0 the observed rate constant increases with increasing acid concentration. Plots of k_{obs} versus acid concentration, (graphs 6.7 for malonic acid and phenylmalonic acid and 6.8 for methylmalonic acid and ethylmalonic acid and also table 6.9), both show that the relationship is non-linear. It is a mixture of first and zero order dependence. Referring to table 6.8, the only possible reaction pathway which has a proportionality to acid concentration greater than zero is that of acid catalysed enol formation.

The results appear to show that at higher pH, 2.0 to 4.0, the enol intermediate is formed by an intramolecular acid catalysed pathway and also by an intermolecular acid catalysed pathway.

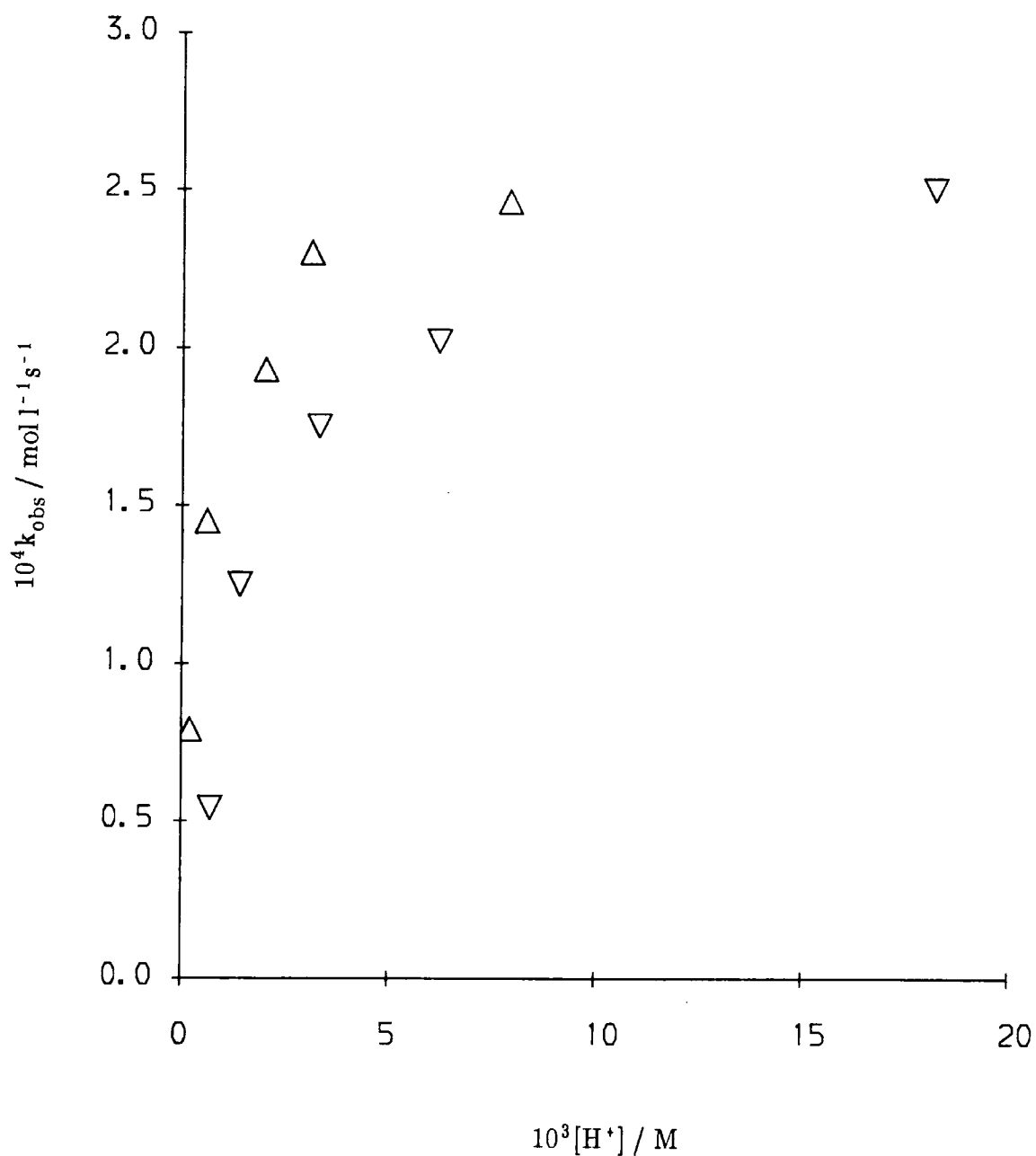
As the acidity increases the intramolecular pathway becomes totally dominant and the observed rate constant is independent of the acid concentration. It is, of course, possible that some or all of the other pathways in table 6.8 occur to a small extent. This kinetic study has not been able to differentiate between some of the possibilities. Also outside the pH range studied, at higher pH values, it is possible that the reaction intermediate or route to its formation alter once again. This behaviour has been shown, by Leopold And Haim²², to be the case when the enolate (or carbanion) became involved as a reaction intermediate at even higher pH values.

As previously mentioned the change in acid concentration dependence occurs at pH values close to the pKa values for the first dissociation constants for the acid substrates. One would expect more carboxylate to be present in solution at these higher pH values. The carboxylate could become involved in the reaction process, acting both as a basic catalyst and as a substrate which undergoes enolisation.

TABLE 6.9: Change in k_{obs} with $[\text{H}^+]$ for MA, MMA, EtMA and PhMA

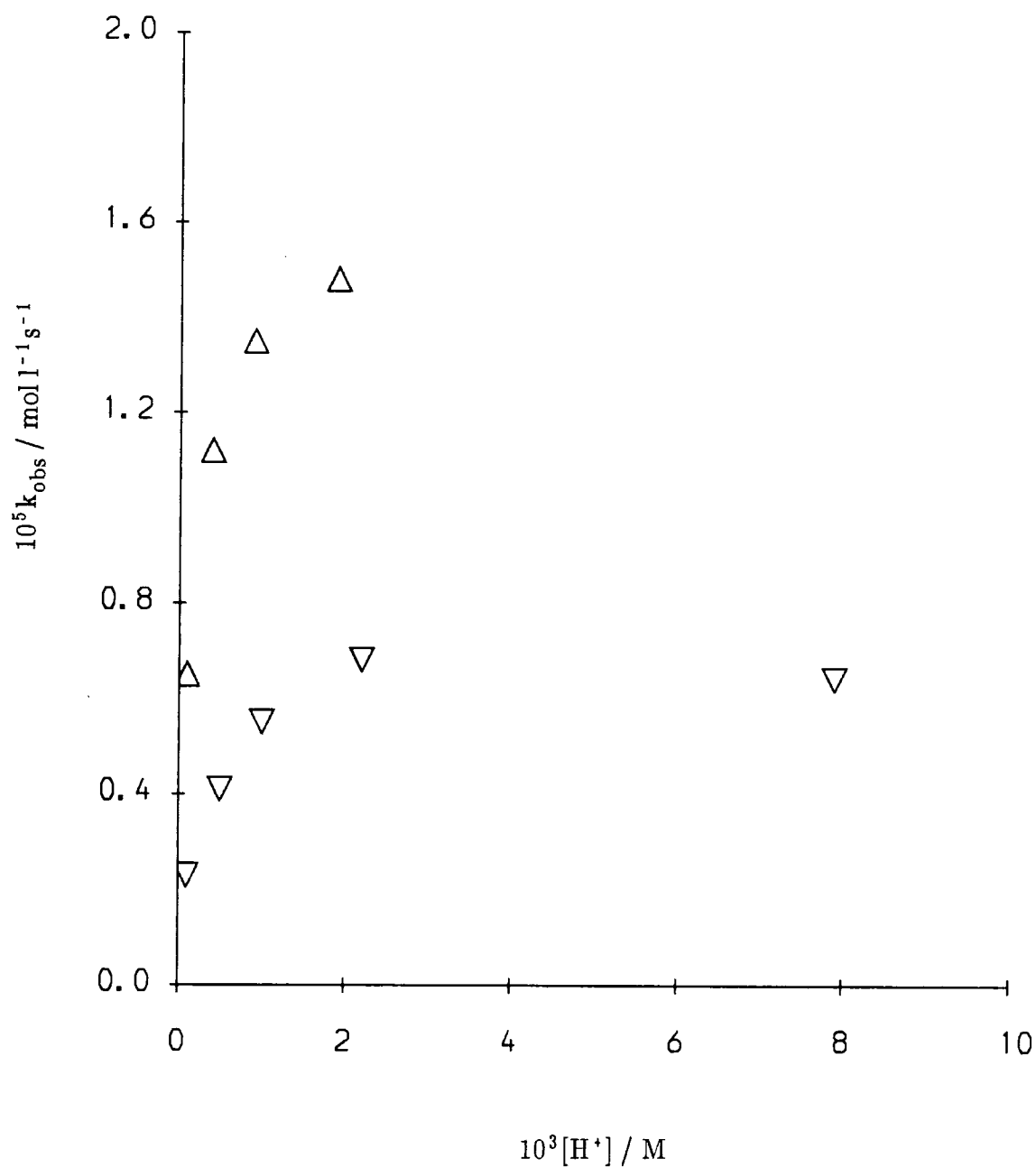
M A	$10^4 k_{\text{obs}} / \text{mol l}^{-1} \text{s}^{-1}$	pH	$10^3 [\text{H}^+] / \text{M}$
	0.79	3.78	0.2
	1.45	3.20	0.6
	1.93	2.79	2.0
	2.30	2.51	3.1
	2.46	2.10	7.9
M M A	$10^5 k_{\text{obs}} / \text{mol l}^{-1} \text{s}^{-1}$	pH	$10^3 [\text{H}^+] / \text{M}$
	0.65	3.93	0.1
	1.12	3.44	0.4
	1.35	3.07	0.9
	1.48	2.73	1.9
	2.27	2.00	10.0
E t M A	$10^6 k_{\text{obs}} / \text{mol l}^{-1} \text{s}^{-1}$	pH	$10^3 [\text{H}^+] / \text{M}$
	2.33	4.04	0.1
	4.13	3.31	0.5
	5.48	2.99	1.0
	6.84	2.65	2.2
	6.40	2.10	7.9
P h M A	$10^4 k_{\text{obs}} / \text{mol l}^{-1} \text{s}^{-1}$	pH	$10^3 [\text{H}^+] / \text{M}$
	0.54	3.51	0.7
	1.25	2.85	1.4
	1.75	2.48	3.3
	2.02	2.21	6.2
	2.50	1.74	18.2

GRAPH 6.7: Zero order observed rate constant relationship to acid concentration
for malonic acid and phenylmalonic acid.



▽ PhMA
△ MA

GRAPH 6.8: Zero order observed rate constant relationship to acid concentration
for methylmalonic acid and ethylmalonic acid.



▽ EtMA
△ MMA

In graph 6.6, for malonic acid, the plot for reaction at pH 3.2 would appear to have a very large negative intercept. This can not be possible as it should pass through the origin. A possible explanation is that at very low substrate concentrations the dependence of the observed rate constant upon substrate concentration is greater than one. Table 6.8 shows that this dependence of more than one only occurs in the base catalysed enol formation and base catalysed enol carboxylate formation pathways. Both processes involve the carboxylate ion. It is perhaps possible therefore that at higher pH values the reaction also contains a base catalysed component.

Both acid and base catalysed enolisation have been proposed here as additional reaction pathways (additional to the intramolecular process). Acid and base catalysis have been shown to take place in the enolisation of many substrates under many reaction conditions^{2 3}.

The values of k_1 , the enolisation rate constant, found at high acidity and almost totally due to an intramolecular acid catalysed process, are independent of the nature of the species which attacks electrophilically. The k_1 values found for the nitrosation, iodination and bromination of these substrates should, therefore, be the same. These values are tabulated, (table 6.10), along with some enolisation rate constants observed by some other authors.

TABLE 6.10: Enolisation rate constants, k_1 , for MA, MMA, EtMA and PhMA obtained from nitrosation, iodination and bromination reactions and some earlier work.

Substrate	k_1 / s^{-1}
MA	$4.68 (\pm 0.18) \times 10^{-3} \text{ a}$ $4.77 (\pm 0.04) \times 10^{-3} \text{ a}$ $3.44 (\pm 0.06) \times 10^{-3} \text{ b}$ $3.80 (\pm 0.01) \times 10^{-3} \text{ b}$ $2.69 (\pm 0.08) \times 10^{-3} \text{ b}$ $2.4 \times 10^{-3} \text{ ref. 22}$ $1.066 \times 10^{-3} \text{ ref. 25}$
MMA	$3.96 (\pm 0.30) \times 10^{-4} \text{ a}$ $1.91 (\pm 0.26) \times 10^{-4} \text{ b}$ $1.75 (\pm 0.09) \times 10^{-4} \text{ b}$ $2.26 (\pm 0.03) \times 10^{-4} \text{ b}$ $2.13 \times 10^{-4} \text{ c}$ $1.68 \times 10^{-4} \text{ ref. 24}$ $5.7 \times 10^{-5} \text{ ref. 25,26}$
EtMA	$1.33 (\pm 0.04) \times 10^{-4} \text{ a}$ $1.04 (\pm 0.42) \times 10^{-4} \text{ b}$ $1.27 (\pm 0.02) \times 10^{-4} \text{ b}$
PhMA	$4.98 (\pm 0.08) \times 10^{-3} \text{ a}$ $2.99 (\pm 0.26) \times 10^{-3} \text{ b}$ $4.39 (\pm 0.02) \times 10^{-3} \text{ b}$

a – this work, bromination

b – this work, iodination

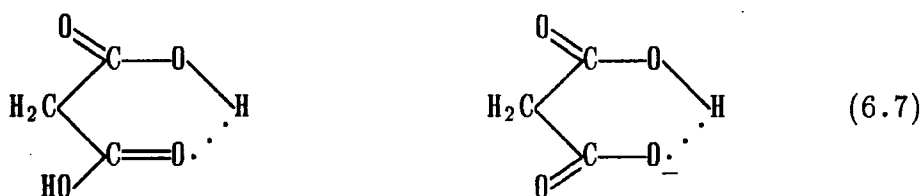
c – this work, nitrosation

For all four acids the values of k_1 , for each, are all in reasonable agreement, not only with those from this work but also from work involving similar reactions^{22,24} by other authors.

In many previous studies the effect of changing structure of the substrate has been discussed^{27,28,29} in terms of the relative magnitudes of the keto-enol equilibrium constants. Polar effects, conjugation, cis interactions and hyperconjugative stabilisation are the major factors used to account for these

structural effects. This work has concentrated on measurements of the rate constants for enolisation k_1 (or k_e) and no attempt has been made to evaluate the equilibrium constants, K_E .

Comparisons of the structural changes, with respect to their effect upon k_e , with a set of structurally similar compounds has not been possible. In many cases the values are not available. In others the quoted k_e values are second order rate constants, due to intermolecular catalysis. The substrates in this work undergo intramolecular catalysis, under the conditions used and so first order enolisation rate constants are obtained. The presence of the second carboxylic acid group within the molecule and also its proximity to the other acid group are responsible for this catalysis taking place. It has been shown, in the case of malonic acid³⁰ and its monocarboxylate ion³¹ that the acid groups within the molecule can form intramolecular hydrogen bonds, which give a relatively stable six membered ring structure, (equation 6.7).



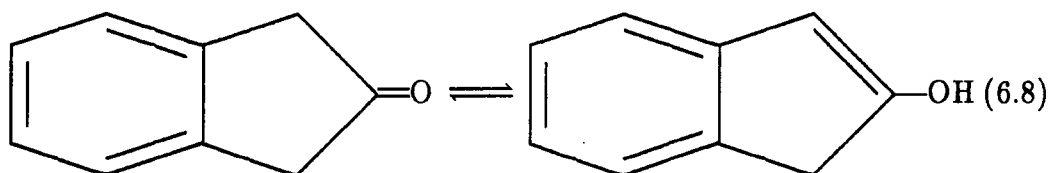
The rate of enol formation depends upon the ability of the second carboxylic acid group to catalyse the enolisation. From malonic acid to methylmalonic acid the difference in structure is the replacement of a methylene proton with a methyl group. The methyl group alters the geometry of the molecule such that the hydrogen bonded six membered ring is probably less favourable and that the carboxylic acid groups are further apart. With the acid groups further apart the intramolecular acid catalysis is somewhat more difficult. This is consistent with a decrease in the rate constant for enolisation, from malonic acid to methylmalonic acid. In table 6.10 it can be seen that there is an approximate decrease in magnitude of ten, from the k_e value for malonic acid to that for methylmalonic acid.

The ethyl group of ethylmalonic acid would be expected to cause a similar

effect upon the value of k_e , as the methyl group in methylmalonic acid, when compared to malonic acid. Again this effect can be seen in the relative magnitudes of k_e for malonic acid and ethylmalonic acid, (table 6.10). Methylmalonic acid and ethylmalonic acid have both shown a change in magnitude of k_e , from malonic acid. The effective change between methyl and ethyl groups is very small by comparison to the effective change from proton to methyl (or ethyl) group. Hence there is very little difference, as expected, in the experimentally obtained k_e values, (table 6.10).

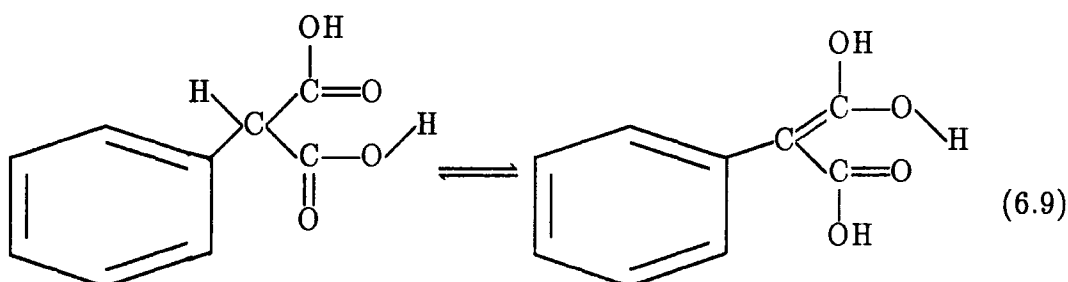
Phenylmalonic acid differs from malonic acid by the proton being replaced by the phenyl group. This is much larger than both the methyl and ethyl groups and so may be expected to cause a similar and possibly larger effect upon the acid catalysis, producing an even larger decrease in the magnitude of k_e . It is apparent, from table 6.10, that this is not the case as k_e for phenylmalonic acid appears to be slightly larger than the k_e for malonic acid. The phenyl group, unlike the methyl and ethyl groups is aromatic and unsaturated. It is possible therefore that the phenyl group has another effect upon enol formation. This effect is positive as far as enol formation is concerned and is sufficiently large to negate the steric effect discussed with methylmalonic acid and ethylmalonic acid.

Kresge and coworkers^{3,2} have shown that the presence of a phenyl group in a ketone (2-indanone) has caused an increase in k_e value for this ketone which led to a larger K_E value. This has been attributed to the enol tautomer being a fully conjugated structure and the keto tautomer not being fully conjugated, (equation 6.8).



It is possible that the effects exerted by the phenyl group of phenylmalonic acid are similar to those in 2-indanone. This enhancement of the acid catalysis results in a countering effect, against the deformation of the six membered ring

structure, which is sufficiently large for a slight increase in the k_e value for phenylmalonic acid relative to that for malonic acid. In the enol tautomer structure the enol double bond is conjugated to the phenyl group, whereas in the keto tautomer no such conjugation is present, (equation 6.9).



At high acid concentrations, for all four acid substrates, it has been shown that intramolecular acid catalysis is the dominant pathway to enol formation. As the acidity decreases (approaching the values of the first dissociation constants) there is a change in the nature of the route to intermediate formation. Acid or base catalysis are possible as is the presence of another intermediate, the enol carboxylate. Although at these lower acidities this work has been able to eliminate some of the possible reaction pathways others still fit the experimental results. Intramolecular acid catalysis is still possible and intermolecular acid and base catalysis of the enolisation, or base catalysed enol carboxylate formation all could take place. It is clear at the lower acidities studied in this work that one of the pathways is not dominant and the experimental k_e values obtained come from a combination of all of these processes, whereas at the higher acidities one reaction pathway predominates, i.e. intramolecular acid catalysed enolisation.

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CHAPTER 7

EXPERIMENTAL DETAILS

7.1 Chemical Reagents

Commercially available malononitrile was purified by sublimation and then stored in the dark below -4°C . All other substrates; ethyl cyanoacetate, diethyl malonate, malonic, methylmalonic, ethylmalonic and phenylmalonic acids were available at very high purity and used as supplied.

Sodium nitrite, thiourea and the salts used to provide nucleophilic catalysts, sodium chloride, sodium bromide and sodium thiocyanate were used as supplied. Solutions of perchloric acid were prepared by the dilution, with distilled water, of $>70\%$ perchloric acid, supplied by Aldrich. These acidic solutions were standardised against a standard solution of sodium hydroxide with phenolphthalein indicator.

The acetic acid, sodium acetate, chloroacetic acid and sodium chloroacetate used in buffer solutions were used as supplied. *n*-Butyl nitrite, used in the synthesis of oxime products was prepared by the Noyes method¹. This involved the slow addition of commercially available *n*-butyl alcohol in water and concentrated sulphuric acid, to an aqueous solution of sodium nitrite. The reaction was performed in an ice-bath, maintaining the temperature at 0°C . The alkyl nitrite was separated from the aqueous layer and purified by fractional distillation at reduced pressure (since at atmospheric pressure *n*-butyl nitrite boils with some decomposition).

Iodine and bromine solutions were made up in distilled water. Concentrations of these solutions were obtained from titration results of the halogen and added iodide, with a standard solution of sodium thiosulphate² and starch indicator.

7.2 pH measurements

All pH measurements were carried out using a PTI-6 Universal digital pH meter which has an accuracy of ± 0.02 pH units. All standard buffer solutions used were BDH buffer powders, made to specification and replaced at regular intervals.

7.3 Experimental methods used

7.3.1 U.V./Visible spectrophotometry

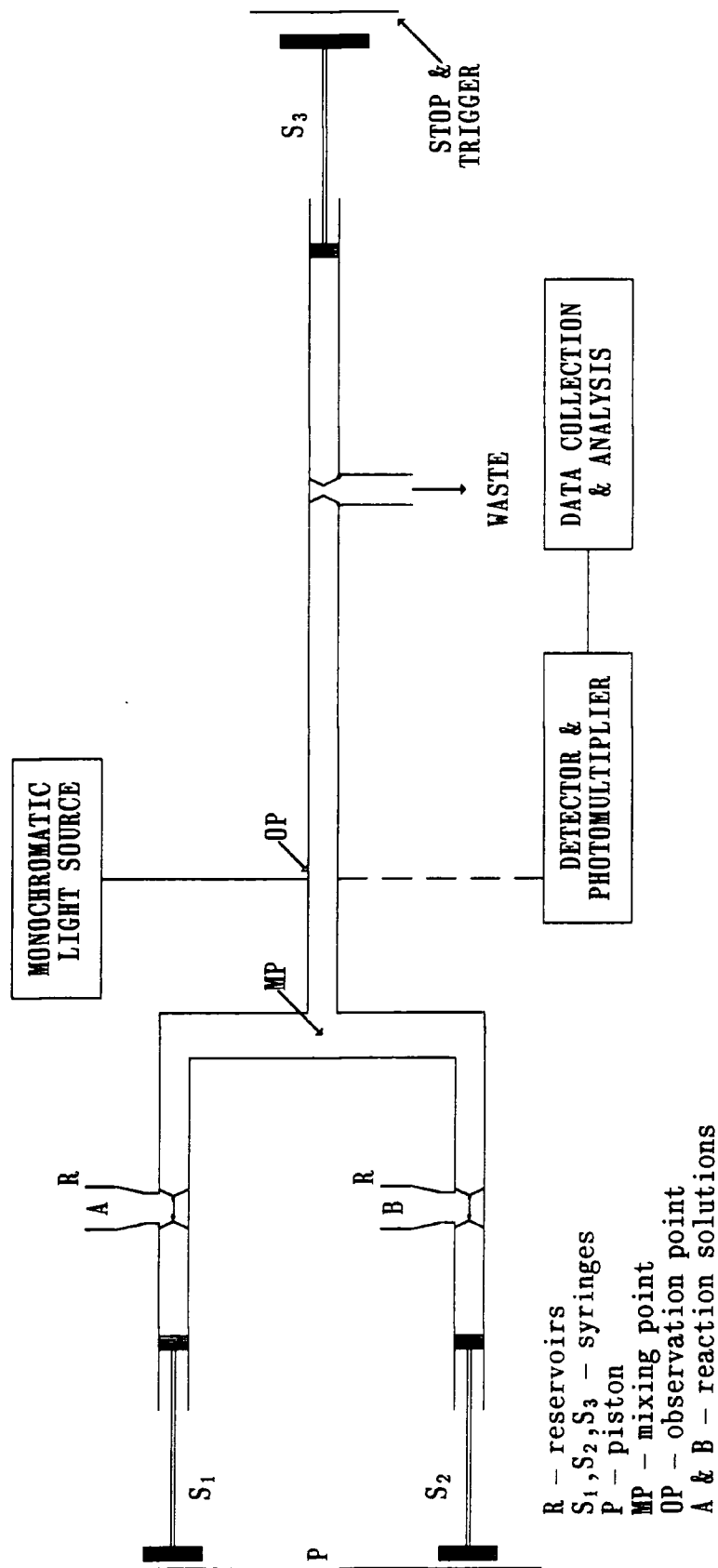
Rate measurements for the nitrosation of ethyl cyanoacetate, diethyl malonate, malonic acid, methylmalonic acid, ethylmalonic acid and phenylmalonic acid as well as the bromination of ethylmalonic acid and phenylmalonic acid, except those reactions where the half-life was less than ten seconds, were performed on conventional u.v./visible spectrophotometers. Those used were the Perkin Elmer Lambda 2 connected to an Epson PC AX2, Perkin Elmer Lambda 3 or Philips PU 8720.

The typical reaction procedure was to prepare appropriate solutions such that the required concentrations of reagents were obtained in the reaction mixture. These solutions were then thermostatted at 25° C in a water bath. A 1cm quartz cell containing solvent was used as a reference. Required volumes of reagent solutions were mixed. A portion of the reaction solution was placed in an identical quartz cell and placed in the thermostatted cell holder of the spectrophotometer. The change in absorbance, at a fixed wavelength, due to a reagent or product was then monitored as a function of time.

7.3.2 Stopped-flow spectrophotometry

Rate measurements of the iodination of malonic acid, methylmalonic acid, ethylmalonic acid and phenylmalonic acid and the bromination of malonic acid and phenylmalonic acid, except those reactions where the half-life was greater than ten seconds, were performed on a HI-TECH Scientific SF-3 series stopped-flow spectrophotometer (shown schematically in figure 7.1) connected to an Apple IIe microcomputer.

FIGURE 7.1: Schematic representation of stopped-flow spectrophotometer



The typical reaction procedure was to prepare two solutions. Typically one contained the sodium nitrite or halogen solution and the remaining components of the reaction were in the other solution. These solutions were stored in the reservoirs (R). A single piston (P) was used to drive the two syringes (S_1, S_2), thus causing equal mixing of both solutions at the mixing point (MP). The reaction solution passed on into a third syringe (S_3). Upon filling, this syringe was forced against the stop which was also the trigger. At this point the flow was stopped and the reaction monitoring commenced.

At the observation point (OP) the reaction was followed by observing the change in intensity of the beam of monochromatic light passed through the cell. The intensity of the beam is converted into an electrical signal which is amplified by the photomultiplier, across which is an accurately known voltage of approximately -6 V , known as the standing voltage. Application of an equal but opposite voltage (biasing), to the standing voltage, will give amplification, by the recording equipment, of the voltage caused by the changing absorbance in the reaction solution. Observing the voltage changes as a function of time made it possible to calculate observed rate constants. The Apple IIe microcomputer running a kinetic analysis program supplied by HI-TECH was used in the case of first order observed rate constants. For zero order rate constants the voltage variation versus time plots were analysed manually.

7.4 Determination of rate constants

7.4.1 Zero order observed rate constants

The iodination of malonic acid, methylmalonic acid, ethylmalonic acid and phenylmalonic acid under certain experimental conditions gave zero order kinetics. The reactions were followed by the disappearance of reagent with time.

The rate of formation of product, $\frac{d[P]}{dt}$, and the rate of disappearance of reagent, $-\frac{d[R]}{dt}$, for a zero order process, where R is a reagent and P a product, are independent of their respective concentrations, and can be expressed by equation 7.1

$$\frac{d[P]}{dt} = -\frac{d[R]}{dt} = k \quad (7.1)$$

Integration of equation 7.1 gives an expression for the zero order observed rate constant, (equation 7.2).

$$k_0 = \frac{1}{t}([R]_0 - [R]_t) \quad (7.2)$$

$[R]_0$ and $[R]_t$ are the concentrations of R corresponding to times $t = 0$ and $t = t$ respectively. If we consider the Beer-Lambert Law, (equation 7.3),

$$I_t = I_0 \cdot 10^{-\epsilon cl} \quad (7.3)$$

where I_t is the intensity of the transmitted beam of monochromatic light passed through a solution, I_0 is the intensity of the incident light, c is the concentration of the absorbing species and l is the solution path length. The Beer-Lambert Law is more commonly used in the form shown in equation 7.4, where A is the absorbance.

$$A = \epsilon cl = \log_{10} \left[\frac{I_0}{I_t} \right] \quad (7.4)$$

If we now assume the path length to be 1cm, then the expressions for the absorbances at times $t = 0$, $t = t$ and $t = \infty$ can be obtained, (equations 7.5, 7.6 and 7.7).

$$A_0 = \epsilon_R [R]_0 \quad (7.5)$$

$$A_t = \epsilon_R [R]_t + \epsilon_P [P]_t \quad (7.6)$$

$$A_w = \epsilon_P [P]_w = \epsilon_P [R]_0 \quad (7.7)$$

since $[P]_w = [R]_0$

However $[P]_t = [R]_0 - [R]_t$, so substituting for $[P]_t$ in equation 7.6 gives,

$$A_t = \epsilon_R [R]_t + \epsilon_P ([R]_0 - [R]_t)$$

$$A_t = \epsilon_R [R]_t + \epsilon_P [R]_0 - \epsilon_P [R]_t \quad (7.8)$$

Thus combining equations 7.5 and 7.7,

$$(A_0 - A_w) = \epsilon_R [R]_0 - \epsilon_P [R]_0$$

$$= [R]_0 (\epsilon_R - \epsilon_P)$$

$$[R]_0 = \frac{(A_0 - A_w)}{(\epsilon_R - \epsilon_P)} \quad (7.9)$$

Similarly with equations 7.7 and 7.8,

$$(A_t - A_w) = \epsilon_R [R]_t + \epsilon_P [R]_0 - \epsilon_P [R]_t - \epsilon_P [R]_0$$

$$= [R]_t (\epsilon_R - \epsilon_P)$$

$$[R]_t = \frac{(A_t - A_w)}{(\epsilon_R - \epsilon_P)} \quad (7.10)$$

Substitution of equations 7.9 and 7.10 into equation 7.2 gives equation 7.11,

$$k_0 t = \frac{(A_0 - A_\infty)}{(\epsilon_R - \epsilon_P)} - \frac{(A_t - A_\infty)}{(\epsilon_R - \epsilon_P)},$$

$$k_0 t = \frac{(A_0 - A_t)}{(\epsilon_R - \epsilon_P)} \quad (7.11)$$

A plot of $(A_0 - A_t)$ versus time will be linear for a zero order reaction, the slope of which will be $k_0(\epsilon_R - \epsilon_P)$.

Reactions followed on a conventional u.v./visible spectro-photometer were analysed by the P.E.C.S.S. (Perkin Elmer Computerised Spectroscopy Software) kinetics program. This program gave the best fit slope to the linear absorbance versus time plots. Reactions performed on the stopped-flow spectrophotometer were analysed by use of the Beer-Lambert Law and the voltage light intensity relationship, (equation 7.12).

$$\frac{I_0}{I_t} = \frac{V_0}{V_t} \quad (7.12)$$

Now V_0 is the voltage across the cell with no absorbing species present and V_t the transmitted voltage. However $V_t = V_0 - \Delta V$, where ΔV is the voltage due to the absorbing species in the cell, hence

$$\frac{I_0}{I_t} = \frac{V_0}{V_0 - \Delta V} \quad (7.13)$$

Substituting equation 7.13 into the Beer-Lambert Law we get equation 7.14.

$$A = \log_{10} \left[\frac{V_0}{V_0 - \Delta V} \right] \quad (7.14)$$

Using this conversion of the voltage change with respect to time in a reaction yielded linear ($A_0 - A_t$) versus time plots, the slopes of which gave values for k_o , (equation 7.11).

7.4.2 First order observed rate constants

The nitrosation of the series of difunctional compounds under certain reaction conditions, and the iodination of the four dibasic acids under certain reaction conditions gave first order kinetics. These reactions were followed either by the appearance of product or the disappearance of reagent with time. The rate of formation of a product, $\frac{d[P]}{dt}$, and the rate of disappearance of a reagent, $-\frac{d[R]}{dt}$, for a first order process, where R is a reagent and P a product, are equal and can be expressed by equation 7.15.

$$\frac{d[P]}{dt} = -\frac{d[R]}{dt} = k[R] \quad (7.15)$$

Integration of equation 7.15 gives an expression for the first order observed rate constant, (equation 7.16).

$$k_o = \frac{1}{t} \ln \left[\frac{[R]_0}{[R]_t} \right] \quad (7.16)$$

$[R]_0$ and $[R]_t$ are the concentrations of R corresponding to times $t = 0$ and $t = t$ respectively. Substitution of equations 7.9 and 7.10, derived from the Beer-Lambert Law, into equation 7.16 gives

$$k_o = \frac{1}{t} \ln \left[\left(\frac{A_0 - A_\infty}{\epsilon_R - \epsilon_P} \right) / \left(\frac{A_t - A_\infty}{\epsilon_R - \epsilon_P} \right) \right]$$

$$k_0 = \frac{1}{t} \ln \left[\frac{A_0 - A_\infty}{A_t - A_\infty} \right] \quad (7.17)$$

Rearrangement of equation 7.17 gives

$$\ln(A_t - A_\infty) = -k_0 t + \ln(A_0 - A_\infty)$$

A plot of $\ln(A_t - A_\infty)$ or $\ln(A_\infty - A_t)$ versus time will be linear for a first order reaction, the slope of which will be $-k_0$. The appearance / disappearance of absorbance during the reaction was followed for at least two half-lives and A_∞ , the infinity absorbance, was measured after at least ten half-lives.

For experiments carried out on the conventional u.v./visible spectrophotometer the value of k_0 was calculated using either the F.O.R.C.E. (First Order Rate Constant Evaluator) or DOS:KIN. kinetics programs. Both of these obtain the k_0 value from a plot of $\ln(A_\infty - A_t)$ versus time, in conjunction with a least squares fit and linear regression method.

Experiments performed on the stopped-flow spectrophotometer used the HI-TECH program to calculate values of k_0 . This program initially calculates a k_0 value from the slope of a $\ln(V_\infty - V_t)$ versus time plot (where V is the output voltage, and the experimental conditions used are such that the voltage is directly proportional to the absorbance). The program then uses an iterative non-linear regression analysis to optimise the value of k_0 . Due to errors in the measurements of reactions, more particularly fast reactions, the k_0 values stated for reactions are the means of at least four separate identical runs. The errors quoted are the population standard deviations from the mean.

7.5 Kinetic measurements

7.5.1 Reactions involving zero order observed rate constants

The kinetic rate measurements of reactions giving good zero order observed rate constants from $A_0 - A_t$ (or $V_0 - V_t$) versus time plots were performed on both conventional u.v./visible spectrophotometers and stopped-flow spectrophotometer using the conversion of voltages to absorbances described in section 7.4.1. The experiments were carried out by the methods explained in section 7.3. In the case of the nitrosation of methylmalonic acid the reaction was followed at 370 nm, observing the decrease in absorbance due to the nitrous acid. The iodination of the dibasic acids by iodine was followed at 459 nm, the absorbance drop here was due to the disappearance of iodine. Bromination of the same acids by bromine was followed at 393 nm, observing the absorbance decrease due to the disappearance of the bromine.

Reaction conditions were such that the concentrations of all other reagents were at least in a twenty fold excess to that of the nitrous acid, iodine or bromine in the nitrosation, iodination and bromination reactions respectively. Tables 7.1 to 7.4 show typical zero order kinetic runs and table 7.5 shows a typical set of observed zero order rate constants from which a mean k_0 value is obtained.

TABLE 7.1: Bromide ion catalysed nitrosation of methylmalonic acid.

[MMA] = 0.30M, [Br⁻] = 0.50M, [H⁺] = 1.36M,
[HNO₂] = 5.0 x 10⁻³M, followed at 370 nm

t/s	A _t	10 ⁵ k _o / mol l ⁻¹ s ⁻¹
0	0.420	—
10	0.393	4.95
20	0.362	5.32
30	0.333	5.32
40	0.303	5.37
50	0.273	5.39
60	0.242	5.44

$k_o = 5.30 (\pm 0.18) \times 10^{-5} \text{ mol l}^{-1}\text{s}^{-1}$

TABLE 7.2: Iodination of malonic acid.

[MA] = 0.10M, [I₂] = 6.01 x 10⁻⁴M, followed at 459 nm.

t/s	ΔV _t /V	10 ⁴ k _o / mol l ⁻¹ s ⁻¹
0	1.148	—
0.125	1.068	3.29
0.250	0.992	3.23
0.375	0.925	3.09
0.500	0.844	3.18
0.625	0.791	3.00
0.750	0.710	3.09
0.875	0.621	3.22

$k_o = 3.16 (\pm 0.10) \times 10^{-4} \text{ mol l}^{-1}\text{s}^{-1}$

TABLE 7.3: Bromination of methylmalonic acid in aqueous acidic solution.

$[\text{MMA}] = 0.050\text{M}$, $[\text{Br}_2] = 2.5 \times 10^{-3}\text{M}$, $[\text{HClO}_4] = 0.050\text{M}$,
followed at 393 nm.

t/s	A_t	$10^5 k_0 / \text{mol l}^{-1} \text{s}^{-1}$
0	0.372	—
15	0.342	1.56
30	0.312	1.56
45	0.278	1.63
60	0.243	1.67
75	0.210	1.68
90	0.176	1.70

$$k_0 = 1.63 (\pm 0.06) \times 10^{-5} \text{ mol l}^{-1} \text{s}^{-1}$$

TABLE 7.4: Bromination of phenylmalonic acid in aqueous acidic solution.

$[\text{PhMA}] = 0.050\text{M}$, $[\text{Br}_2] = 2.50 \times 10^{-3}\text{M}$, $[\text{HClO}_4] = 1.00\text{M}$,
followed at 393 nm.

t/s	$\Delta V_t/V$	$10^4 k_0 / \text{mol l}^{-1} \text{s}^{-1}$
0	0.924	—
1	0.850	2.00
2	0.763	2.19
3	0.707	1.98
4	0.641	1.94
5	0.560	2.01
6	0.480	2.06

$$k_0 = 2.03 (\pm 0.09) \times 10^{-4} \text{ mol l}^{-1} \text{s}^{-1}$$

TABLE 7.5: Iodination of phenylmalonic acid in aqueous acid solution.

A typical set of identical runs.

$[\text{PhMA}] = 0.050\text{M}$, $[\text{I}_2] = 5.24 \times 10^{-4}\text{M}$, $[\text{HClO}_4] = 0.050\text{M}$,
followed at 393 nm.

Run	$10^4 k_0 / \text{mol l}^{-1} \text{s}^{-1}$
1	1.595
2	1.575
3	1.609
4	1.575

Mean $k_0 = 1.589 (\pm 0.017) \times 10^{-4} \text{mol l}^{-1} \text{s}^{-1}$

7.5.2 Reactions involving a first order observed rate constant

Reactions which gave good first order observed rate constants from $\ln(A_t - A_\infty)$ or $\ln(V_t - V_\infty)$ versus time plots were performed on both the conventional u.v./visible spectrophotometers and the stopped-flow spectrophotometer. The experiments were carried out in the manner explained in section 7.3.

In the case of the nitrosation of malononitrile the reaction was followed at 310 nm, observing the increase in absorbance due to the formation of 2-oximino-1,3-propanedinitrile product. However, nitrosation of the other substrates, ethyl cyanoacetate, diethyl malonate, malonic acid, methylmalonic acid, ethylmalonic acid and phenylmalonic acid was followed at either 370 nm or 386 nm. Both wavelengths follow the decrease in absorbance due to the disappearance of nitrous acid or at 260 nm in one or two cases, following the increase of absorbance due to product formation. The iodination of the acids was followed at 459 nm for reactions with iodine, following the disappearance of iodine by the decrease in absorbance, and at 351 nm when the effective iodinating species was the triiodide anion, the decrease in absorbance corresponding to the disappearance of the triiodide anion.

Tables 7.6 to 7.9 show typical first order kinetic runs and table 7.10 shows a typical set of observed first order rate constants from which a mean k_o value is obtained.

TABLE 7.6: Thiocyanate ion catalysed nitrosation of malononitrile in an acidic dioxan/water (30/70) solution.

$[MNL] = 0.20M$, $[SCN^-] = 0.30M$, $[HNO_2] = 5.0 \times 10^{-3}M$, followed at 310 nm.

t/s	$\Delta V_t/V$	$10^2 k_o/s^{-1}$
0	0.271	—
15	0.707	2.46
30	1.009	2.47
45	1.211	2.44
60	1.330	2.32
75	1.432	2.31
90	1.508	2.33
∞	1.681	—

$$k_o = 2.39 (\pm 0.08) \times 10^{-2} s^{-1}$$

TABLE 7.7: Bromide ion catalysed nitrosation of ethyl cyanoacetate in acidic dioxan/water (30/70) solution.

$[ECA] = 0.25M$, $[Br^-] = 0.14M$, $[HNO_2] = 2.5 \times 10^{-3}M$, followed at 260 nm.

t/s	A_t	$10^5 k_o/s^{-1}$
0	0.393	—
450	0.450	5.30
900	0.505	5.27
1350	0.562	5.36
1800	0.608	5.17
2250	0.655	5.09
2700	0.699	5.01
∞	2.813	—

$$k_o = 5.20 (\pm 0.13) \times 10^{-5} s^{-1}$$

TABLE 7.8: Chloride ion catalysed nitrosation of methylmalonic acid in water.

[MMA] = 0.30M, [Cl⁻] = 0.15M, [HNO₂] = 5.0 x 10⁻³M, followed at 370 nm.

t/s	A _t	10 ⁴ k _o / s ⁻¹
0	0.307	—
375	0.277	3.50
750	0.254	3.27
1125	0.230	3.37
1500	0.213	3.24
1875	0.197	3.20
2250	0.181	3.23
∞	0.063	—

$$k_o = 3.30 (\pm 0.11) \times 10^{-4} \text{ s}^{-1}$$

TABLE 7.9: Iodination of ethylmalonic acid in aqueous acidic solution.

[EtMA] = 0.05M, [I₂] = 1.0 x 10⁻⁴M, [HClO₄] = 0.10M, followed at 459 nm.

t/s	ΔV _t /V	k _o / s ⁻¹
0	0.136	—
2.2	0.117	0.137
4.4	0.103	0.137
6.6	0.093	0.135
8.8	0.084	0.142
11.0	0.080	0.132
13.2	0.075	0.137
∞	0.063	—

$$k_o = 0.137 (\pm 0.03) \text{ s}^{-1}$$

TABLE 7.10: Nitrosation of malonic acid in water. A typical set of repeat runs.

$[\text{MA}] = 0.75\text{M}$, $[\text{HNO}_2] = 5.0 \times 10^{-3}\text{M}$, followed at 260 nm.

Run	$10^4 k_o / \text{s}^{-1}$
1	4.882
2	4.905
3	4.947
4	4.883

Mean $k_o = 4.904 (\pm 0.030) \times 10^{-4} \text{s}^{-1}$

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APPENDIX

RESEARCH COLLOQUIA, SEMINARS, LECTURES & CONFERENCES

It is a requirement of the Board of Studies in Chemistry that each postgraduate research thesis contains an appendix of:

1. all research colloquia, seminars and lectures arranged by the Department of Chemistry during the period of the author's residence as a postgraduate student,
2. lectures organised by Durham University Chemical Society,
3. all research conferences attended and papers presented by the author in the period during which research for the thesis was carried out,
4. details of the postgraduate induction course,

1. Research Colloquia, seminars and lectures organised by the Chemistry Department, Durham University, Aug. 1988 to Jul. 1991.

(* denotes lectures attended)

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|----------|--|
| 18-10-88 | Dr.J.Dingwall, (Ciba Geigy) |
| * | "Phosphorus-containing Amino Acids: Biologically Active Natural and Unnatural Products." |
| 09-11-88 | Dr.G.Singh, (Teesside Polytechnic) |
| | "Towards Third Generation Anti-leukaemics." |
| 16-11-88 | Dr.K.A.McLauchlan, (University of Oxford) |
| * | "The Effect of Magnetic Fields on Chemical Reactions." |
| 02-12-88 | Dr.G.Hardgrove, (St. Olaf College, U.S.A.) |
| | "Polymers in the Physical Chemistry Laboratory." |
| 09-12-88 | Dr.C.Jager, (Friedrich-Schiller University, Germany) |
| | "NMR Investigations of Fast Ion Conductors of the NASICON Type." |
| 23-01-89 | Dr.L.Harwood, (University of Oxford) |
| | "Synthetic Approaches to Phorbols via Intramolecular Furan Diels-Alder Reactions: Chemistry under Pressure." |
| 13-02-89 | Prof.R.R.Schrock, (M.I.T.) |
| | "Recent Advances in Living Metathesis." |

- 15-02-89 Dr.A.R.Butler, (University of St. Andrews)
"Cancer in Linxiam: The Chemical Dimension."
- 22-02-89 Dr.G.MacDougall, (University of Edinburgh)
"Vibrational Spectroscopy of Model Catalytic Systems."
- 01-03-89 Dr.R.J.Errington, (University of Newcastle-upon-Tyne)
"Polymetalate Assembly in Organic Solvents."
- 09-03-89 Dr.I.Marko, (University of Sheffield)
"Catalytic Asymmetric Osmylations of Olefins."
- 15-03-89 Dr.R.Aveyard, (University of Hull)
"Surfactants at your Surface."
- 20-04-89 Dr.M.Casey, (University of Salford)
"Sulphoxides in Stereoselective Synthesis."
- 27-04-89 Dr.D.Crich, (University College, London)
* "Some Novel Uses of Free Radicals in Organic Synthesis."
- 03-05-89 Dr.P.C.B.Page, (University of Liverpool)
"Stereocontrol of Organic Reactions Using 1,3-dithiane-
1-oxides."
- 10-05-89 Prof.P.B.Wells, (University of Hull)
"Catalyst Characterisation and Activity."

- 11-05-89 Dr.J.Frey, (University of Southampton)
 * "Spectroscopy of the Reaction Path: Photodissociation Raman Spectra of NOCl."
- 16-05-89 Dr.R.Stibr, (Czechoslovak Academy of Sciences)
 "Recent Developments in the Chemistry of Intermediate-sited Carboranes."
- 17-05-89 Dr.C.J.Moody, (Imperial College, London)
 "Reactive Intermediates in Heterocyclic Synthesis."
- 23-05-89 Prof.P.Paetzold, (Aachen)
 "Iminoboranes $\text{XB}\equiv\text{NR}$: Inorganic Acetylenes?"
- 15-06-89 Prof.J.Pola, (Czechoslovak Academy of Sciences)
 "Carbon Dioxide Laser Induced Chemical Reactions– New Pathways in Gas–Phase Chemistry."
- 17-10-89 Dr.F.Palmer, (University of Nottingham)
 * "Thunder and Lightning."
- 25-10-89 Prof.C.Floriani, (University of Lausanne, Switzerland)
 * "Molecular Aggregates– A Bridge Between Homogeneous and Heterogeneous Systems."
- 01-11-89 Dr.J.P.S.Badyal, (University of Durham)
 "Breakthroughs in Heterogeneous Catalysis."

- 10-11-89 Prof.J.E.Bercaw, (California Institute of Technology)
 * "Synthetic and Mechanistic Approaches to Ziegler-Natta
 Polymerisation of Olefins."
- 13-11-89 Dr.J.Becher, (University of Odense)
 "Synthesis of New Macrocyclic Systems Using Heterocyclic
 Building Blocks."
- 29-11-89 Prof.D.J.Cole-Hamilton, (University of St. Andrews)
 "New Polymers from Homogeneous Catalysis."
- 04-12-89 Dr.D.Graham, (British Petroleum Research Centre)
 "How Proteins Absorb to Interfaces."
- 06-12-89 Prof.R.L.Powell, (I.C.I.)
 * "The development of CFC Replacements."
- 13-12-89 Dr.J.Klinowski, (University of Cambridge)
 "Solid State NMR Studies of Zeolite Catalysts."
- 15-12-89 Prof.R.Huisgen, (Universitat Munchen)
 "Recent Mechanistic Studies of [2+2] Additions."
- 24-01-90 Dr.R.N.Perutz, (University of York)
 "Plotting the Course of C-H Activations with Organo-
 metallics."
- 31-01-90 Dr.U.Dyer, (Glaxo)
 "Synthesis and Conformation of C-Glycosides."

- 07-02-90 Dr.D.P.Thompson, (University of Newcastle-upon-Tyne)
"The Role of Nitrogen in Extending Silicate Crystal
Chemistry."
- 12-02-90 Prof.L.Lunazzi, (University of Bologna)
Application of Dynamic NMR to the Study of
Conformational Enantiomerism."
- 14-02-90 Prof.D.Sutton, (Simon Fraser University, Vancouver B.C.)
"Synthesis and Applications of Dinitrogen and Diazo
Compounds of Rhenium and Iridium."
- 21-02-90 Dr.C.Bleasdale, (University of Newcastle-upon-Tyne)
* "The Mode of Action of Some Anti-tumour Agents."
- 28-02-90 Dr.R.K.Thomas, (University of Oxford)
"Neutron Reflectometry from Surfaces."
- 08-03-90 Dr.A.K.Cheetham, (University of Oxford)
"Chemistry of Zeolite Cages."
- 21-03-90 Dr.I.Powis, (University of Nottingham)
* "Spinning Off in a Huff: Photodissociation of Methyl
Iodide."
- 23-03-90 Prof.J.M.Bowman, (University of Emory)
"Fitting Experiment and Theory to Ar-OH."

- 09-07-90 Prof.L.S.German, (U.S.S.R. Academy of Sciences, Moscow)
"New Syntheses in Fluoroaliphatic Chemistry: Recent
Advances in the Chemistry of Fluorinated Oxidiranes."
- 09-07-90 Prof.V.E.Platonov, (U.S.S.R. Academy of Sciences,
Novosibirsk)
"Polyfluoroindanes: Synthesis and Transformation."
- 09-07-90 Prof.I.N.Rozhkov, (U.S.S.R. Academy of Sciences, Moscow)
"Reactivity of Perfluoroalkyl Bromides."
- 24-10-90 Dr.M.Bochmann, (University of East Anglia)
* "Synthesis, Reactions and Catalytic Activity of Cationic
Tritium Alkyls."
- 26-10-90 Prof.R.Soulen, (South Western University, Texas)
"Preparation and reactions of Bicycloalkenes."
- 31-10-90 Dr.R.Jackson, (University of Newcastle-upon-Tyne)
* "New Synthetic Methods: α -Amino Acids and Small Rings."
- 06-11-90 Dr.P.Kocovsky, (University of Uppsala)
* "Stereo-controlled Reactions Mediated by Transition and
Non-transition Metals."
- 07-11-90 Dr.G.Gerrard, (British Petroleum)
"Raman Spectroscopy of Industrial Analysis."

- 14-11-90 Prof.T.Bell, (SUNY, Stoney Brook, U.S.A.)
* "Functional Molecular Architecture and Molecular Recognition."
- 21-11-90 Prof.J.Pritchard, (Queen Mary & Westfield College,
University of London)
"Copper Surfaces and Catalysts."
- 28-11-90 Dr.B.J.Whitaker, (University of Leeds)
* "Two Dimensional Velocity Imaging of State Selected Reaction Products."
- 05-12-90 Dr.P.G.Pringle, (University of Bristol)
* "Metal Complexes with Functionalised Phosphines."
- 13-12-90 Prof.A.H.Cowley, (University of Texas)
"New Organometallic Routes to Electronic Materials."
- 15-01-91 Dr.B.J.Alder, (Lawrence Livermore Laboratories,
California)
"Hydrogen in All It's Glory."
- 30-01-91 Prof.E.Sinn, (University of Hull)
"Coupling of Little Electrons in Big Molecules.
Implications for the Active Sites of (Metalloproteins
and Other) Macrocycles."
- 06-02-91 Dr.R.Bushby, (University of Leeds)
* "Biradicals and Organic Magnets."

- 20-02-91 Prof.B.L.Shaw, (University of Leeds)
 * 'Synthesis with Coordinated, Unsaturated Phosphine
 Ligands."
- 06-03-91 Dr.C.M.Dobson, (University of Oxford)
 * "NMR Studies of Dynamics in Molecular Crystals."
- 24-04-91 Prof.R.R.Schrock, (Massachusetts Institute of Technology)
 "Metal-ligand Multiple Bonds and Metathesis Initiators."
- 25-04-91 Prof.T.Hudlicky, (Virginia Polytechnic Institute)
 "Biocatalysis and Symmetry Based Approaches to the
 Efficient Synthesis of Complex Natural Products."
- 20-06-91 Prof.M.S.Brookhart, (University of North Carolina)
 "Olefin Polymerisations, Oligomerisations and
 Dimerisations Using Electrophilic Late Transition Metal
 Catalysts."
- 29-07-91 Dr.M.A.Brimble, (Massey University, New Zealand)
 * "Synthetic Studies Towards the Antibiotic Griseusin-A."

2. Lectures organised by Durham University Chemical Society, Aug. 1988 to Jul. 1991.

(* denotes lectures attended)

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| 06-10-88 | Prof.R.Schmutzler, (Technische Universitat Braunschweig) |
| * | "Fluorophosphines Revisited. New Contributions to an Old Theme." |
| 18-10-88 | Dr.C.J.Ludman, (University of Durham) |
| * | "The Energetics of Explosives." |
| 21-10-88 | Prof.P.Von Rague Schleyer, (Universitat Erlangen,
Nurnberg) |
| * | "The Fruitful Interplay Between Calculational and Experimental Chemistry." |
| 27-10-88 | Prof.C.W.Rees, (Imperial College, London) |
| | "Some Very Heterocyclic Compounds." |
| 10-11-88 | Prof.J.I.G.Cadogan, (British Petroleum) |
| * | "From Pure Science to Profit." |
| 24-11-88 | Dr.R.R.Baldwin & Dr.R.W.Walker, (University of Hull) |
| * | "Combustion: Some Burning Problems." |
| 01-12-88 | Dr.R.Snaith, (University of Cambridge) |
| * | "Egyptian Mummies: What, Where, Why and How?" |

- 26-01-89 Prof.R.R.Jennings, (University of Warwick)
* "Chemistry of the Masses."
- 02-02-89 Prof.L.D.Hall, (Addenbrooke's Hospital, Cambridge)
* "NMR- A Window on the Human Body."
- 09-02-89 Prof.J.E.Baldwin, (University of Oxford)
* "Recent Advances in the Bioorganic Chemistry of Penicillin Biosynthesis."
- 16-02-89 Prof.B.J.Aylett, (Queen Mary College, London)
* "Silicon Based Chips: The Chemist's Contribution."
- 23-02-89 Dr.B.F.G.Johnson, (University of Cambridge)
* "The Binary Carbonyls."
- 09-11-89 Prof.N.N.Greenwood, (University of Leeds)
* "Novel Cluster Geometries in Metalloborane Chemistry."
- 16-11-89 Dr.D.Parker, (University of Durham)
"Macrocycles, Drugs and Rock 'n' Roll."
- 30-11-89 Dr.M.N.Hughes, (King's College, London)
* "A Bug's Eye View of the Periodic Table."
- 07-12-89 Dr.A.R.Butler, (University of St. Andrews)
* "The discovery of Penicillin: Fact or Fancies."
- 01-02-90 Prof.J.H.Holloway, (University of Leicester)
* "Noble Gas Chemistry."

- 08-02-90 Rev.R.Lancaster, (Kimbolton Fireworks)
 * "Fireworks- Principles and Practice."
- 15-02-90 Prof.L.Crombie, (University of Nottingham)
 "The Chemistry of Cannabis and Khat."
- 22-02-90 Prof.D.T.Clark, (I.C.I., Wilton)
 * "Spatially Resolved Chemistry (Using Natures Paradigm) in
 the Advanced Materials Arena."
- 01-03-90 Dr.J.F.Stoddart, (University of Sheffield)
 * "Molecular Lego."
- 11-10-90 Dr.W.A.MacDonald, (I.C.I., Wilton)
 "Materials for the Space Age."
- 01-11-90 Dr.N.Logan, (University of Nottingham)
 * "Rocket Propellants."
- 08-11-90 Dr.S.K.Scott, (University of Leeds)
 "Clocks, Oscillations and Chaos."
- 29-11-90 Prof.D.Crout, (University of Warwick)
 * "Enzymes in Organic Synthesis."
- 17-01-91 Dr.P.Sarre, (University of Nottingham)
 "Comet Chemistry."

- 24-01-91 Dr.P.J.Sadler, (Birkbeck College, University of London)
* "Design of Inorganic Drugs: Precious Metals,
Hypertension and HIV."
- 31-01-91 Dr.D.Lacey, (University of Hull)
* "Liquid Crystals."
- 14-02-91 Dr.M.C.Petty, (University of Durham)
* "Molecular Electronics."
- 28-02-91 Dr.J.Brown, (University of Oxford)
* "Can Chemistry Provide Catalysts Superior to Enzymes?"
- 07-03-91 Dr.J.Markam, (I.C.I. Pharmaceuticals)
* "DNA Fingerprinting."

3. Conferences and courses attended and papers presented.

European Symposium on Organic Reactivity II, University of Padova, Italy, 27th August to 1st September 1989. Co-author on a paper presented by Prof.D.L.H.Williams.

Royal Society of Chemistry, Organic Mechanisms Group, Postgraduate Conference, I.C.I. Blackley, 1st October 1990. Paper presented, "Enol and Carbanion Intermediates in C-Nitrosation."

Postgraduate Winter School on Organic Reactivity, Bressanone, Italy, 11th to 20th January 1991.

Royal Society of Chemistry Graduate Symposia,
University of Durham, April 1989,
University of Newcastle-upon-Tyne, April 1990,
University of Newcastle-upon-Tyne, May 1991, paper presented, "Enols Derived From Carboxylic Acids as Reaction Intermediates."

4. First year postgraduate induction course, October 1988.

The course consisted of a series of one hour presentations on the services available within the department.

- (i) Departmental organisation
- (ii) Safety matters
- (iii) Electrical appliances and infrared spectroscopy
- (iv) Chromatography and microanalysis
- (v) Library facilities
- (vi) Mass spectroscopy
- (vii) Nuclear magnetic resonance spectroscopy
- (viii) Glassblowing techniques

