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ENOLS AS INTERMEDIATES IN NITROSATION AND HALOGENATION OF MALONAMIDE AND MALONIC ACID

by

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碩士論文

夏　玲

To my husband, mum and dad

MEMORANDUM

The work for this thesis has been carried out in the Department of Chemistry at the University of Durham between May 1991 and December 1992. It is the original work of the author unless otherwise stated. None of the work has been submitted for any other degree.

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To my supervisor, Professor D.L.H.Williams, I am deeply indebted not only for providing me with financial support, but also for all of his instruction, encouragement and kindheartedness.

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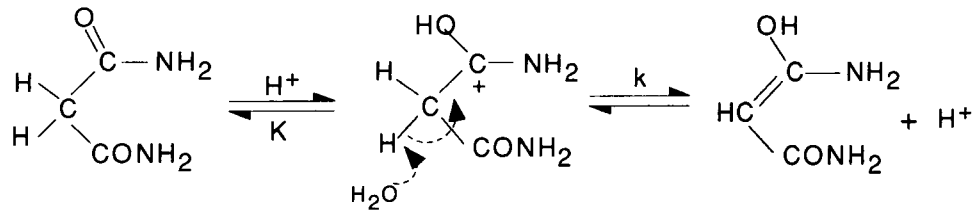
ENOLS AS INTERMEDIATES IN NITROSATION AND HALOGENATION OF MALONAMIDE AND MALONIC ACID

LING XIA

ABSTRACT

Catalysed nitrosation of malonamide(MA) was carried out in aqueous acidic solution at 25°C. In the presence of bromide ion as a catalyst, the reaction was always first order in [HNO_2] despite the changes in acidity. However, the kinetic behaviour of SCN^- catalysed reaction varied from first order to zero order with [SCN^-], suggesting that the reaction occurs via an enol intermediate and the rate limiting step can move from enolisation to nitrosation under certain conditions.

Iodination and bromination of malonamide were investigated in aqueous acidic solution at 25°C. At low acidity, the iodination of malonamide was zero order in [I_2], which is in good agreement with the proposed mechanism where the reaction occurs via an enol intermediate and enolisation is the rate limiting step. The deuterium isotope effect on iodination of malonamide was also examined and the result strongly confirmed the existence of enol form in the reaction. The acid catalysed enolisation can be expressed as follows:



$k_1 = Kk$ (k_1 - enolisation rate constant)

At higher acidity and lower $[I_2]$ reaction was first order in $[I_2]$, when now iodination of the enol is rate limiting. When enolisation is rate limiting the rate equation was established as:

$$Rate=k_{obs}=k_1[H^+][MA]$$

The values of enolisation rate constant k_1 ($3.72(\pm0.4)\times10^{-3}$ $l.mol^{-1}.s^{-1}$) is significantly larger than that measured for simple ketones such as acetone (3.8×10^{-5} $l\cdot mol^{-1}\cdot s^{-1}$), reflecting the greater acidity of the central hydrogen atom in malonamide structure brought about by the second $-CONH_2$ group or possibly the greater concentration of the O-protonated intermediate. Bromination was perfectly first-order in $[Br_2]$ at all acidities. Attempts to achieve rate-limiting enolisation by increasing $[Br_2]$ were only partially successful. Perfect zero order behaviour could not be obtained. A possible explanation is that dibromination occurs in the reaction.

By combination of the above three reactions, K_E the equilibrium constant of enolisation of malonamide was estimated as $4(\pm2)\times10^{-10}$, with an assumption that the rate limiting step of electrophilic addition occurs at the encounter limit.

The bromination of malonic acid (MAL) was studied under pH 1.0-4.65 at 25°C. The reaction was zero order in $[Br_2]$ and the plots of $k_0/[MAL]_T$ vs $[MAL]_T$ were linear, implying that the enolisation reaction is via the malonate ion catalysed pathway.

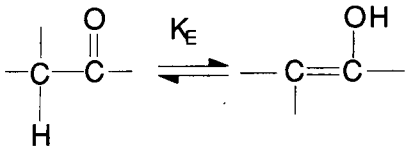
CONTENTS

CHAPTER 1

INTRODUCTION

1.1. Enolisation

Enols as the isomers of aldehydes and ketones are essential intermediates in many carbonyl compound reactions such as halogenation, alkylation, nitrosation and condensation. A number of biological reactions also involve enol formation. Enolisation or enol formation has long been of interest as an example of tautomeric rearrangement, in which a proton is transferred from a carbon atom to a heteroatom as shown in equation 1.1.



(1.1)

Since the pioneer work of Lapworth (1904)[1] who first suggested that enol formation was rate limiting in ketone halogenation, a large number of papers on enolisation have appeared. As enol formation involves proton transfer, the early works in this area played an important role in the development of the ideas on the mechanism of acid-base catalysis[2,3]. Since the 1970s, not only the relative stable enols formed by dicarbonyl compounds such as ß-diketones, ß-keto esters which produce the stabilised enols have been widely studied, but with the advances of the methodology on enol determination the studies on those simple enols also become very active. Most recent reviews deal with the investigations on the properties of enols by theoretical calculation and thermodynamic methods, on the methods of enol determination, on the structures of enols in gaseous phase, and on the kinetics and mechanism of enolisation and keto-enol equilibrium[4].

A large amount of data on keto-enol equilibrium are seen in the literature and textbooks. However, due to the limitations in the techniques of enol determination, until very recently reliable data were only obtained for some

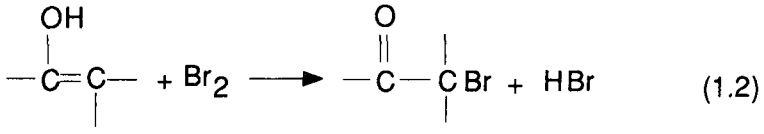
dicarbonyls or other compounds which contain relatively high proportions of the enol form.

Recently, there has been much interest in chemistry of enols derived from carbonyl group-containing compounds other than ketones, including carboxylic acids and esters[5,6,7]. However, there is only a very limited information on the enols derived from amides. In this work, the enolisation of malonamide has been investigated by means of kinetic study of its nitrosation, halogenation and of isotopic exchange. This is the first work involving the search, by kinetic technique, for the enol form of malonamide.

1.2. Methods for the determination of keto-enol equilibrium constants or enol contents

The determination of enol content and keto-enol equilibrium constants has been at the centre of the study on the chemistry of enols. It is generally based either on titration by halogen or on spectroscopic analysis by various techniques such as NMR, UV, IR and MS. These techniques have been studied for a long time and greatly advanced by the development of modern instrumentation. Some other techniques such as HPLC, GC and photochemical methods have also been developed for enol determination. Indirect determination through kinetic studies also becomes an efficient way to obtain keto-enol equilibrium constant in some cases.

The earliest report for the determination of enol content goes back to Meyer's pioneering work in 1911[8], which consisted of titrating the enol content of a ketone directly with a standard bromine solution according to equation 1.2.



(1.2)

However, this method suffers from some disadvantages. For instance, the end point is sometimes not sharp enough for observation due to the catalytical effect of hydrogen bromide on enolisation or due to the requirement that the keto-enol transformation needs to be much slower than bromination. This method was improved by working at low temperature[9] or by using the indirect titration[10]. Schwarzenbach and Wittwer[11] modified it by using a flow technique and potentiometric measurement of bromine uptake. Gero[12] chose the most polar halogen, i.e. iodine monochloride, instead of bromine in order to speed up the reaction of halogenation. Later amperometric[13] and spectroscopic[14] methods were used to titrate the enol. But the titration methods are only suitable for the determination of relatively high enol contents (>1%)[15] and are unable to distinguish between enol and other fast-reacting species.

With the development and use of new techniques to analyse keto-enol equilibrium or enol content, many of the early values of enol content obtained by titration method have been questioned, and the values for those monoketones have been found to be in error. For example, NMR measurements done by Allinger[16] *et al* have shown that the enol contents reported by Gero are much too high. Hine and Arata[17] found that the relevant values reported by Bell for cyclopentanone and cyclohexanone are not as expected if the ring size effect is considered.

In the past 30 years, NMR has been a powerful tool to investigate the structure of enols and determine the keto-enol equilibrium constants. This method is not only suited in condensed phase[18] but also in gas phase[19]. Many dicarbonyls, tricarbonyls and some monocarbonyls containing high enol content (>1%) have been analysed by this method, and a large number of NMR data have been reported in detail[4]. However, in the early work, the fact that any solvent effect on the enol content was ignored caused some results to be brought into question. Only recently were reliable data obtained. For example,

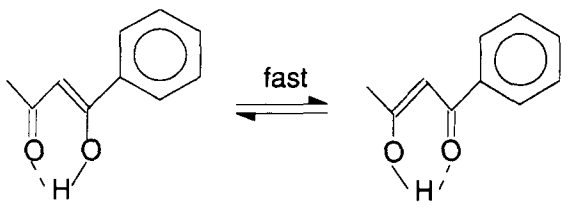
table 1 gives a comparison of enol content presented by different authors. Although the results by bromination titration[20] are comparable with those by Jarrett and coworkers[21], concentration of the samples and solvent used were not given. Bassetti and coworkers[22] used samples of 0.05 molar solution of chloroform-d ($CDCl_3$) and dimethylsulfoxide-d_6 (DMSO) at 40°C and obtained more accurate result.

Table 1. Comparison of enol content obtained by different methods

	Enol Content (%)			
compounds	bromination titration	^{1}H HMR by Jarrett	^{1}H HMR by Bassetti	
2,4-pentanedione	76	85	83.5*	55.7**
3-methyl-2,4-pentanedione	31.5	30	40*	21.5**

* CDl_3 as solvent ** DMSO as solvent

^{17}O NMR and ^{13}C NMR methods are very efficient in dealing with the determination of the question of regioselectivity, as in the case of ß-dicarbonyls. For example, Lazaar and Bauer[23] succeeded in distinguishing regiosomeric enols 1a and 1b in equation 1.3 by ^{13}C NMR and estimated the ratio of 1a and 1b.



1a 1b (1.3)

Although NMR has been widely used to study keto-enol equilibria, other methods such as IR, UV absorption spectroscopy, mass spectroscopy and

photochemical method show their own advantages. UV spectrophotometry enables the measurement of a small quantity of enol because of the higher UV absorption by the enol than by the keto tautomer at λ_{max}. Many ß-diketones[24], ß-ketoesters[25], ß-ketoamides[26] and α-diketones[27] have been measured by the UV method. Recently, Moriyasu[28] attempted to use HPLC to study keto-enol tautomerism of aliphatic and alicyclic ß-dicarbonyl compound at low temperature (-20 to 50°C) and obtained satisfactory results. Hence this method seems worth development.

Kinetic data for simple enols are not always available from direct measurement due to experimental difficulties. Indirect kinetic determinations have provided an efficient way of estimating keto-enol equilibrium constant K_E. Dubois and Toullec[29] used an approach based on the kinetic study of the acid-catalysed halogenation of acetone, diethylketone and di-isopropylketone under low halogen concentrations. At the conditions where the rate limiting step is halogen addition, the apparent rate coefficients K_{II} ($K_{II}=K_E k_2$, where K_E is the keto-enol equilibrium and k_2 is the rate constant for halogen addition) for iodination, bromination and chlorination are approximately equal. Therefore the K_E values were calculated on an assumption of encounter-controlled addition of halogen to the enol. The enol content of simple carbonyl compounds in water have also been estimated by Guthrie through this approach. Another indirect method to estimate K_E is based on determining the rate constants of enolisation and of ketonisation ($K_E=k_{enol}/k_{keto}$). The rate constants of enolisation can be obtained by direct method or the kinetic study of halogenation and nitrosation. However, estimating the rate constants of ketonisation depended on some assumptions in the early years. Guthrie and coworkers[30] proposed an assumption that the rate constant for acid-catalysed ketonisation of enol is the same as that for acid-catalysed hydrolysis of the corresponding enol ether. The equilibrium constant for enolisation can be calculated as the ratio of the rate constant of enolisation to that of hydrolysis. In

the same year, they reported a thermochemical method based on thermodynamic determination of the Gibbs free energy change for enol ether formation[31]. Although these two independent methods of estimation have led to concordant results which usually corresponded to a much lower enol content than those obtained by halogen titration, a number of problems were not solved, especially the doubt on the assumption that the enol ketonisation rate constants are equal to those of enol ether hydrolysis.

In the last 10 years, modern flash photolytic methods[32] have been developed to determine keto-enol equilibrium constant. These methods are based completely on experimentally determined quantities and so the results are believed to be more reliable.

To make a comparison, a group of pK_E values of acetophenone obtained by different methods are given in Table 2.

Table 2. pK_E values of acetophenone obtained by different methods

A	B	C	D	E
3.46	6.7±1.0	6.6	8.15±0.30	7.90±0.02

A — halogen titration[33]

B — thermodynamic method[31]

C — a kinetic method on the assumption about enol ethers[30]

D — a kinetic method on the assumption about encounter controlled process[34]

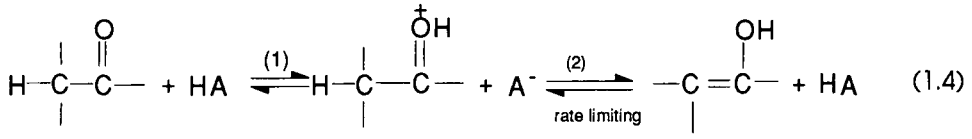
E — flash photolytic method[35]

1.3. The mechanism of enolisation

Enol and enolate ions are essential intermediates in many important carbonyl compound reactions. Studies of enolisation have played a fundamental role in the development of the ideas on acid base catalysis. Until now, catalysis of enolisation has been one of the most thoroughly studied of all organic catalytic processes.

Investigation of the mechanism of enolisation for carbonyl compounds often involves rate studies. Most kinetic studies have made use of the property that the enolisation is the rate limiting step of some stepwise reactions under certain conditions. The process of interconversion between keto and enol form have been known to involve acid and base catalysis since the pioneering work of Lapworth[1] who reported that the acid catalysed halogenation of acetone is zero order with respect to halogen and suggested that enol formation of acetone was rate limiting and was followed by fast reaction of the halogen with the enol. Dawson and coworkers[36] examined the effect of weak acids and bases and realised that the enolisation is catalysed not only by the hydronium and hydroxide ions but also by general acids (carboxylic acids) and general bases (carboxylate ions). Later, Bell and coworkers[2,37] developed the ideas in the examination of the mechanism of acid-base catalysis. So far, many papers concerning general acid and base catalysis for enolisation have been documented. For instance, in the early work, Bell and Lidwell[37] only studied the catalysis by four aliphatic carboxylate bases in the enolisation of acetone. Recently, Venimadhavan and coworkers[38] have re-examined the results of Bell and Lidwell and greatly extended their series of acids and bases which included a considerable number of dicarboxylic acid dianions. Shelly and coworkers[39] studied arylphosphonic acid, arylphosphonate dianions and more than 60 other acids as catalysts for enolisation of acetone.

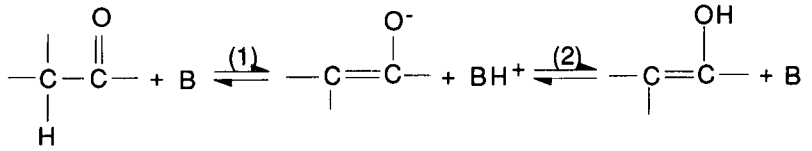
The conversion from keto to enol form with general acid catalysis is a two step process as shown in equation 1.4, which was originally suggested by Pedersen[40].



(1.4)

The process includes an initial rapid formation of a hydroxycarbonium ion, the conjugate acid of ketone, followed by α-H^+ elimination. The second step is the rate limiting step. The possibility that the first step is the rate limiting step has been ruled out. Some evidences confirming this mechanism have been presented by Lienhard and Wang[41], Dubois and Toullec[42]. The substrate isotope effect such as k_H/k_D=8 for acid catalysed enolisation of acetone also indicated that the oxygen-hydrogen bond breaking is the rate limiting step[43]. In addition, the Bronsted correlation has been used to establish the nature of the rate limiting step in the two-step acid catalysed enolisation[44].

The general base catalysed reaction is also a two step process (equation 1.5).



(1.5)

The first step is rate limiting proton removal to give an enolate ion. The fact that similar K_E values are obtained for both the acid and base catalysed system strongly supports the mechanism[45,46]. If the second step were rate limiting, enolate rather than enol would react with scavenger and cause differences in K_E values compared with those measured in the acid catalysed reactions.

In addition to the intermolecular catalysis, intramolecular catalysis also exists for the enolisation of some compounds. The enolisation of a number of

aliphatic ketones such as levulinic acid[44], aminoketones and their N-methylated derivatives[47], and O-acylbenzoic acid[48] have been investigated. Sufficient data indicate that their enolisation was through intramolecular catalysis. This intramolecular catalysis usually happens within compounds which contain acidic and basic groups at certain positions to the carbonyl group in the same molecule. These acidic or basic groups may function as catalysts as the external acids and bases do in the intermolecular catalysis.

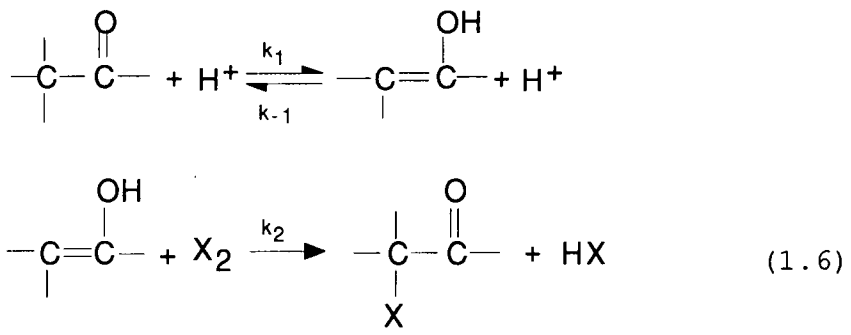
1.4. Halogenation of enols

When the keto form is converted to the enol or enolate, the latter become the reactive forms in which electrophilic addition can occur.

Halogenation is one of the best known examples of electrophilic addition reaction on enol or enolate. Halogenation can be carried out directly by the halogen molecule X_2 and the trihalide species X_3^- in acid or by X_2, X_3^-, OX^- in base due to hydrolysis of halogen. Halogen molecules are the most widely used reagents.

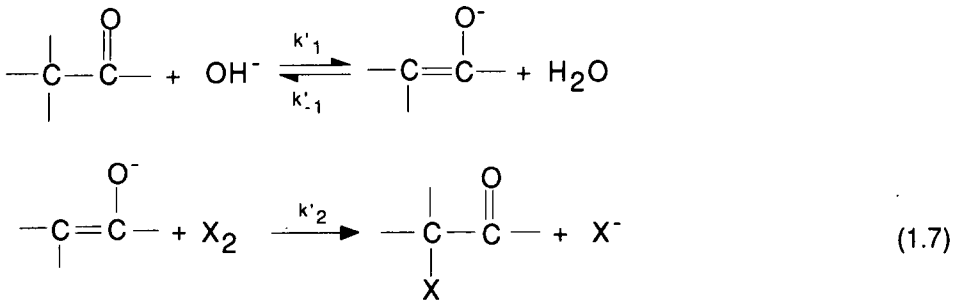
Halogenation of ketones in acid and base solution is well known to proceed by the pathway shown in equations 1.6 and 1.7. In addition, the electrophilic addition of halogen to the enol or enolate has also been known to be a two step process, as in the example of equation 1.8.

in acid solution:

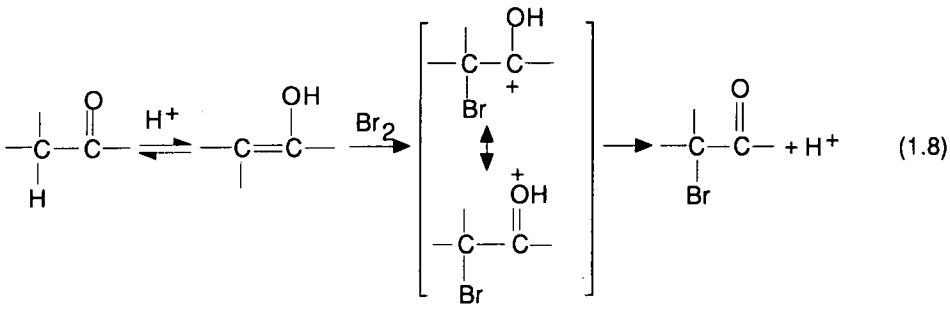


(1.6)

in base solution:

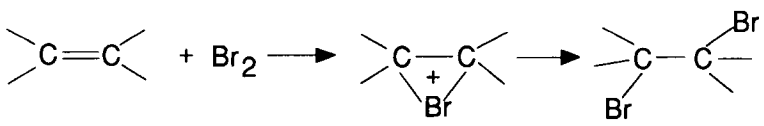


(1.7)



(1.8)

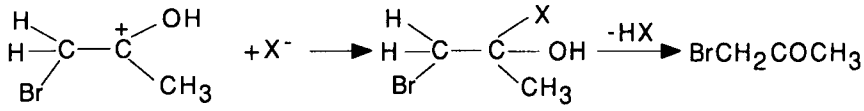
In equation 1.8, the keto form transfers to enol form with acid catalysis. The positive end of the polarised bromine molecule attacks the double bond of enol to form a brominated carbonium ion, and then the loss of a proton from oxygen yields the neutral α-substitution product. The intermediate is different from the bromonium ion occurring in the electrophilic addition of olefins by bromine[49] as shown in equation 1.9.



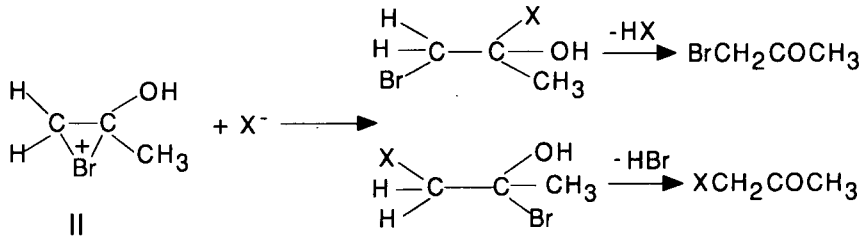
(1.9)

Evidence supporting the idea that the intermediate is the brominated carbonium ion rather than bromonium ion was first presented by Yates and Wright[50] while they were studying the kinetics and products of the bromination of

acetone in dilute aqueous acid. They thought that the two different intermediates would cause different products if the reaction is carried out in the presence of a nucleophile X^- as shown in equations 1.10 and 1.11.

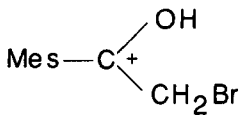


I (1.10)



II (1.11)

Brominated carbonium ion I only gives rise to bromoacetone whereas bromonium ion II could add X^- at either carbon to produce a mixture of bromoacetone and X-acetone. But actually only bromoacetone was observed, thus the intermediate is probably the brominated carbonium ion. Recently, enolisation of a Grignard reagent[51,52] was studied, which involved acid-catalysed bromination of some hindered alkyl aryl ketones such as 2,4,6-trimethylacetophenone[53], and it was also proposed that a carbocation (equation 1.12) instead of a bromonium ion was the intermediate for the reaction of the enol with bromine. This conclusion is consistent with the mechanism proposed by Yates and Wright (equations 1.10 and 1.11).



(1.12)

As for acid catalysed halogenation, the steady state assumption gives the following reaction rate law (equation 1.13):

$$\frac{d[P]}{dt} = \frac{k_1 k_2 [keto][X_2][H^+]}{k_{-1}[H^+] + k_2[X_2]} \qquad (1.13)$$

When the halogen concentration is high and $k_{-1}[H^+] << k_2[X_2]$, the above expression reduces to equation 1.14, implying that the rate limiting step is enolisation.

$$\frac{d[P]}{dt} = k_1[keto][H^+] \qquad (1.14)$$

The evidence which shows that the reaction is zero order in halogen and first order in $[H^+]$ well supports the assumption. The rate constants of enolisation for many keto substrates have been determined based on this assumption[54-56].

The rate limiting step could shift from enolisation to the halogenation of enol if (1) an inactive halogenating agent were used whose rate of attack on the enol was slow[57]; (2) the concentration of halogenation agent was made very low[58] and (3) the level of acidity was increased[59] to make the keto-enol equilibration rapid. The rate law could therefore change to equation 1.15. The phenomenon has been observed by changing the halogen and the H_2SO_4 concentration[60].

$$\frac{d[P]}{dt} = \frac{k_1}{k_{-1}} k_2 [keto][X_2] \qquad (1.15)$$

In the past decades, there has been much interest in chemical reactions that occur with rates at or near the diffusion-controlled limit in solution. One of these possible processes, addition of halogen to simple ketones, has been studied by examining acid catalysed and base catalysed halogenation of the corresponding carbonyl compounds in aqueous solution at very low halogen

concentration where the halogenation step is rate limiting. Dubois and Toullec[61] studied the kinetics of the bromination, chlorination and iodination of acetone at low halogen concentration (10^{-7} to 10^{-5}M) and found that the enol halogenation rate constants k_{obs} ($k_{obs}=K_E k_2$) were approximately equal. This result was attributed to diffusion controlled kinetics and led to the new values of K_E of acetone in solution ($1.5x10^{-8}$), which was based on the diffusion controlled value (10^9 $M^{-1}S^{-1}$) of the enol halogenation rate constant. The K_E values is much smaller than that ($2.5x10^{-6}$) obtained by Schwarzenbach[11] by the flow method, but is likely to be more reliable. Later, Dubois and Toullec applied this method to the determination of K_E values of other simple ketones[62], cycloalkanones[63], and ring-substituted acetophenones.

More accurate values of K_E were determined by using flash photolytic method. The new values of rate constants for enol halogenation calculated on the new K_E values were slightly lower than the diffusional limit[64]. This implies that the substrate structure has some effect on the rate constant of halogenation. Nevertheless, the Dubois-Toullec approach can be considered qualitatively correct.

Base catalysed halogenation of ketone in buffered alkaline solution has been studied despite the instability and complexity of the halogenating species in alkaline solution[65]. Bartlett[66] has determined the rate constants of the chlorination of ketones at pH 11, and the reaction of hypobromite with acetone has also been examined in alkaline solution[67]. Guthrie and coworkers[68] determined the rate constants for hypobromite and hypochlorite reaction with acetone in alkali and estimated the K_E of acetone. Tapuli and Jencks[69] have examined the kinetics of iodination and bromination of acetone in basic aqueous solution buffered with trifluoroethanol under conditions at which halogenation of the enolate ion is the rate limiting step. With the assumption of diffusion controlled halogenation of the enolate ion by I_2 and HOBr with k= $5x10^9$ M^{-1} S^{-1}, rate constants for other halogenating agents such as BrO^-, IO^-, IOH and I_3^-

were calculated. Their results are similar to those obtained by Guthrie and coworkers.

1.5. C-nitrosation involving enol

Nitrosation is a reaction introducing -NO bound to nitrogen, oxygen, carbon or sulphur atom in some molecules. This process involves electrophilic attack like halogenation. The reaction of nitrosation has been studied for more than one century. Piria in 1846[70] and Hofman in 1850[71] nitrosated aliphatic primary amines and aromatic amines, respectively. In 1873[72], Victor Meyer paid first attention to nitrosation at carbon, and produced nitrolic acids from aliphatic nitrocompounds. Since then nitrosation chemistry including synthesis of nitrosation products and mechanisms of these reactions has been well examined. Now many nitrosation reactions have become standard procedures both in the laboratory and on the industrial scale. For instance, ε-caprolactam is produced by the nitrosation of cyclohexane derivatives[73] and alkyl nitrites, and metal nitrosyl complexes are used as vasodilators in medicine[74].

In the early work, main interest lay in N-nitrosation. Later, the area extended to O-nitrosation and S-nitrosation. More recently, much interest has focused on the kinetic study of C-nitrosation.

1.5.1. Nitrosating species

Nitrous acid is the most widely used reagent in nitrosation. Solution of nitrous acid can be routinely made from the combination of sodium nitrite (or any other nitrite salt) and aqueous mineral acids. Nitrous acid is a weak acid with a pK_a of 3.148 at 25°C[75]. In the presence of acid, aqueous nitrous acid decomposes quite readily (equation 1.16). This is the reason why the solutions need to be used immediately.

$$3HNO_2 \rightleftharpoons 2NO + HNO_3 + H_2O \qquad (1.16)$$

It is noted that molecular nitrous acid itself is not a nitrosating agent. Effective nitrosating agents come from its equilibrium products, which vary with acidity. One equilibrium involves the formation of dinitrogen trioxide N_2O_3 (equation 1.17). The other includes the production of nitrosonium ion NO^+ (equation 1.18). These products are the true nitrosating species.

$$2HNO_2 \rightleftharpoons N_2O_3 + H_2O \qquad (1.17)$$

$$H_3O^+ + HNO_2 \rightleftharpoons NO^+ + 2H_2O \qquad (1.18)$$

The addition of non-basic nucleophilic species such as halide ion (X^-)[76] to the acidic nitrous acid solution leads to another equilibrium (equation 1.19). The nitrosyl species XNO acts as the nitrosating agent.

$$HNO_2 + H_3O^+ + X^- \rightleftharpoons XNO + 2H_2O \qquad (1.19)$$

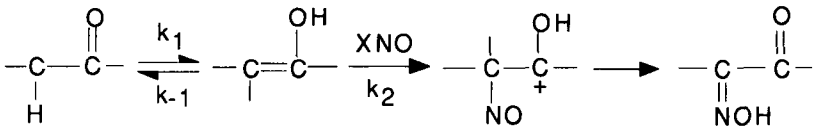
1.5.2. Nitrosation of ketones, acids and esters

It has long been known that ketones react with a variety of nitrosating agents to give rise to nitroso ketones or keto oximes, depending on whether the substituted group is a primary or secondary structure (equation 1.20).

$$MeCOCHR'R'' \xrightarrow[HNO_2]{H^+} MeCOCR'R'' \quad (NO) \xrightarrow{\text{If } R'=H} MeCOCR'' \quad (NOH) \qquad (1.20)$$

The reaction is quite general and occurs very readily at room temperature when using nitrous acid, alkyl nitrites, nitrosyl halides or dinitrogen trioxide.

Although the nitrosation of ketone has been widely used for synthesis process, the studies on the reaction mechanisms started only in the past decade. Recently there is much experimental evidence[77] showing that nitrosation of ketones occurs via their enol or enolate form. The corresponding mechanism is outlined in equation 1.21.



(1.21)

The reaction is analogous to halogenation. Features such as acid catalysis, base catalysis, diffusion controlled processes and rate limiting process have been established in nitrosation reaction under various experimental conditions. For instance, in aqueous acid solution, nitrosation of acetone and ethyl methyl ketone in the presence of Cl^-, Br^- or SCN^- is first order in [Ketone] and $[H^+]$ and zero order in $[HNO_2]$ as well as in $[Cl^-]$, $[Br^-]$ and $[SCN^-]$, indicating that the reaction occurs by nitrosating the enol form of the ketone and enolisation is rate limiting. The rate constant of enolisation in the nitrosation experiment is in excellent agreement with those obtained earlier from the kinetics of halogenation and of hydrogen-isotope exchange. With lower concentration of halide ion the reaction is first order in $[HNO_2]$, $[Cl^-]$ and $[Br^-]$, indicating that the reaction of enol with the nitrosating species is now rate limiting. Analysis of the kinetic data reveals the reactivity sequence NOCl> NOBr> NOSCN as expected. In the absence of added nucleophiles, both the pathways via N_2O_3 and $H_2NO_2^+/NO^+$ have been identified kinetically from the kinetic order with respect to $[HNO_2]$.

Nitrosation occurs not only via the enol but also the enolate depending on the types of solvent, the acidity of the medium and the structure of substrate[78].

Dimedone[79] as a cyclic diketone was studied. The kinetic data confirmed the existence of enol and enolate as intermediates, and their ratio varied with the acidity of the medium. At 0.01M H^+, 60% of the reaction occurs via the enolate whereas at 0.1M H^+, this drops to *ca.*13%. In this case, the enolate is much more reactive than enol, and the former reacts in an encounter controlled process when ClNO and BrNO were used as nitrosating species. Similar results were obtained for the reaction of the enolate ion derived from 1,1,1-trifluoropentane-2,4-dione.

Many carbonyl-containing compounds other than ketones such as ß-ketoacids[80], ß-ketoesters[81], malonic acid[82] and esters[83] also react readily with a variety of nitrosating agents. These reactions give rise to the corresponding oximes. Examples are given in equations 1.22 and 1.23.

$$CH_3COCH_2CO_2C_2H_5 \xrightarrow{XNO} CH_3COC(=NOH)CO_2C_2H_5 \qquad (1.22)$$

$$RCH(CO_2H)_2 \xrightarrow{XNO} RC(=NOH)CO_2H + CO_2 \qquad (1.23)$$

Enols derived from a carboxylic acid and ester have been synthesised by Fuson's approach[5], and enols from simple carboxylic acids and esters were proved by flash photolysis[6] methods to be involved in halogenation[84,85]. Recently the kinetic studies on nitrosation of malonic acid, methylmalonic acid[7], ethyl cyanoacetate and diethyl malonate[86] have been reported and enol and enolate as intermediates have been further confirmed[87].

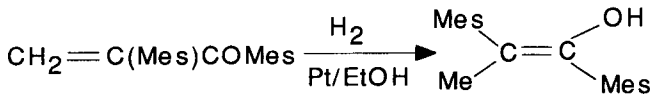
1.6. Unstable and relatively stable simple enols

Simple enols described here are derived from simple monofunctional aldehydes and ketones or monocarbonyl compounds. The enol contents of these

compounds are quite low and on the order of ppm or even ppb. This is because most simple enols are unstable thermodynamically with respect to their keto tautomers and tend to convert to their keto form immediately. Therefore, such enols usually can not be observed directly in an equilibrium mixture even by sensitive spectroscopic methods.

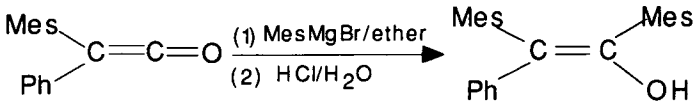
The kinetics of the enolisation of monocarbonyl compounds have been extensively studied[88,89]. Three methods have been most widely used: (1) trapping the enol with halogen and measuring the disappearance of the latter, (2) measuring the exchange of the α-hydrogen with a deuterium or tritium label, and (3) measuring the racemisation of a carbonyl compound with an asymmetric α-carbon. However, the reverse reaction, the ketonisation of enols, has been less extensively studied owing to the difficulty in obtaining simple enols, so the accurate data on the equilibrium constants K_E for simple enols were relatively scarce in the early works.

In the past decade, the progress in the preparation of simple enols makes it possible to use a direct method to study the rates of enolisation and ketonisation. Combination of the ketonisation rate constant with the enolisation rate constant of the ketone yields accurate K_E values. A number of simple enols have been formed under different conditions and characterised[90-92] by NMR, IR, and CIDNP. The generation of simple enols are based on some methods which retard or prevent the enol from transferring to keto. One of the methods is to stabilise enol by the introduction of bulkyl groups like mesityl onto the α-carbon to the carbonyl group to generate kinetically and thermodynamically stable tautomer. The best example of aryl-substituted stable enols is Fuson's enol. The first crystalline simple enol reported by Fuson[93] is 1,2-dimesityl-1-propenol prepared by 1,4 addition of hydrogen to the ketone (equation 1.24). The presence of a hydroxyl group in enol was demonstrated by an infrared spectrum.

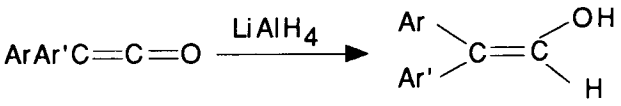


(1.24)

Later, a rather large number of similar enols were prepared such as those shown in equation 1.25 and equation 1.26[94,95].

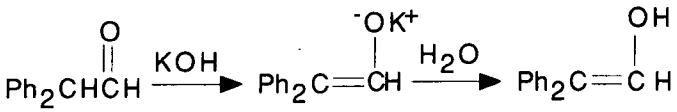


(1.25)



(1.26)

Remarkable progress in the synthesis of simple enols in recent years was achieved by the groups led by Capon and Kresge. For example, Capon and coworkers[96] have shown that vinyl alcohol can be generated in solution from several precursors such as ketone acetal or ortho ester. Kresge[97] measured the keto-enol equilibrium constant of diphenylacetaldehyde whose enol form was generated from its potassium salt (equation 1.27).

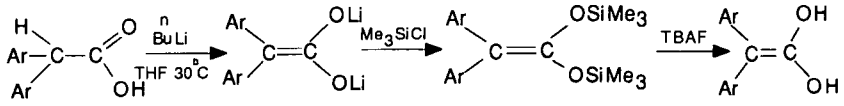


(1.27)

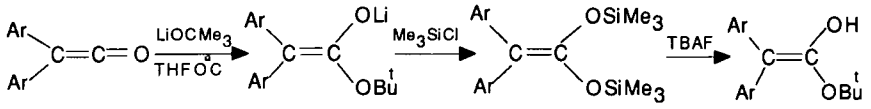
In addition, he compared the behaviour of sterically hindered stable 'Fuson' enols bearing mesityl substituents with that of enol containing unsubstituted phenyl groups on their carbon-carbon double bonds and suggested that a substantial portion of the thermodynamic stability of Fuson enols is provided by similar phenyl group stabilisation of their double bonds. However, the methyl of the mesityl subtituents of Fuson enols does appear to play a critical role in conferring stability upon these substances. Rappoport and coworkers extended the old work of Fuson to prepare a series of stable ß,ß-dimesityl α-alkyl[91] or

α-aryl enols[92] and measured their keto-enol equilibrium constants K_E in hexane. They found that in the aliphatic substituted series, K_E decreased along the series H> Me>Et>i-Pr >t-Bu. In contrast, in the aromatic series K_E increased on increasing the bulk of the α-aryl group. This is because the combined steric and polar effects of aliphatic and aromatic substituents on K_E values are opposite. The electron withdrawal on the α-aryl group increases K_E value due mainly to the destabilisation of the ketone. The main effect of α-alkyl group on the change in K_E values is steric. The polar effects are either small or constant along the series.

Some stable enols from simple carboxylic acids and derivatives such as esters have been generated by the ways mentioned above. As precursors for the acid and ester enols, O'Neill[5] used the silylate ketone acetals, which provide sufficient steric hindrance to stabilise these acid and ester enols (see equations 1.28 and 1.29).

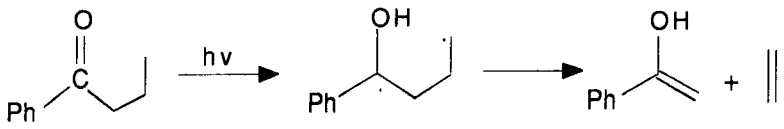


(1.28)



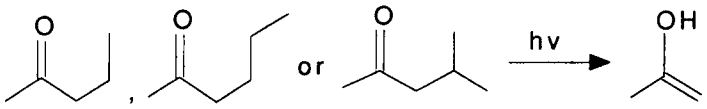
(1.29)

Another important method of generating simple enols in an aqueous solvent is flash photolysis using the Norrish type II photoelimination reaction or the photohydration of acetylenes. Wirz and coworkers[98] first used Norrish type II photoelimination to prepare the enol of acetophenone from phenyl butyl ketone (equation 1.30) and measured accurately its rate of ketonisation by fast-absorption spectroscopy.

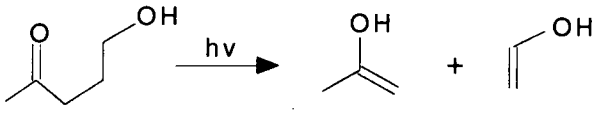


(1.30)

The flash photolytic generation works well for enols of aromatic ketones because the quantum yield of the photochemical reaction is high and the absorption band that must be irradiated is strong. The situation is less favourable for enols of aldehydes and aliphatic ketones, but such enols as that of acetone were prepared from one of three ketone precursors[99] (equation 1.31) and also from 5-hydroxy-2-pentanone[100] (equation 1.32).



(1.31)



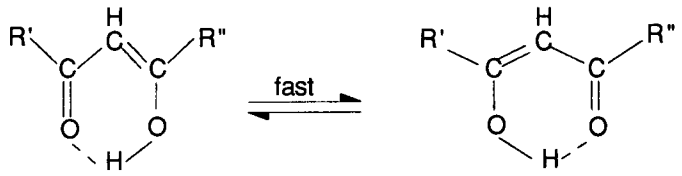
(1.32)

Chiang *et al*[35,101] and another group[102] have used these methods to examine the enols of acetophenone, isobutyraldehyde, acetone and vinyl alcohol, and measured their K_E values and dissociation constants of these substances. The subject of simple enols has been reviewed by Hart[103], Kresge[100], Toullec[89] and Rappoport[95].

1.7. The enols from dicarbonyl compounds

The enols of dicarbonyl compounds are relatively stable compared to monocarbonyl compounds, in some case more stable than the corresponding keto tautomers. For example, Emsley[104] prepared a crystalline ß-diketone, 3-(4-methoxyphenyl) pentane-2,4-dione, whose IR and ^1H NMR spectra indicated it to be entirely of the enol tautomer.

It is well known that most enol forms of ß-dicarbonyl compounds usually exist as the conjugated *cis*-enols[4] (1a and 1b) stabilised by intramolecular hydrogen bond between the OH and the remaining carbonyl group.



(1.33)

(1a) (1b)

As for structural investigation of enols, major interest is focused on whether the proton lies in an unsymmetrical hydrogen bond corresponding to C_S symmetry or in a symmetrical bond. Although Sharpet'Ko[105] favoured the symmetry of the enol molecule from ^{13}C NMR data, the large quantity of information from *ab initio* calculation[106], as well as ^{1}H and ^{2}H NMR[107] and IR[108] presented important evidence supporting the view that *cis* enol had C_S structure for common compounds under usual conditions.

Enol content in equilibrium depends also on the polarity of the solvent. This is because the enol tautomer is less polar than the keto tautomer. Therefore, polar solvent favours the more polar keto form over the corresponding enol tautomer or the proportion of enol form is higher in non-polar solvents. For example, the enol content of 2,4-pentanedione[109] in CCl_4 is 95% at 298K but falls to 19% in water at the same temperature. The effect of solvent on the equilibrium constants has been determined and a wide variety of theoretical and empirical solvation parameters have been tested on the basis of free energy relationship[110,111].

The ratio between the keto form and the enol form is also sensitive to concentration of the substrates[24]. The proportion of enol form is usually higher when the concentration is low. This phenomenon has been reported by

another group[113]. In addition, the enol content generally decreases as the temperature increases due to the disruption of hydrogen bonds[114,115].

The effect of substituent on ß-dicarbonyls of the typical formula $R^1COCHR^2COR^3$ is more complicated than that of solvent effects due to competition between factors stabilising and destabilising the keto and enol groups. K_E values depend on interaction between R^2 and R^1 or R^3, and the α-substituent effect is usually higher than γ-substituent effect. It is known that α-alkyl substituent (R^2=Me, Pr, Bu, Et) dramatically reduces the enol content[116-118] and the enol content decreases as R^2 bulk expands although intramolecular hydrogen bond proved to be slightly stronger in the substituted product ($R^2 \neq H$) than in the unsubstituted one (R^2=H)[119]. This result may be explained on a combination of the steric effects and inductive effects. The electron density in the vicinity of the α-proton should be enhanced by the substitution of alkyl groups at the α-position. For both ß-diketones[120] and ß-ketoesters[121], substitution of electron-withdrawing group such as chlorine at the position (R^2=Cl) results in the increase of the enol tautomer. However, bromine causes a marked decrease in enolisation. This is because the latter has a predominant steric effect. α-Aryl substituent[122] increases the enol content probably due to resonance stabilisation of the enol tautomer. γ-Substituents[121] usually have only a little effect. It is known that the equilibrium moves in favour of the enol tautomer as the electron-withdrawing group is substituted at the γ-position.

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CHAPTER 2

NITROSATION AND HALOGENATION OF MALONAMIDE

2.1. Introduction

There has been extensive study in the chemistry of enols in the past decade, focusing on the synthesis of stable enols[1,2], the measurement of rate constants of ketonisation and keto-enol equilibrium constants for simple ketones[3,4]. Recently, a particular interest in this field has been the recognition of enols derived from carbonyl-containing compounds including carboxylic acids and esters[5,6]. The involvement of enol forms of malonic acid and its derivatives has been reported[7,8]. Most recently, Chiang and Kresge[9] measured keto-enol equilibrium constants for the pyruvic acid system in aqueous solution by Meyer halogen titration and by another kinetic method which determines these constants from the ratios of enolisation to ketonisation rate constants.

Amides should in principle show similar kinetic behaviour i.e. capable of enolisation and subsequent electrophilic addition. However, no adequate evidence has been presented experimentally in the literature. Some reports on malonamide only involved its synthesis and kinetics and mechanism of alkaline-hydrolysis[10,11]. Therefore, in this work, enolisation of malonamide was investigated through the kinetic study of its nitrosation, iodination and bromination in acidic aqueous solution.

2.2. The catalysed nitrosation of malonamide

2.2.1. Results

The nitrosation of malonamide was carried out in acidic aqueous solution at 25°C in the presence of Br^- or SCN^- as catalyst. Kinetic measurement for this reaction was based on determining the absorbance of nitrous acid at 371 nm. Malonamide concentration was at least twenty-fold greater than the initial

concentration of nitrous acid. The product has been characterised as the oxime [12,13] (see equation 2.1).

$$CH_2(CONH_2)_2 \xrightarrow[Br^- \text{ or } SCN^-]{H^+/HNO_2} HON{=}CH(CONH_2)_2 \qquad (2.1)$$

The mechanism of the nitrosation reaction was analysed by varying one of the factors including acidity and substrate or catalyst concentrations while keeping the other parameters constant.

In the presence of bromide ion, the nitrosation of malonamide was consistently first order in $[HNO_2]$, regardless of the changes in $[HClO_4]$, [MA] or $[Br^-]$. The variation of the observed first order rate constant k_{obs} with [MA], $[H^+]$ and $[Br^-]$ are shown in tables 2.1-2.3 and figures 2.1-2.3, respectively. Plots of k_{obs} versus [MA] and $[Br^-]$ were both linear, indicating that the reaction is first order in [MA] and $[Br^-]$. The small positive intercept in figure 2.3 implies the existence of an uncatalysed nitrosation. The plot of k_{obs} vs $[H^+]$ at 0.1-0.5M was a curve in spite of the ionic strength having been kept constant. This was probably caused by activity effects requiring the need for an appropriate acidity function. However, the reaction could be regarded as having linear dependence on $[H^+]$ at low acidity.

Table 2.1. Dependence of k_{obs} upon [MA] for the nitrosation of malonamide with Br^- as catalyst.

$[HNO_2]$=0.0071M $[Br^-]$=0.598M

$[H^+]$=0.072M

[MA]/M	$10^3 k_{obs}/s^{-1}$
0.072	0.497
0.108	0.740
0.162	1.16
0.216	1.52
0.252	1.90
0.288	2.20
0.324	2.50
0.361	2.79
0.405	3.12

Table 2.2 Variation of k_{obs} with $[H^+]$ for the nitrosation of MA with Br^- as catalyst

$[HNO_2]$=0.0099M [MA]=0.201M

$[Br^-]$=0.600M ionic strength=1.20M ($NaClO_4$)

$[H^+]$/M	$10^2\ k_{obs}/s^{-1}$
0.10	0.322
0.20	0.826
0.25	1.14
0.30	1.47
0.35	1.94
0.40	2.26
0.50	3.06

Table 2.3 Variation of k_{obs} upon $[Br^-]$ for the nitrosation of malonamide with Br^- as catalyst

$[HNO_2]$=0.0072M $[H^+]$=0.072M

[MA]=0.2026M

$[Br^-]$/M	$10^3\ k_{obs}/s^{-1}$
0.14	0.408
0.21	0.590
0.28	0.734
0.35	0.902
0.42	1.05
0.49	1.21
0.56	1.38

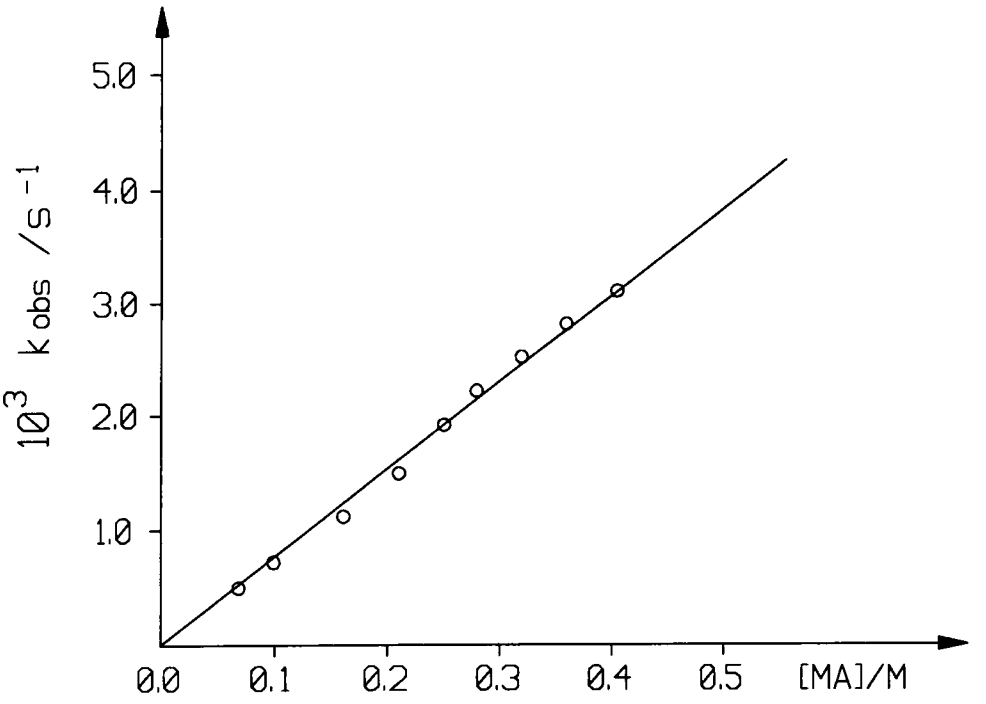


Figure 2.1 Dependence of k_{obs} upon [MA] for the nitrosation of MA with Br^- as catalyst.

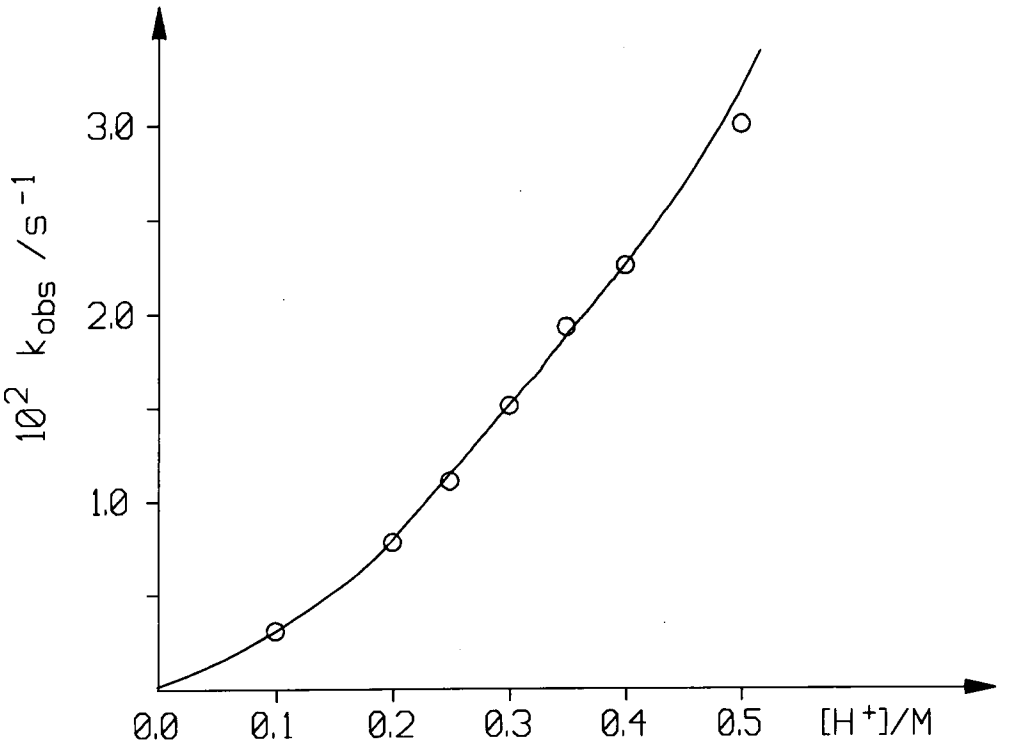


Figure 2.2 Variation of k_{obs} with $[H^+]$ for the nitrosation of MA with Br^- as catalyst.

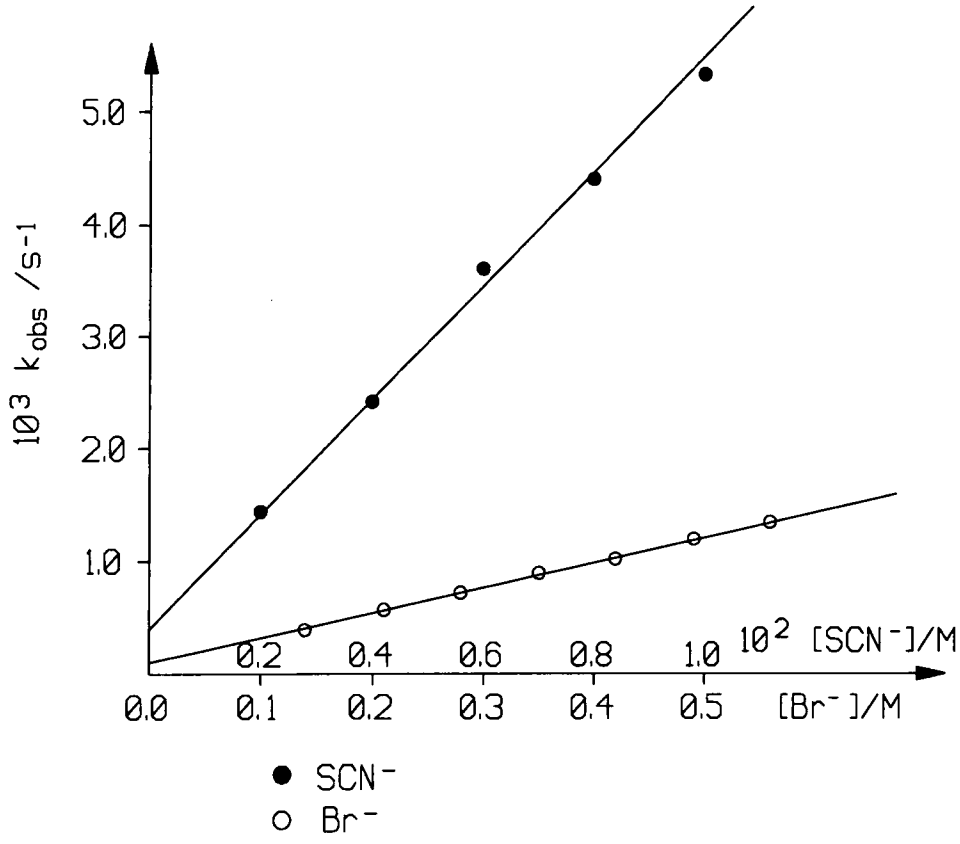


Figure 2.3. Dependence of k_{obs} upon [Br^-] or [SCN^-] for the nitrosation of MA

The nitrosation of MA was also catalysed by SCN^-. The reaction was perfect first order in $[HNO_2]$ in the presence of SCN^- (0.002-0.01M) and k_{obs} had a good linear dependence on $[SCN^-]$, as shown in table 2.4 and figure 2.3. At higher $[SCN^-]$ (0.01-0.5M), the kinetic behaviour tended to become zero order in $[HNO_2]$. However, perfect zero order could not be obtained, possibly due to decomposition of NOSCN.

Table 2.4 Dependence of k_{obs} upon $[SCN^-]$ for the nitrosation of MA with SCN^- as catalyst.
$[HNO_2]$=0.010M $[H^+]$=0.07M
[MA]=0.200M

10^2 $[SCN^-]$/M	$10^3 k_{obs}/s^{-1}$
0.200	1.45
0.400	2.39
0.600	3.61
0.800	4.42
1.00	5.33

2.2.2. Discussion

The data from the Br^- catalysed nitrosation reactions in table 2.2 support the mechanism shown in scheme 2.1, where the nitrosation of malonamide occurs via the enol form. The fact that the reaction was first order in $[HNO_2]$ implies that the rate limiting step is not the enolisation of malonamide but nitrosation of

enol. Thus acid and base catalysed process of enol formation could not be distinguished. The reaction via carbanion can be ruled out under the experimental conditions because the first order k_{obs} increased with acidity at 0.1-0.5M acid. A reaction via carbanion should be otherwise independent of $[H^+]$. This is reflected in equation 2.2 and 2.3 respectively. That the plot of k_{obs} versus $[H^+]$ is not linear at high $[H^+]$ as predicted from equation 2.2 is probably caused by activity effects.

$$MA \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} Enol$$

$$HNO_2 + H^+ + X^- \overset{K_{NOX}}{\rightleftharpoons} NOX + H_2O$$

$$Enol + NOX \xrightarrow{k_2} oxime$$

Scheme 2.1

The overall rate equation under this scheme can be obtained by the Steady State Hypothesis:

$$\text{Rate} = \frac{k_1 k_2 K_{NOX}[H^+][MA][X^-][HNO_2]}{k_{-1} + k_2 K_{NOX}[H^+][X^-][HNO_2]} \qquad (2.1)$$

The nitrosation is the rate limiting step if $k_{-1} >> k_2 K_{XNO}[H^+][X^-][HNO_2]$ so equation 2.1 will be simplified to equation 2.2,

$$\text{Rate} = K_E k_2 K_{XNO}[H^+][X^-][HNO_2][MA] \qquad (2.2)$$

$(K_E = k_1/k_{-1})$

If carbanion is the intermediate instead of enol, the overall rate equation will become equation 2.3,

$$\text{Rate} = \frac{k_1 k_2 K_{NOX}[MA][X^-][HNO_2]}{k_{-1} + k_2 K_{NOX}[X^-][HNO_2]} \qquad (2.3)$$

Acid and base catalysed enolisation could be examined by the SCN^- catalysed nitrosation in acidic solution. When increasing $[H^+]$, the reaction could change from first order to zero order with respect to $[HNO_2]$. This suggests that the rate-limiting step has changed from the nitrosation to the enolisation. Under this condition, the overall rate of nitrosation through acid catalysed and base catalysed enolisation can be expressed by equations 2.4 and 2.5 respectively. The acid catalysed or base catalysed enolisation can thus be distinguished by examining the variation of reaction rate with the change of $[H^+]$. However, this experiment was not done because perfect zero order could not be obtained, possibly due to decomposition of NOSCN.

$$\text{Rate} = \frac{k_1 k_2 K_{NOX}[H^+]^2[MA][X^-][HNO_2]}{k_{-1}[H^+] + k_2 K_{NOX}[X^-][HNO_2][H^+]} \qquad (2.4)$$

$$\text{Rate} = k_1[MA][H^+]$$

$$(k_2 K_{NOX}[X^-][HNO_2][H^+] >> k_{-1}[H^+])$$

$$\text{Rate} = \frac{k_1 k_2 K_{NOX}[B][H^+][MA][X^-][HNO_2]}{k_{-1}[B] + k_2 K_{NOX}[H^+][X^-][HNO_2]} \qquad (2.5)$$

$$\text{Rate} = k_1[MA][B]$$

$$(k_2 K_{NOX}[H^+][X^-][HNO_2] >> k_{-1}[B])$$

The values of k_2K_E obtained from the variation of k_{obs} with [Br^-] and [SCN^-] (Figure 2.3) are 3.33 and 1.16 (l mol^{-1} s^{-1}), respectively (The literature values of K_{NOBr} and K_{NOSCN}, $5.1x10^{-2}$[14] and 30[15] (l^2 mol^{-2}) respectively, were used for the calculation). Since K_E is constant, then k_2 with Br^- as catalyst is a little greater than k_2 with SCN^- as catalyst. Normally, for example with reactions of amines and other substrates, NOBr is much more reactive than NOSCN. This implies that here in reaction with the enol from malonamide, both reactions are close to the diffusion controlled limit. If the assumption is valid, and we use a value for k_2 of $7x10^9$ l mol^{-1} s^{-1}, then we can estimate a minimum value of K_E of *ca.* 1.6-5.6 $x10^{-10}$. Recently, K_E value of diethyl malonate has been estimated by this way as $2x10^{-11}$[16], suggesting that the enolisation constants for the two compounds are similar.

As mentioned earlier, there was no evidence that carbanion is an alternative intermediate to enol in the nitrosation of malonamide. A pathway through carbanion (or enolate anion) has been identified for several compounds with high acidity of the hydrogen at α-carbon, such as Meldrum's acid (pKa=4.83) at low acidity[17], trifluoroacetylacetone (pKa=6.7)[18] and dimedone (pKa of enol 5.2)[19]. For some compounds, the concentration of the carbanion is not sufficiently high for reaction to occur, as in the case of ethyl acetoacetate (pKa 10.7) [19] and acetylacetone (pKa 8.8)[20]. The pKa of malonamide is not available. Its structure compares with acetylacetone, but the acidity at the α-carbon of malonamide may be lower due to conjugation of NH_2 to C=O. If this is the case, there would be little possibility that nitrosation of malonamide occurs via carbanion at the above experimental conditions.

2.3. Iodination of malonamide

2.3.1. Results

Kinetic measurement for iodination of malonamide was carried out on the conventional UV/Visible spectrophotometer. The reaction was followed through the disappearance of absorption by the iodine molecule in the aqueous acidic solution at 460 nm, where the molar extinction coefficient ε is 697 mol^{-1} l cm^{-1}. The reaction mechanism was investigated by varying the concentration of either $HClO_4$ or MA. In all the experiments, malonamide was in a large excess over iodine.

At low acidity (lower than 0.1M), the kinetic runs showed a zero order behaviour with respect to iodine. But perfect zero order was obtained only at around 0.01M acidity. The variation of the observed rate constant k_{obs} with $[H^+]$ or [MA] at low acidity is shown in tables 2.5 and 2.6 as well as figures 2.4 and 2.5. The plots of k_{obs} versus $[H^+]$ and [MA] are both linear. But there was a small intercept in the plot of k_{obs} versus $[H^+]$, possibly due to the presence of uncatalysed enolisation. These results suggest that iodination of MA proceeds via enol through the acid catalysed pathway and the enol formation is the rate limiting step. At high acidity ($[H^+]$>0.4M), the reaction rate constant had a good first order dependence on $[I_2]$ and the k_{obs} did not vary with acid concentration (as shown in table 2.7). This indicates that the rate limiting step has changed from enolisation to iodination as the acidity increased up to 0.4M. The first order k_{obs} had good linear dependence on [MA] as shown in table 2.8 and figure 2.6 .

Table 2.5 Variation of k_{obs} with $[H^+]$ at low acidity for the iodination of malonamide.

[MA]=0.0197M

$[I_2]=6.19x10^{-4}M$

$[H^+]/M$	$10^6\ k_{obs}/mol.l^{-1}.s^{-1}$
0.01	1.11
0.02	1.84
0.03	2.44
0.04	3.06
0.05	3.89
0.06	4.45
0.07	5.01
0.08	5.83
0.09	6.34
0.10	7.01

Table 2.6 Variation of k_{obs} with [MA] at low acidity for the iodination of malonamide.

$[H^+]$=0.051M

$[I_2]$=6.5x10^{-4} M

10^2 [MA]/M	10^5 k_{obs}/mol.l^{-1}.s^{-1}
1.47	0.335
2.46	0.541
3.69	0.789
4.91	1.05
5.90	1.28
7.37	1.57

Table 2.7 Variation of k_{obs} with $[H^+]$ at high acidity for the iodination of malonamide.

$[MA]=5.21\times10^{-3}M$

$[I_2]=2.1\times10^{-4}M$

$[H^+]/M$	$10^2\ k_{obs}/s^{-1}$
0.300	1.75
0.375	2.23
0.437	2.50
0.500	2.50
0.550	2.50

Table 2.8 Variation of k_{obs} with [MA] at high acidity for the iodination of malonamide

$[H^+]=0.45M$

$[I_2]=1.8\times10^{-4}M$

10^2 [MA]/M	$10^2\ k_{obs}/s^{-1}$
0.404	1.88
0.605	2.81
0.807	3.76
1.01	4.57
1.16	5.38

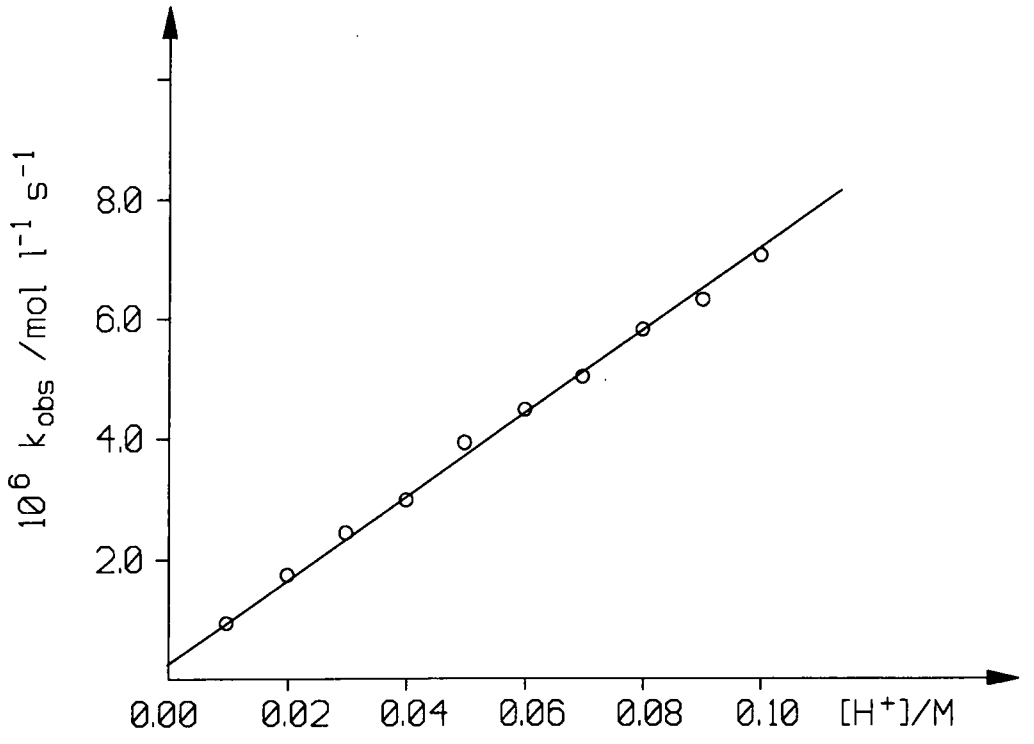


Figure 2.4. Variation of k_{obs} with $[H^+]$ at low acidity for the iodination of malonamide.

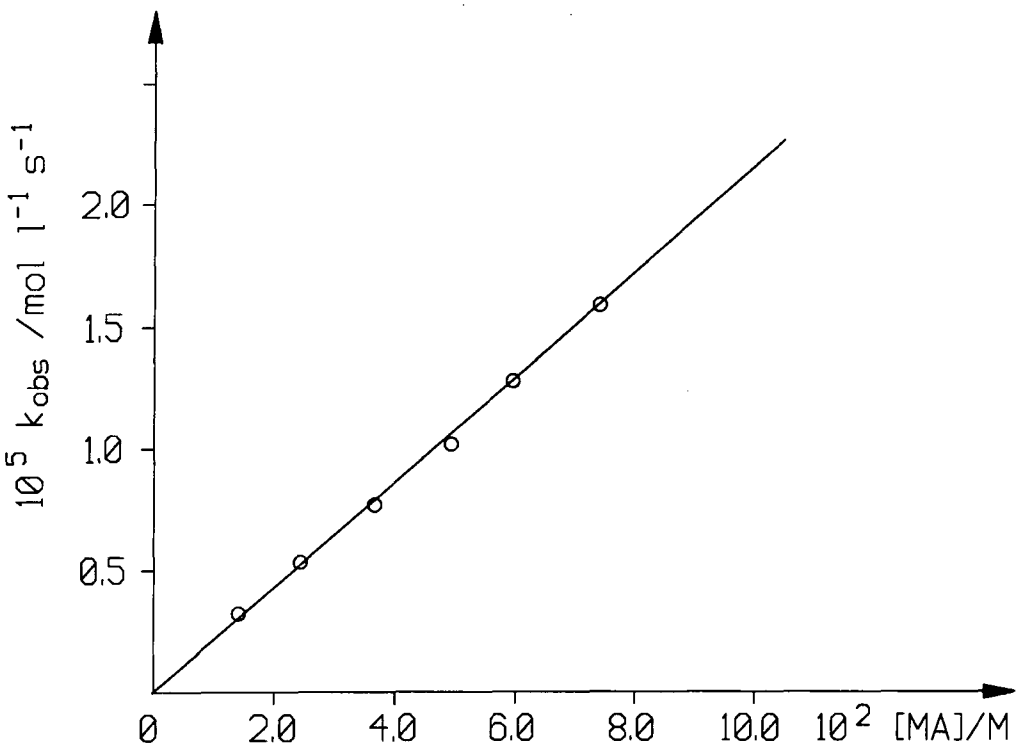


Figure 2.5. Variation of k_{obs} with [MA] at low acidity for the iodination of malonamide.

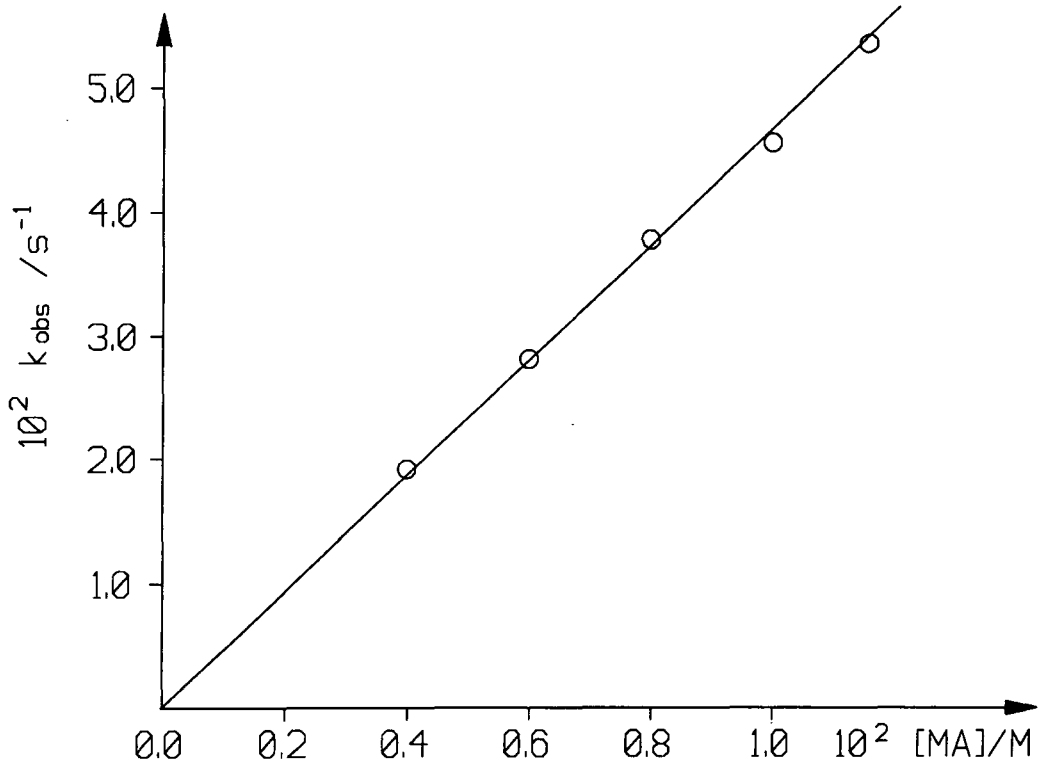


Figure 2.6 Variation of k_{obs} with [MA] at high acidity for the iodination of malonamide.

2.3.2. Discussion

The experimental results indicate that the iodination of malonamide proceeds via acid-catalysed enolisation. The kinetic mechanism can be expressed by scheme 2.2 and equation 2.6.

$$CH_2(CONH_2)_2 + H^+ \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} H_2NOCCH{=}C(OH)NH_2 + H^+$$

$$H_2NOCCH{=}C(OH)NH_2 + I_2 \xrightarrow{k_2} ICH(CONH_2)_2 + HI$$

Scheme 2.2

$$\text{Rate} = \frac{k_1 k_2 [MA][H^+][I_2]}{k_{-1}[H^+] + k_2[I_2]} \qquad (2.6)$$

The kinetic behaviour of the iodination of malonamide at both low and high acidity described above were in good agreement with the two limiting cases (equations 2.7 and 2.8) of equation 2.6.

$$\text{Rate}=k_{obs}=k_1[MA][H^+] \qquad (2.7)$$

$$(k_{-1}[H^+] \ll k_2[I_2])$$

$$k_{obs}=k_2K_E[MA] \qquad (2.8)$$

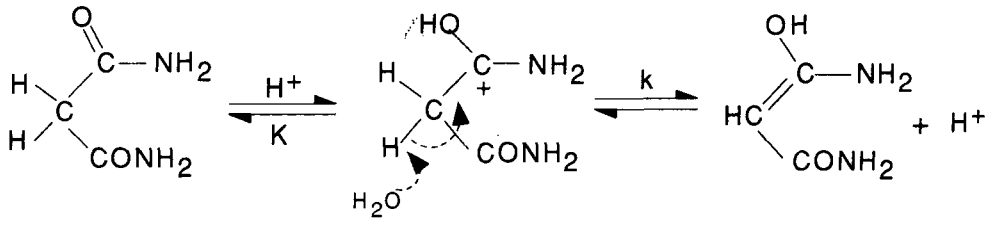
$$(k_{-1}[H^+] \gg k_2[I_2],\ \text{Rate}=k_{obs}[I_2])$$

The enolisation rate constant k_1 can be calculated by equation 2.7 and results are shown in table 2.9.

Table 2.9 Calculation results of enolisation rate constant for the iodination of malonamide

	slope/s^{-1}	k_1/l.mol^{-1}.s^{-1}
The plot of k_{obs} vs [MA]	$2.10x10^{-4}$	$4.12x10^{-3}$
The plot of k_{obs} vs [H^+]	$6.54x10^{-5}$	$3.32x10^{-3}$
Mean values of k_1		$3.72(\pm0.4)x10^{-3}$

The values of k_1 are significantly larger than that measured for simple ketone such as acetone ($3.8x10^{-5}$ l.mol^{-1}.s^{-1}), no doubt reflecting the greater acidity of the methylene protons brought about by the second $CONH_2$ group (see scheme 2.3). Alternatively there may be a higher concentration of the O-protonated intermediate in the case of malonamide (larger K value).



Scheme 2.3

The enol form of malonic acid has been identified by similar kinetic procedures both with halogenation and nitrosation as the scavenging reactions. For malonic acid however acid catalysis is brought about intramolecularly and so no comparison can be made with the malonamide reaction.

2.4. Bromination of malonamide

2.4.1. Results

The reaction was followed by the stopped-flow spectrophotometer at 393 nm at 25°C in aqueous acidic solution.

The absorbance-time curve showed that the bromination of malonamide was perfectly first order in $[Br_2]$ when the ratio of [MA] to $[Br_2]$ was greater than 27. The observed first order rate constant k_{obs} remained basically constant when acid concentration varied between 0.01-0.1M. However, the k_{obs} increased unlinearly with $[H^+]$ as acidity was higher than 0.1M, as shown in table 2.10 and figure 2.7.

Table 2.10 variation of k_{obs} with $[H^+]$ for the bromination of malonamide

[MA]=0.100M, $[Br_2]=3.7x10^{-3}M$

$[H^+]/M$	k_{obs}/s^{-1}
0.01	0.134
0.02	0.147
0.03	0.135
0.04	0.142
0.05	0.146
0.06	0.144
0.07	0.147
0.08	0.143
0.09	0.150
0.10	0.149
0.13	0.163
0.15	0.180
0.20	0.202
0.25	0.228
0.30	0.241
0.40	0.275
0.45	0.288
0.50	0.306
0.60	0.330

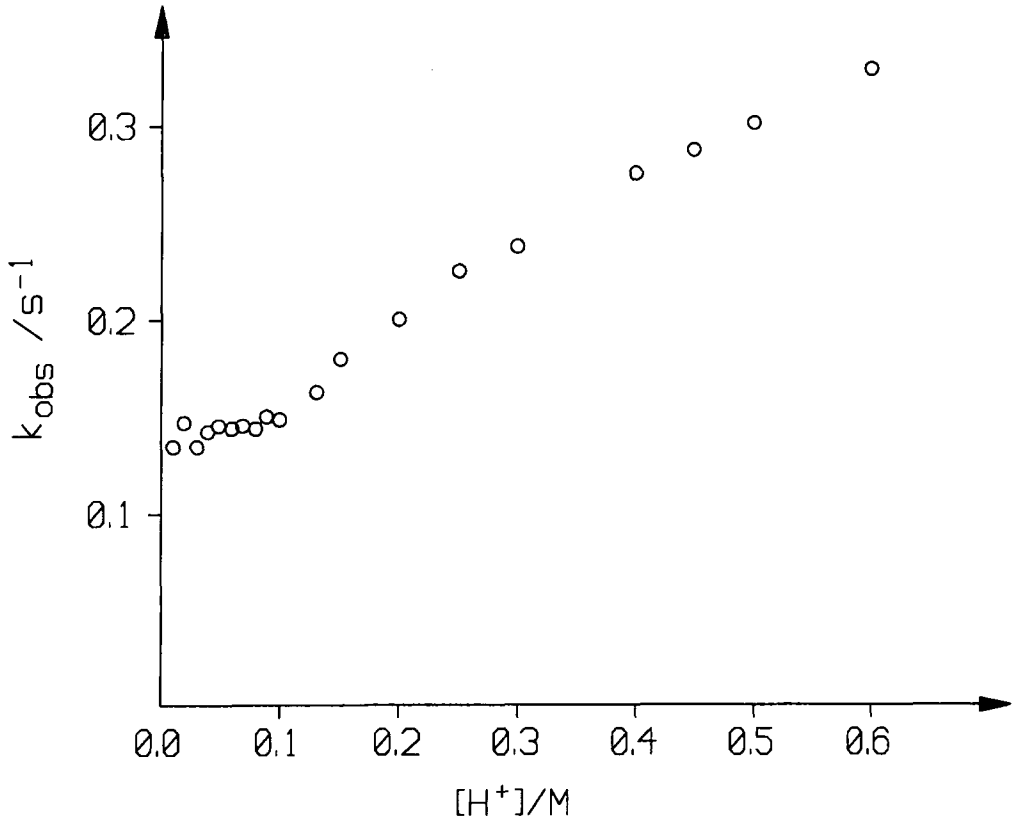


Figure 2.7 Variation of k_{obs} with $[H^+]$ for the bromination of malonamide.

2.4.2. Discussion

Experimental results obtained so far can not fully explain the kinetic mechanism of bromination of malonamide. The fact that the bromination behaved as first order in $[Br_2]$ and was independent of acid concentration ($[H^+]<0.1M$) suggests that the bromination is the rate limiting step assuming the kinetic mechanism follows scheme 2.4.

$$MA \overset{K_E}{\rightleftharpoons} Enol$$

$$MA + Br_2 \xrightarrow{k_2} MABr + HBr$$

Scheme 2.4

The k_2K_E values calculated by equation 2.8 under this assumption together with those for nitrosation and iodination, are summarised in table 2.11.

Table 2.11 Values of K_2K_E for different electrophiles

electrophile	k_2K_E/l mol^{-1}s^{-1}
I_2	4.60
Br_2	1.45
NOBr	3.92
NOSCN	1.17

These values are reasonably constant considering the wide range of reaction involved, and implies that all of the reagents react with the enol at encounter

limit. This is not an unreasonable suggestion as the enol of malonamide would be predicted to be a very reactive species due to the presence of both OH and NH_2 groups conjugated with the double bond. If we assume that the limiting value for k_2 is ~$7x10^9$ $l.mol^{-1}.s^{-1}$ for reaction in water at 25°C, then we obtain a value for K_E of $4(\pm2)x10^{-10}$ which is comparable with the measured value for acetone of $6.0x10^{-9}$ and estimated value of diethyl malonate ~$2x10^{-11}$.

It was not possible to achieve perfect zero order behaviour with bromine, probably because dibromination occurs and at the necessary high [Br_2] it is a serious complication.

The acid catalysis found above about 0.1 M H^+ could arise from a contribution due to bromination of the protonated form of the enol, or from an acidity function effect, or possibly a salt effect.

2.5. Isotope effects

2.5.1. Results

(1) Isotope exchange reaction of malonamide

Malonamide was dissolved in D_2SO_4-D_2O and D_2O, respectively and the ^1H NMR spectrum of the solution was determined at different times. As shown in figure 2.8, there is a peak, which corresponds to the hydrogens attached to the central carbon at δ 5.7 ppm. No peaks of the hydrogen in -NH_2 group were observed. The peaks due to the methylene hydrogen atoms gradually disappeared. In the D_2SO_4-D_2O system, the disappearance of these peaks was much faster than in D_2O alone as shown in table 2.12.

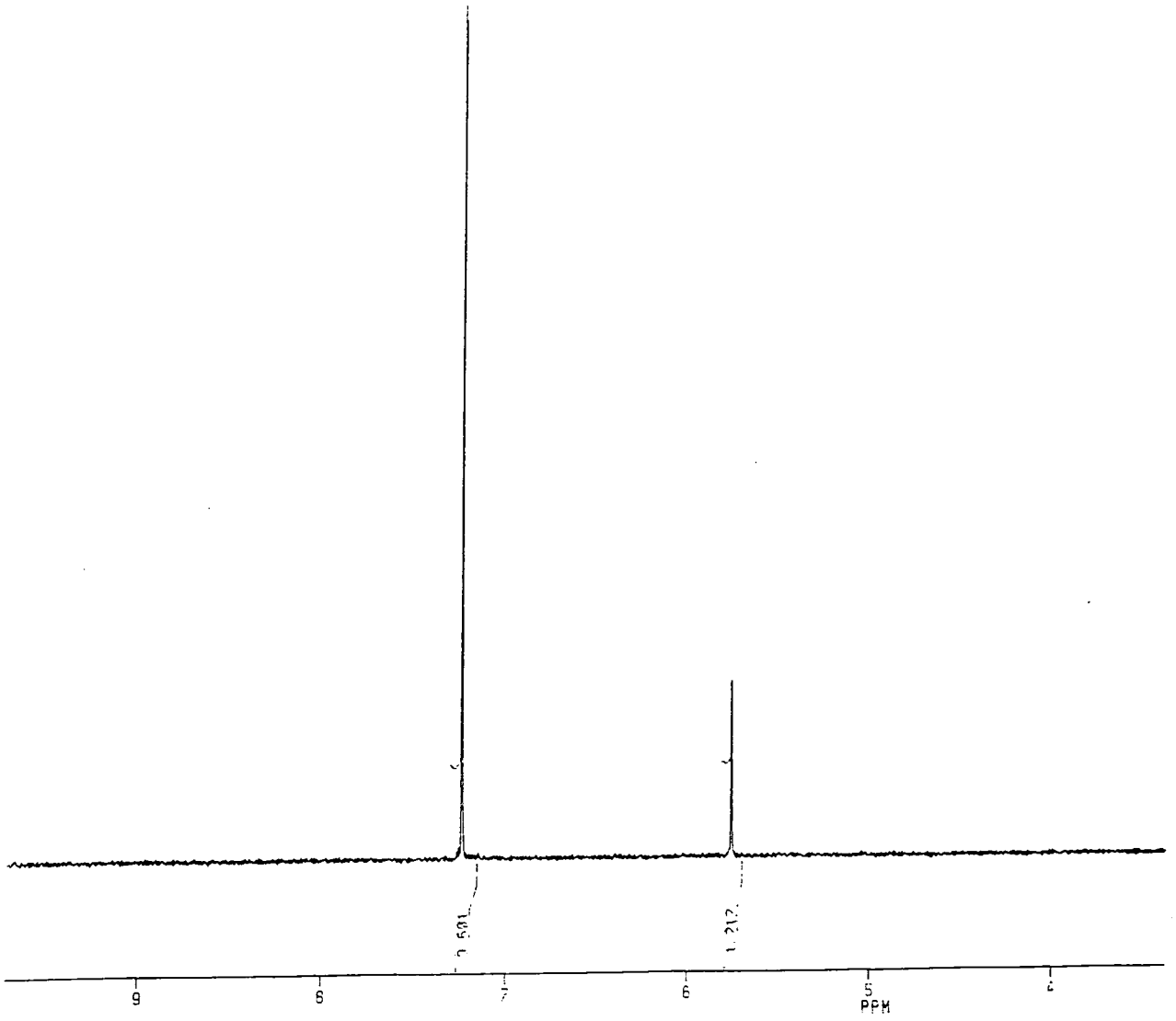


Figure 2.8. ^{1}H NMR spectrum of malonamide in D_2SO_4-D_2O.

Table 2.12 The conversion of $CH_2(CONH_2)_2$ to $CD_2(CONHD_2)_2$ in D_2SO_4-D_2O and D_2O with time

relative values of peaks between -CH_2 and H_2O (%)	5 min	16 min	42 min	one day	seven days
in D_2SO_4-D_2O	13.96	6.37	4.26	0.0	
in D_2O	30.13			17.88	2.0

(2) Kinetic isotope effect in the iodination of malonamide

Deuterated or undeuterated malonamide was reacted with iodine in both H_2SO_4-H_2O and D_2SO_4-D_2O system. Under these conditions, the iodination reaction was zero order in $[I_2]$. The results are shown in tables 2.13-2.16 and figures 2.9-2.10. The kinetic isotopic effect and solvent isotopic effect are summarised in table 2.17.

Table 2.13 Variation of zero order rate constants k_{obs} with [MA] for the iodination of malonamide in H_2SO_4-H_2O.

$[H^+]$=0.0103M

$[I_2]$=5.73x10^{-4}M

[MA]/M	10^6 k_{obs}/ mol.l^{-1}.s^{-1}
0.0175	1.28
0.0264	2.00
0.0398	2.97
0.0530	3.79

Table 2.14 Variation of zero order rate constants k_{obs} with [MA] for the iodination of malonamide in D_2SO_4-D_2O.

$[D^+]$=0.0100M

$[I_2]$=6.02x10^{-4}M

[MA]/M	10^6 k_{obs}/mol.l^{-1}.s^{-1}
0.0167	1.14
0.0277	1.80
0.0399	2.52
0.0539	3.49

Table 2.15 Variation of zero order rate constant with deuterated malonamide concentration for the iodination of malonamide in H_2SO_4-H_2O.

$[H^+]$=0.0103M

$[I_2]$=5.73x10^{-4}M

$[D_2MA]$/M	10^6 k_{obs} / mol.l^{-1}.s^{-1}
0.0165	0.541
0.0290	0.954
0.0411	1.34
0.0513	1.60

Table 2.16 Variation of zero order rate constants k_{obs} with $[D_2MA]$ for the iodination of deuterated malonamide in D_2SO_4-D_2O.

$[D^+]$=0.0100M

$[I_2]$=6.02x10^{-4}M

$[D_2MA]$/M	10^6 k_{obs}/ mol.l^{-1}.s^{-1}
0.0145	0.395
0.0260	0.683
0.0384	1.04
0.0488	1.36

Table 2.17 Enolisation rate constants for the iodination of MA or D_2MA

	k_{1MA} / $l.mol^{-1}s^{-1}$	$k_{1\,D_2MA}$ / $l.mol^{-1}.s^{-1}$	$k_{1MA}/k_{1\,D_2MA}$
H_2SO_4-H_2O	$6.84x10^{-3}$	$2.97x10^{-3}$	2.30
D_2SO4-D_2O	$6.28x10^{-3}$	$2.83x10^{-3}$	2.20
solvent effect	1.09	1.05	

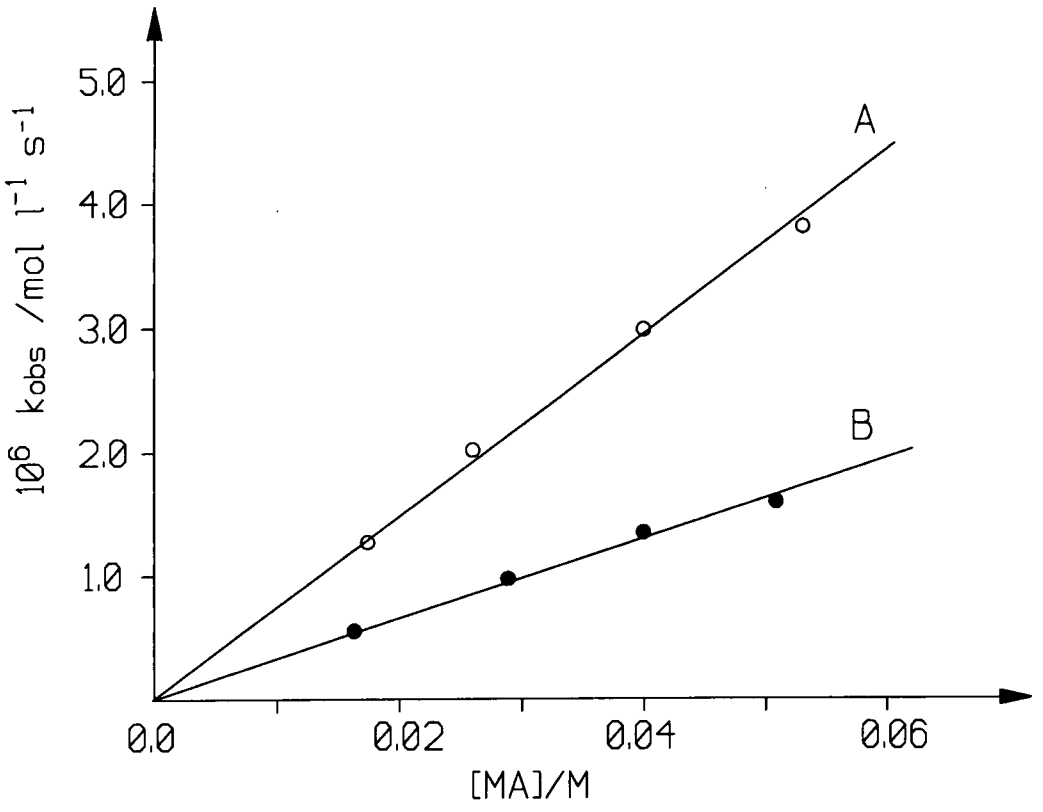


Figure 2.9 Variation of zero order rate constants with [MA] or $[D_2MA]$ in H_2SO_4-H_2O.

A- MA

B- D_2MA

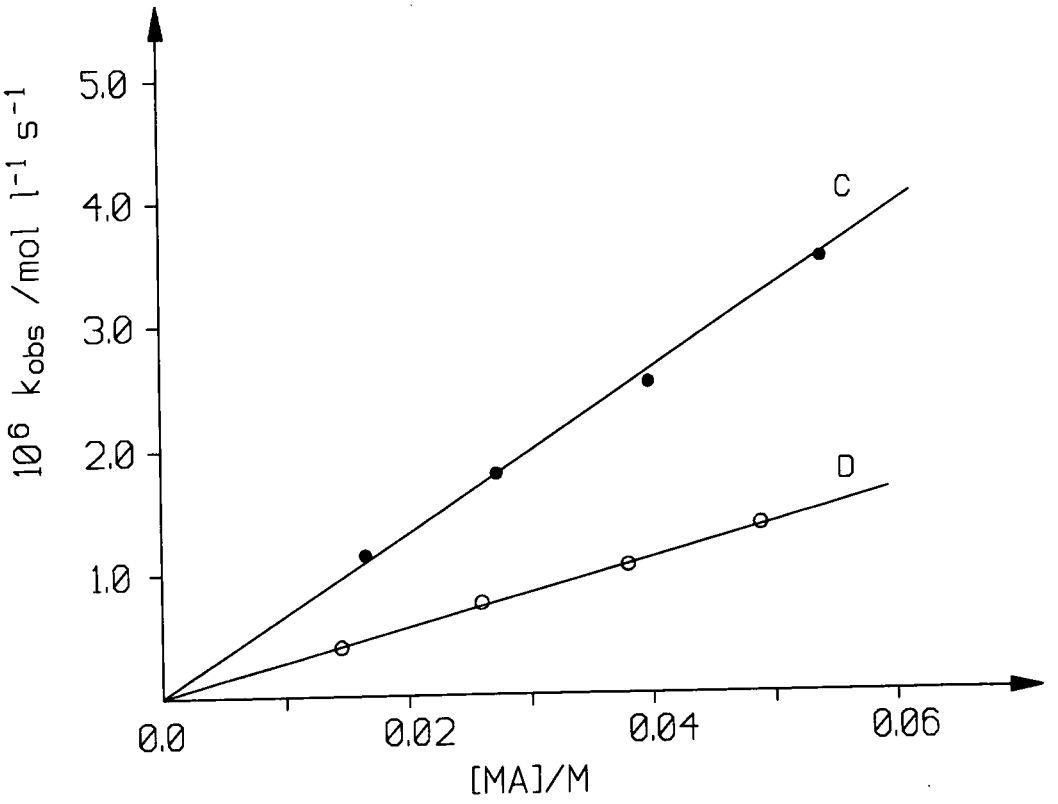


Figure 2.10 Variation of zero order rate constants k_{obs} with [MA] or [D_2MA] in D_2SO_4-D_2O.

C- MA

D- D_2MA

2.5.2 Discussion

The isotopic exchange reaction provided evidence that hydrogen atom exchange occurs readily between the solvent and the protons in malonamide, which involves acid-catalysed enolisation. As determined by ^1H NMR, when malonamide was dissolved in D_2SO_4 and D_2O, no peaks of the $-NH_2$ hydrogen could be detected and the peak of the methylene hydrogens gradually disappeared. The same phenomenon was observed when malonamide was dissolved in D_2O alone, although the disappearance of the methylene hydrogen peaks took much longer time than when D_2SO_4 was present. This can be interpreted by two types of isotopic exchange reaction.

The first is the very rapid exchange of the amide protons by D^+ so that the ^1H NMR peaks of $-NH_2$ on the malonamide could not be observed. The second process is the slower exchange of the hydrogens attached to the central carbon. This in fact is a process of acid-catalysed enolisation. These two processes are shown in equations 2.9 and 2.10, respectively.

$$CH_2(CONH_2)_2 + 2D^+ \longrightarrow CH_2(CONH_2D)_2^{2+} \longrightarrow CH_2(CONDH)_2 + 2H^+$$

$$CH_2(CONDH)_2 + 2D^+ \longrightarrow CH_2(COND_2)_2 + 2H^+ \qquad (2.9)$$

$$-CH_2-\underset{\underset{ND_2}{|}}{C}=O + D^+ \rightleftharpoons -CH_2-\underset{\underset{ND_2}{|}}{C}=OD^+ \longrightarrow -CH=\underset{\underset{ND_2}{|}}{C}-OD + H^+$$

$$-CH=\underset{\underset{ND_2}{|}}{C}-OD \longrightarrow -CHD-\underset{\underset{ND_2}{|}}{C}=O \qquad (2.10)$$

Results of kinetic isotopic effect from the iodination experiments shown in Table 2.12 further confirmed the involvement of acid-catalysed enolisation in the reaction. The zero-order nature of iodination indicated that enolisation is the rate-limiting step.

In general, acid-catalysed enolisation is a two-step process, including reversible fast proton transfer followed by a rate-limiting process of enol formation, as shown in scheme 2.5.

$$S + H_3O^+ \overset{K}{\rightleftharpoons} SH^+ + H_2O$$

$$SH^+ \xrightarrow{k} Enol$$

Scheme 2.5

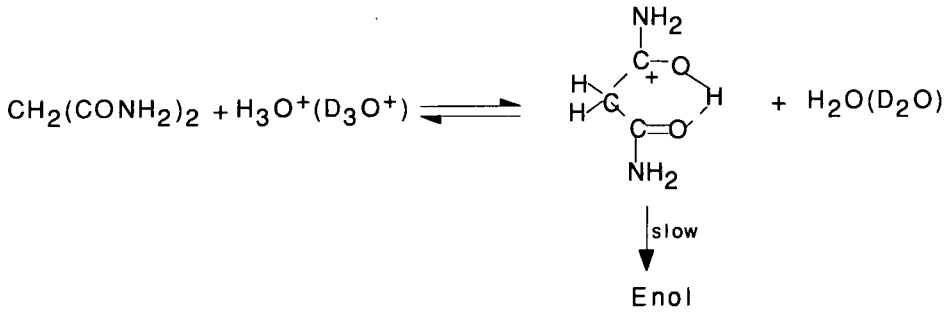
$$-\frac{d[S]}{dt} = Kk[S][H_3O^+]$$

$$= k_1[S][H_3O^+] \qquad (2.11)$$

(k_1— enolisation rate constant)

The rate-limiting second step involves the breaking-up of the central C-H bond. Since C-D bond is stronger than C-H bond, it is anticipated that the overall enolisation rate of deuterated malonamide is lower than that of the undeuteriated. This is reflected by the data in Table 2.17, where k_{1H}/k_{1D} was 2.3.

The solvent isotopic effect was about 1.06. The mechanism shown in scheme 2.5 predicts that k_{D_2O} should be greater than k_{H_2O} by a factor of about 2-3 (specific H^+-catalysis). A possible explanation for the difference is that the O-protonated intermediate is stabilised (see scheme 2.6) by intramolecular H-bonding which diminishes the effect on the equilibrium caused by the substitution of solvent. The fact that H_2O is a better proton receiver than D_2O may account for the slight bigger k_{H_2O} than k_{D_2O}.



scheme 2.6

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CHAPTER 3

BROMINATION OF MALONIC ACID

3.1. Introduction

The bromination and iodination of malonic acid(MAL) has been studied for a long time [1-3]. The involvement of the enol tautomer as an intermediate for these reactions has been reported in the early work[4]. Under certain experimental conditions, the reaction was found to be zero order in [halogen], indicating that the rate limiting enolisation is followed by halogenation of the enol, enolate ion, enol carboxylate anion or protonated enol forms depending on the pH of the medium.

Recently, the rate constant for enolisation of malonic acid has been measured through an isotopic-exchange reaction using ^1H NMR spectroscopy[5] and by the kinetic studies of halogenation and nitrosation[6]. The values are all in reasonable agreement.

There can be both acid and base catalysed enolisation for the ß-dicarbonyl compounds, whose enol tautomer can be stabilised by the formation of intramolecular hydrogen bonded ring structure. For malonic acid, Leopold and Haim[7] have proposed a mechanism involving intramolecular acid-catalysis via a six-membered ring transition state at high acidity. The process involves the transfer of a proton from one of the two carboxylic acid groups to the carbonyl oxygen of the other acid group. Williams and Graham's work has also confirmed this mechanism through bromination and iodination of malonic acid. However, base catalysed reaction of malonic acid has not been fully investigated. Bhale[8] noted that the rate equation for enolisation of malonic acid consisted of two kinetic terms (see equation 3.1).

$$\text{Rate}=k[\text{MAL}] + k'[\text{MAL}]^2 \qquad (3.1)$$

The term $[MAL]^2$ seems to be related to base catalysed process brought about by the malonate ion, but no mechanistic explanation was given in the paper.

The work described in this chapter was undertaken to study the base catalysis in the enol formation of malonic acid through its bromination at low acidity.

3.2. Results

The dissociation constants of malonic acid have been reported with pk_1 2.85 and pk_2 5.70[9], so its dissociation is expected to be negligible at pH <1.85 and the malonate ion would be the dominant form at pH 3.85-4.70. We therefore examined the [MAL] dependence of the reaction at pH 1.0-1.85 and 3.75-4.65 respectively. No buffer or other base catalysts were added. The pH values of the malonic acid solution were adjusted with dilute hydrochloric acid and sodium hydroxide solution. The shift of pH values during bromination due to the release of the substituted hydrogen ion was negligible. Within the above pH ranges, the reaction was invariably zero order in $[Br_2]$. The data on the variation of the zero order rate constant with [MAL] at these conditions are given in tables 3.1-3.6 and the plots of $k_o/[MAL]_T$ vs $[MAL]_T$ at different pH values are presented in figures 3.1-3.2 .

Table 3.1. Zero order rate constants k_{obs} for the bromination of malonic acid at pH 1.0

[MAL]/M	10^4 k_{obs}/mol.l^{-1}.s^{-1}	$10^3 k_{obs}$/[MAL] /s^{-1}
0.050	1.93	3.86
0.075	2.94	3.92
0.100	3.96	3.96
0.125	5.02	4.02
0.150	5.98	3.98

Table 3.2 Zero order rate constants k_{obs} for the bromination of malonic acid at pH 1.4

[MAL]/M	$10^4 k_{obs}$/ mol.l^{-1}.s^{-1}	$10^3 k_{obs}$/[MAL]/s^{-1}
0.050	2.08	4.17
0.075	3.15	4.20
0.100	4.25	4.25
0.125	5.43	4.34
0.150	6.63	4.42

Table 3.3. Zero order rate constants k_{obs} for the bromination of malonic acid at pH 1.85.

[MAL]/M	10^4 k_{obs}/mol.l^{-1}.s^{-1}	10^3 k_{obs}/[MAL]/s^{-1}
0.050	2.25	4.50
0.075	3.70	4.93
0.100	5.15	5.15
0.125	6.81	5.44
0.150	8.40	5.60

Table 3.4. Zero order rate constants k_{obs} for the bromination of malonic acid at pH 3.75

[MAL]/M	10^4 k_{obs}/mol.l^{-1}.s^{-1}	$10^4 k_{obs}$/[MAL]/s^{-1}
0.101	0.35	3.51
0.125	0.52	4.15
0.152	0.74	4.88
0.177	1.05	5.94
0.202	1.34	6.66
0.247	1.98	8.02

Table 3.5 Zero order rate constants k_{obs} for the bromination of malonic acid at pH 4.3

[MAL]/M	10^4 k_{obs}/mol.l^{-1}.s^{-1}	10^4 k_{obs}/[MAL]/s^{-1}
0.101	0.222	2.20
0.126	0.346	2.75
0.153	0.474	3.10
0.176	0.648	3.69
0.202	0.797	3.94
0.246	1.18	4.78

Table 3.6 Zero order rate constants k_{obs} for the bromination of malonic acid at pH 4.65

[MAL]/M	10^4 k_{obs}/mol.l^{-1}.s^{-1}	10^4 k_{obs}/[MAL]/s^{-1}
0.101	0.136	1.35
0.125	0.210	1.68
0.151	0.289	1.91
0.176	0.410	2.32
0.212	0.545	2.57
0.248	0.710	2.86

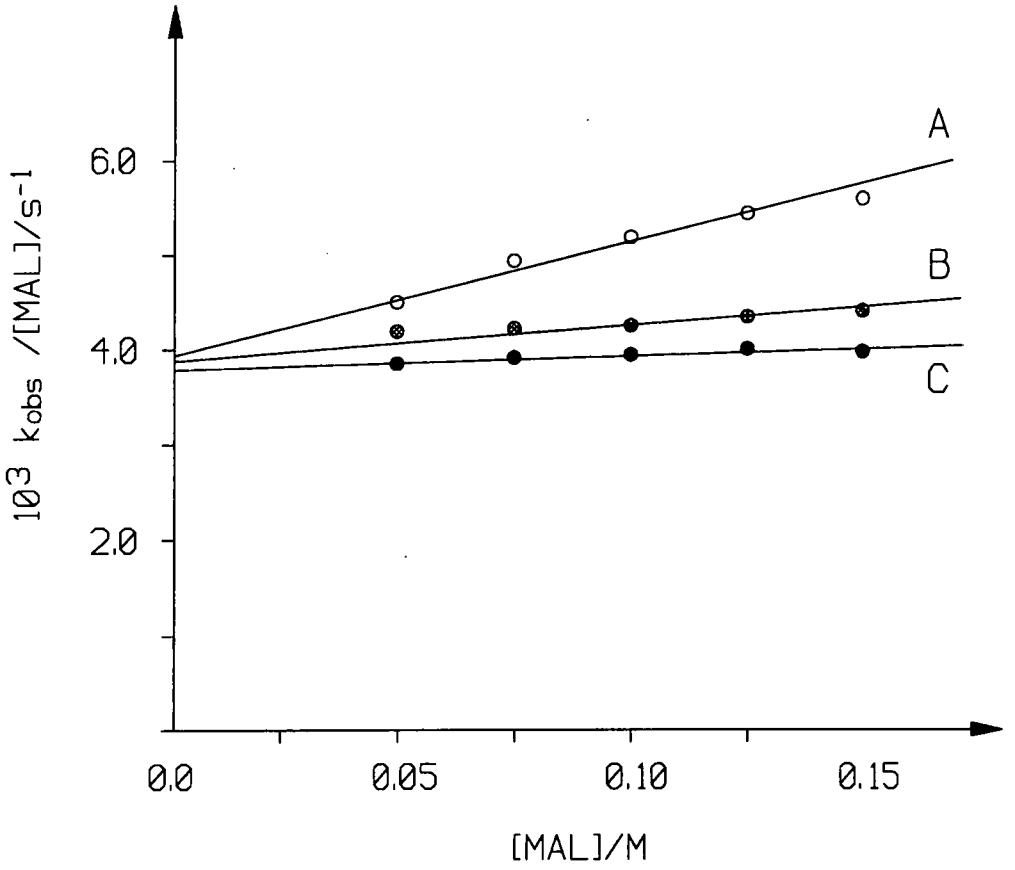

Figure 3.1 Bromination of malonic acid at pH 1.0, 1.4 and 1.85.

A- pH 1.85

B- pH 1.4

C- pH 1.0

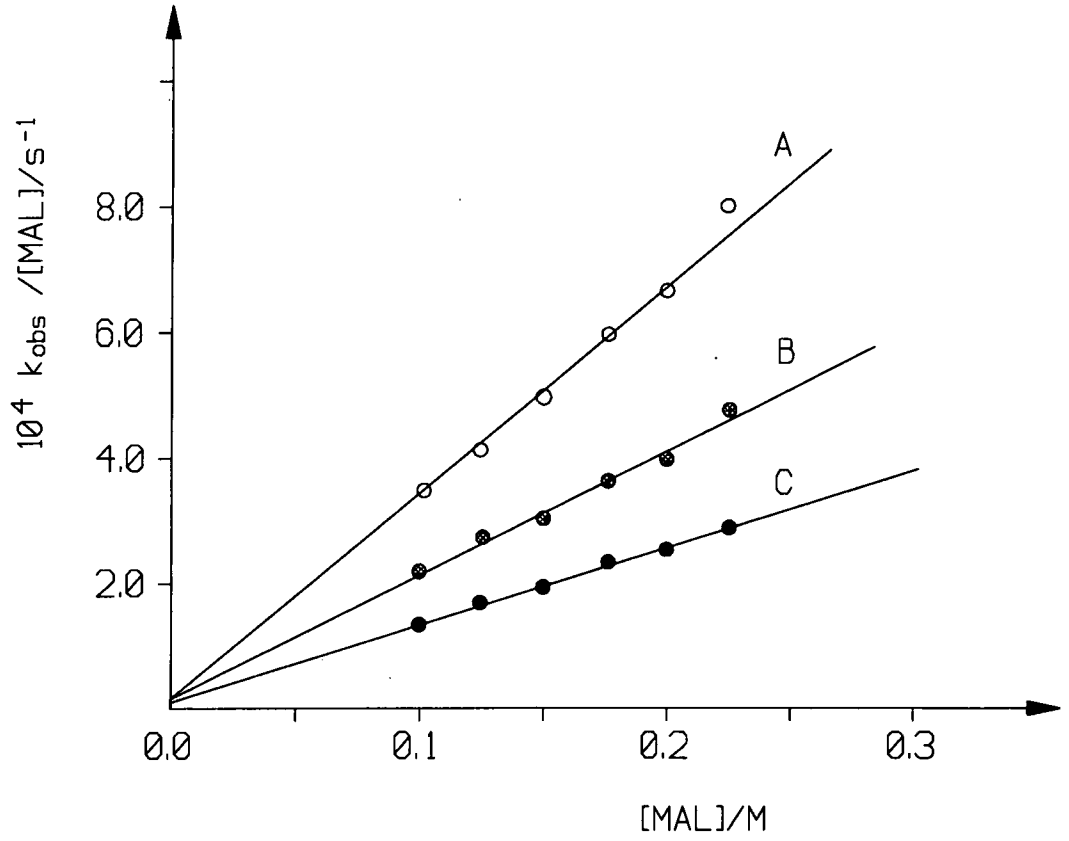

Figure 3.2 Bromination of malonic acid at pH 3.75-4.65.

A- pH 3.75

B- pH 4.30

C- pH 4.65

3.3. Discussion

At high acidity, the zero order rate constant for bromination of malonic acid is independent of $[H^+]$, which is consistent with a rate limiting enolisation process by intramolecular acid catalysis[6]. At low acidity (pH>1.0), the zero order behaviour observed in this work indicated that the enolisation is still the rate limiting step. Assuming that the malonate ion acts as a base catalyst, the bromination process can be expressed as scheme 3.1 and equation 3.2:

$$MAL \xrightarrow{k_1} Enol \xrightarrow{Br_2} product$$

$$\text{plus} \quad MAL + MAL^- \xrightarrow{k_2} Enol \xrightarrow{Br_2} product$$

Scheme 3.1

$$Rate = k_{obs} = k_1[MAL] + k_2[MAL][MAL^-] \qquad (3.2)$$

$$K_a = \frac{[MAL^-][H^+]}{[MAL]} \quad \text{or} \quad [MAL^-] = K_a \frac{[MAL]}{[H^+]} \qquad (3.3)$$

Equation 3.3 is the dissociation equation of malonic acid. Substitution of equation 3.3 into equation 3.2 leads to equation 3.4:

$$k_{obs} = k_1[MAL] + k_2 K_a \frac{[MAL]^2}{[H^+]}$$

$$\text{or} \quad \frac{k_{obs}}{[MAL]} = k_1 + k_2 K_a \frac{[MAL]}{[H^+]} \qquad (3.4)$$

At low pH (<1.85), the dissociation of malonic acid is insignificant, so the undissociated malonic acid concentration is close to the total concentration (see equation 3.5).

$$[MAL] \approx [MAL]_T \qquad (3.5)$$

Substituting equation 3.5 into equation 3.4 gives equation 3.6

$$\frac{k_{obs}}{[MAL]_T} = k_1 + k_2 K_a \frac{[MAL]_T}{[H^+]} \qquad (3.6)$$

In this case, plot of $k_{obs}/[MAL]_T$ vs $[MAL]_T$ should be linear with a slope of $k_2K_a/[H^+]$. This is consistent with figure 3.1. At pH 1.0, a near-horizontal straight line suggests that enolisation occurs exclusively via the intramolecularly acid-catalysed pathway, whereas base catalysis of malonate ion expressed by the second term of equation 3.6 is negligible. At the pH range between 1.4 and 1.85, slopes increased with pH due to the existence of catalysis by the small amount of malonate ion present. However, intramolecular acid-catalysis was persistently dominant in the reaction. Intercepts of above three profiles (in figure 3.1) are close to the k_1 value (~3×10^{-3} $mol.l^{-1}.s^{-1}$) in the literature[5].

At higher pH (>3.85), the majority of the substrate is present as the anion (equation 3.7).

$$[MAL^-] \approx [MAL]_T \qquad (3.7)$$

Combining equations 3.2, 3.3 and 3.7 give rise to equation 3.8.

$$\frac{k_{obs}}{[MAL]_T} = \frac{k_1[H^+]}{K_a} + \frac{k_2[H^+][MAL]_T}{K_a} \qquad (3.8)$$

The slopes ($k_2[H^+]/K_{a)}$ of plots $k_{obs}/[MAL]_T$ vs $[MAL]_T$ increased with $[H^+]$ or decreased with pH as shown in figure 3.2. Now the enolisation reaction is mainly via the malonate ion catalysed pathway. An average value of k_2 is (5.03 $\pm 1.8)x10^{-2}$ $l.mol^{-1}.s^{-1}$.

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CHAPTER 4

EXPERIMENTAL DETAILS

4.1. Chemical Reagents

Malonamide supplied by Aldrich (97%) was purified by recrystallisation and stored in a vacuum desiccator after the crystals had been dried in a 80°C oven. The melting point of purified malonamide was 169-171°C. Results of element analysis on the purified compound are given in table 4.1. All the other chemicals used in this work were commercially available with highest possible purity.

Table 4.1 Element analysis on purified malonamide

Elements	C	H	N	O
Calculated	35.26%	5.88%	27.42%	31.34%
Found	34.71%	5.94%	27.22%	32.13%

Stock solutions of sodium nitrite were made up daily as required. Iodine solutions were prepared as saturated in water at 25°C, whose concentration were obtained by titration with a standard solution of sodium thiosulphate and starch indicator. Bromine solutions were made up in distilled water, whose concentrations were calculated from the absorbance of bromine at 393 nm according to Beer-Lambert Law with a molar extinction coefficient, ε 128.39 mol. l^{-1}. cm^{-1} at 393 nm. Perchloric acid solutions were prepared by dilution of >70% perchloric acid and standardised against standard sodium hydroxide solution using phenolphthalein indicator.

Deuterium-labelled malonamide [$CD_2(COND_2)_2$] was prepared by dissolving malonamide [$CH_2(CONH_2)_2$] in D_2O. The conversion of $CH_2(CONH_2)_2$ into $CD_2(COND_2)_2$ was monitored by ^1H NMR technique (Bruker AC 250 MHz spectrophotometer). The central hydrogen atoms (CH_2) were regarded to be

completely replaced by deuterium as the ^1H NMR peaks of them (δ 5.7 ppm) disappeared. Then the solution was concentrated and vacuum dried.

4.2. pH measurements

A PTI-6 universal digital pH meter was used for all pH measurements, whose accuracy is ±0.02 pH units. All standard buffer solutions used were made from BDH buffer powders.

4.3. Experimental methods

4.3.1. UV/Visible spectrophotometry

Kinetic measurement for the nitrosation and iodination of malonamide were carried out by UV/Visible spectrophotometry. A Perkin Elmer Lambda 2 instrument was connected to an Epson PC AX2. The experiment was basically carried out as follows: (1)Two types of solutions were prepared. One was a mixed solution containing required concentrations of the substrate compound (MA), acid and/or catalysts. The other solution contained one of those which reacted with the former including sodium nitrite and iodine; (2)The two solutions were mixed according to desired proportion and a portion of the mixture was transferred immediately with a pipette into 1cm quartz cell. The cell was placed in the thermostatted cell holder of the spectrophotometer, and an identical quartz cell containing distilled water was used as a reference; (3)The reaction was measured by the change in absorbance at a fixed wavelength as a function of time.

4.3.2. Stopped-flow spectrophotometry

For fast reactions of bromination of malonamide and malonic acid, rate measurements were performed on a HI-TECH scientific SF-3 series stopped-flow spectrophotometer (shown in figure 4.1) connected to an Apple IIe microcomputer.

The typical experimental process is to prepare two solutions, typically bromine solution and that of substrate such as malonamide. The two solutions were stored in the two reservoirs (R) respectively. As the two syringes (S_1, S_2) were driven forward from a single position (P), equal volumes of the two solutions were mixed at the mixing point (MP). The reaction mixture then flowed into a third syringe (S_3). Upon filling, this syringe was forced against the stop trigger to stop the flow. At the same time, the reaction began to be monitored.

At the observation point (OP), the beam of monochromatic light passed through the cell containing the reaction mixture and its intensity is converted into an electrical signal and amplified by the photomultiplier. The output voltage across the photomultiplier with no absorbing species in the cell is approximately -6v, known as standing voltage. When the reaction starts, the changing absorbance in solution causes a small voltage change which superimposed on the standing voltage. In order to allow this small change to be amplified by the recording equipment, an equal but opposite voltage is applied to the standing voltage. The observed rate constants were calculated by observing the voltage variation with time. A kinetic analysis run by the Apple IIe microcomputer supplied by HI-TECH was used in the case of first order observed rate constants. Zero order rate constants were calculated manually by the voltage change with time.

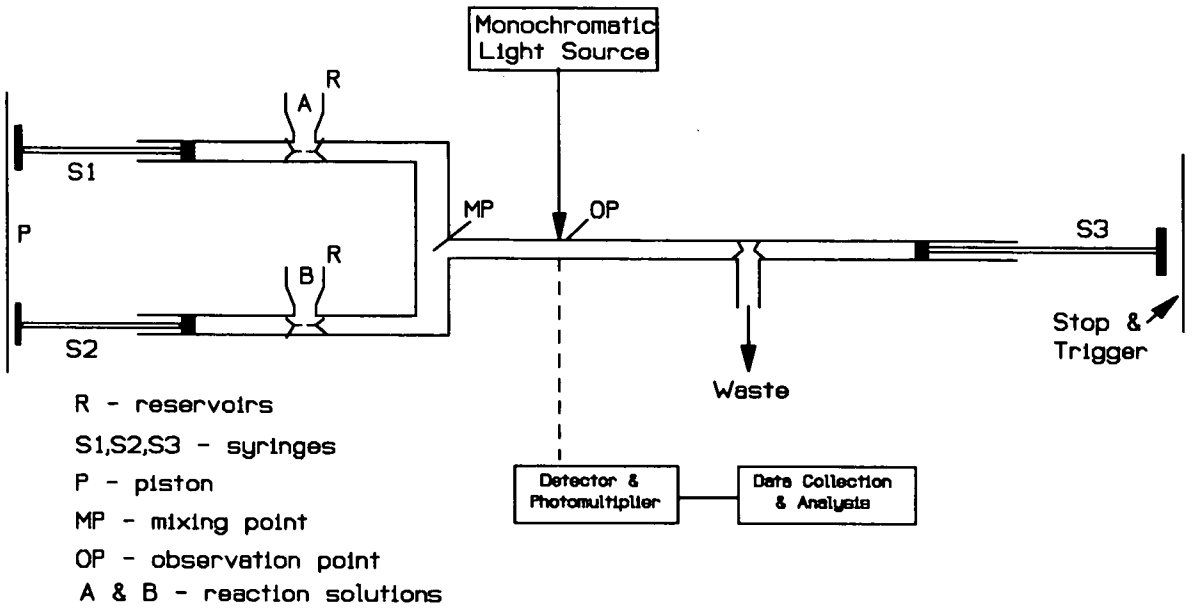

Figure 4.1. Schematic representation of stopped-flow spectrophotometer

4.4. Determination of rate constants

4.4.1. First order observed rate constants

Consider a simple reaction R $\rightarrow$ P, where R is a reagent and P a product. The rate of the reaction is equal to either the rate of decrease in the concentration of R or the rate of increase in the concentration of P with time (equation 4.1).

$$\text{Rate} = \frac{d[P]}{dt} = -\frac{d[R]}{dt} \qquad (4.1)$$

Bromination and nitrosation of malonamide were of first order kinetic behaviour. These reactions were observed by the disappearance of reagent such as bromine or nitrous acid. The first order rate equation is shown in equation 4.2.

$$-\frac{d[R]}{dt} = k_1[R] \qquad (4.2)$$

Integration of equation 4.2 gives rise to equation 4.3, where

$$\ln\frac{[R]_o}{[R]_t} = k_1 t \qquad (4.3)$$

$[R]_O$ and $[R]_t$ are the concentration of R corresponding to times t=0 and t=t respectively. If the reaction solution obeys the Beer-Lambert Law ($A=\varepsilon cl$) and the path length is assumed to be 1cm, the absorbances of A_O, A_t and A_∞ at t=0, t and ∞ can be expressed in equations 4.4, 4.5 and 4.6, respectively.

$$A_o = \varepsilon_R [R]_o \qquad (4.4)$$

$$A_t = \varepsilon_R [R]_t + \varepsilon_P [P]_t \qquad (4.5)$$

$$A_\infty = \varepsilon_P [P]_\infty = \varepsilon_P [R]_o \qquad (4.6)$$

$$([P]_\infty = [R]_o)$$

Since $[P]_t = [R]_o - [R]_t$, substitution in equation 4.5 gives

$$A_t = \varepsilon_R [R]_t + \varepsilon_P [R]_o - \varepsilon_P [R]_t \qquad (4.7)$$

Combining equations 4.4 and 4.6 as well as equations 4.6 and 4.7,

$$(A_o - A_\infty) = \varepsilon_R [R]_o - \varepsilon_P [R]_o$$

$$[R]_o = \frac{(A_o - A_\infty)}{(\varepsilon_R - \varepsilon_P)} \qquad (4.8)$$

$$(A_t - A_\infty) = \varepsilon_R [R]_t + \varepsilon_P [R]_o - \varepsilon_P [R]_t - \varepsilon_P [R]_o$$

$$[R]_t = \frac{(A_t - A_\infty)}{(\varepsilon_R - \varepsilon_P)} \qquad (4.9)$$

Substituting equation 4.8 and 4.9 into equation 4.3 gives

$$\ln \frac{(A_o - A_\infty)}{(A_t - A_\infty)} = k_1 t \qquad (4.10)$$

$$\text{or} \quad \ln(A_t - A_\infty) = \ln(A_o - A_\infty) - k_1 t \qquad (4.11)$$

A plot of $\ln(A_t - A_\infty)$ versus t is linear, the slope of which is equal to $-k_1$. The appearance or 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 reaction performed on the conventional UV/Visible spectrophotometer, the values of k_1 was calculated using First Order Rate Constant Evaluator (F.O.R.C.E), which is based on a plot of $\ln(A_t - A_\infty)$ versus time. As for experiments carried out on the stopped-flow spectrophotometer, the HI-TECH program was used to calculated values of k_1, based on $\ln(V_t - V_\infty)$ versus time plot (V as the output voltage is directly proportional to the absorbance). The program uses an iterative non-linear regression analysis to optimise the values of k_1. The k_1 values presented are the means of at least four separate identical runs.

4.4.2. Zero order observed rate constants

Zero order kinetics were observed for the bromination of malonic acid and iodination of malonamide at low acidity by the disappearance of reagent with time. The zero order rate constant of the reaction (R→P, where R is a reagent and P a product) is expressed as equation 4.12.

$$\frac{d[P]}{dt} = -\frac{d[R]}{dt} = k_o \qquad (4.12)$$

Integration of equation 4.12 gives

$$k_o t = [R]_o - [R]_t \qquad (4.13)$$

Substituting equations 4.8 and 4.9 into equation 4.13 gives

$$k_0 t = \frac{(A_0 - A_\infty)}{(\varepsilon_R - \varepsilon_P)} - \frac{(A_t - A_\infty)}{(\varepsilon_R - \varepsilon_P)}$$

$$k_0 t = \frac{(A_0 - A_t)}{(\varepsilon_R - \varepsilon_P)} \qquad (4.14)$$

A plot of $(A_0\text{-}A_t)$ versus time is linear with a slope of $k_o(\varepsilon_R - \varepsilon_P)$.

For experiments performed on UV/Visible spectrophotometer, the values of k_{obs} were calculated by the P.E.C.S.S. (Perkin Elmer Computerised Spectroscopy Software) kinetic program. Reactions monitored with the stopped-flow spectrophotometer were analysed by combination of the Beer-Lambert Law ($A=\varepsilon cl= \log(I_O/I_t)$ and the voltage light intensity relationship (equation 4.15).

$$\frac{I_o}{I_t} = \frac{V_o}{V_t} = \frac{V_o}{V_o - \Delta V} \qquad (4.15)$$

(since $V_t = V_o - \Delta V$)

I_O— The intensity of the incident light

I_t— The intensity of the transmitted beam of monochromatic light passed through a solution

V_O— The voltage across the cell with no absorbing species present

V_t— The transmitted voltage

ΔV— The voltage due to the absorbing species in the cell

Substitution of equation 4.15 into the Beer-Lambert Law gives equation 4.16 which generates equations 4.17 and 4.18.

$$A = \log_{10} \frac{V_0}{V_0 - \Delta V} \qquad (4.16)$$

$$A_o = 0 \qquad (\text{since } \Delta V = 0) \qquad (4.17)$$

$$A_t = \log_{10} \frac{V_0}{V_0 - \Delta V_t} \qquad (4.18)$$

Combination of equations 4.14, 4.17 and 4.18 leads to equation 4.19.

$$k_o t = -\frac{\log_{10} \frac{V_0}{V_0 - \Delta V_t}}{(\varepsilon_R - \varepsilon_P)} \qquad (4.19)$$

The values of k_O were obtained from the slope of the plot of $-\log_{10} \frac{V_0}{V_0 - \Delta V_t} \Big/ (\varepsilon_R - \varepsilon_P)$ versus time.

4.5. Kinetic measurement

Two examples are given to show typical first order behaviour for nitrosation of malonamide by UV/Visible spectrophotometer and zero order rate constants for bromination of malonic acid by stopped-flow spectrophotometer, respectively.

Example 1: Nitrosation of malonamide (MA)

The rate constants were measured on the Perkin Elmer Lambda 2 spectrophotometer at 25°C by following the disappearance of nitrous acid with time at 370 nm. A typical kinetic run is shown in table 4.2.

Table 4.2. Bromide ion catalysed nitrosation of malonamide

[MA]=0.2101M [HNO_2]=0.0099M

[Br^-]=0.600M [$HClO_4$]=0.300M

t/s	A_t	$10^2\ k_{obs}/s^{-1}$
0	0.452	/
5	0.420	1.60
10	0.392	1.59
15	0.365	1.60
20	0.340	1.60
25	0.317	1.61
30	0.295	1.62
35	0.276	1.62

$k_{obs}=1.61\ (\pm 0.01) \times 10^{-2}\ s^{-1}$

Example 2: Bromination of malonic acid in aqueous solution

The reaction conducted on the stopped-flow spectrophotometer was perfectly zero order in $[Br_2]$ at 393 nm. The values of k_o were calculated manually according to equation 4.19. Four identical runs at same condition brought about the mean values of k_{obs} (see table 4.3).

Table 4.3 Bromination of malonic acid

[MAL]=0.075M

pH=1.85

$[Br_2]=2.52 \times 10^{-3}M$

Run	$10^4 k_{obs}/mol.l^{-1}.s^{-1}$
1	3.67
2	3.67
3	3.68
4	3.77

$k_{obs}=3.70\ (\pm 0.04) \times 10^{-4}\ mol.l^{-1}.s^{-1}$

APPENDIX

1. Colloquia, lectures and seminars organised by the Department of Chemistry and Durham University Society attended during the period 1991-1992.

November 2,1991 Dr. R.More O'Ferrall
(Dublin University)
"Some Acid-Catalysed Rearrangements
in Organic Chemistry"

November 13, 1991 Prof. D.Gani
(St. Andrews University)
"The Chemistry of PLP Dependent Enzymes"

January 22, 1992 Dr. K.D.M.Harris
(St. Andrew University)
"Understanding the properties of Solid
Inclusion Compounds:

February 13, 1992 Dr. J.Saunders
(Glaxo Group Research)
"Molecular Modelling in Drug Discovery"

February 19, 1992 Prof. E.J.Thomas
(Manchester University)
"Application of Organostannanes to Organic Synthesis"

February 6 -	Dr. M.R.Crampton
March 18, 1992	(Durham University)
	"Spectroscopy of Reactions"
February 7-	Prof. D.L.H.Williams
March 13, 1992	(Durham University)
	"Physical Organic Chemistry"
February 6-	Dr. V.C.Gibson
March 18, 1992	(Durham University)
	"Advanced Organometallic Chemistry"
March 5, 1992	Dr. N.C.Billingham
	(University of Sussex)
	"Degradable Plastics-Myth or Magic?"
March 11, 1992	Dr. S.E.Thomas
	(Imperial College)
	"Recent Advances in Organoiron Chemistry"
March 12, 1992	Dr. R.A.Hann
	(ICI Imagedata)
	"Electronic Photography- An Image of the Future"
March 18, 1992	Dr. H.Maskill
	(Newcastle University)
	"Mechanistic Studies of Organic Group Transfer Reactions"

October 22, 1992 Prof. A.G.Davies

(University College, London)

"The Behaviour of Hydrogen as a Pseudometal"

November 18, 1992 Dr. R.Nix

(Queen Mary College, London)

" Characterisation of Heterogeneous Catalysts"

December 2, 1992 Prof. A.F.Hegarty

(University College Dublin)

"Highly Reactive Enols Stabilised by Steric Protection"

2. First year postgraduate induction course, October 1991.

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

A. Departmental organisation

B. Safety matters

C. Electrical appliances and infrared spectroscopy

D. Chromatography and microanalysis

E. Library facilities

F. Mass spectroscopy

G. Nuclear magnetic resonance spectroscopy

H. Glassblowing techniques