Kinetic and mechanistic studies on nitrosation of enols

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KINETIC AND MECHANISTIC STUDIES ON NITROSATION OF ENOLS

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By

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TO MY HUSBAND

MEMORANDUM

The work described in this thesis has been carried out in the Department of Chemistry at the University of Durham between January 1987 and October 1988. 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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ABSTRACT

Kinetic and mechanistic studies involving nitrosation reactions of some carbonyl compounds were undertaken. The nitrosation of the carbonyl compounds proceeded via their corresponding enol forms and the products of the reactions were the oximes. Significant nucleophilic catalysis by chloride, bromide, thiocyanate ions and thiourea was observed in all cases. Most of the kinetic results are consistent with a mechanism involving a rate limiting reaction between $H_2NO_2^+$/ NO^+ or the NOX species (in presence of nucleophile X^-) and the enol.The general mechanistic features of the nitrosation of the enols fitted in well with the pattern now well established in nitrosation at N, S, O, and other C sites.

The reactions of the enol form of ethylacetoacetate with the different nitrosating species were not encounter controlled indicating that the presence of the electron withdrawing group reduces the reactivity of the enol, relative to that derived from acetone.

Kinetic studies on nitrosation of dimedone and 1,1,1-trifluoropentane 2-4-dione revealed that reactions proceeded not only via the neutral enol but also via the enolate ion. The reactions of the latter with all the nitrosating species occurred at the encounter rate. The values of the rate constants suggest that the enolate ion is one of the most reactive species studied in nitrosation. Its high reactivity therefore makes it an excellent potential nitrite trap.

The mechanism of nitrosation of Meldrum's acid has not been completely elucidated. Some of the kinetics are complicated by mixed order reactions involving rate limiting enolisation and nitrosation. However there is kinetic evidence which points to reactions proceeding via both neutral enol and enolate ion.

CONTENTS

CHAPTER 1

Species effecting nitrosation

1.1 INTRODUCTION

Nitrosation is a vast area of chemistry with reactions occurring at nitrogen, carbon, oxygen, sulphur, halogen and metallic sites. There has been a great deal of kinetic investigation in order to gain insight into the detailed mechanisms of these reactions. The discovery that nitrosamines are powerful carcinogens has resulted in a greater interest in the study of some of the mechanistic aspects. These reactions are also very important from a synthetic viewpoint.

Most of the early kinetic studies of nitrosation were concerned mainly with N-nitrosation, particularly diazotisation reactions of aromatic primary amines. Later work has been extended to include nitrosation at oxygen, sulphur, carbon and other nitrogen sites. In the course of these investigations, a number of species have been identified which can effect nitrosation. Most of these reactions in aqueous media are carried out by the *in situ* generation of nitrous acid by using sodium nitrite in presence of mineral acid. In non-aqueous solvents where nitrous acid cannot be used, nitrosation can be brought about by alkyl nitrites. Molecular nitrous acid itself is not a nitrosating agent, but forms several nitrosating species depending upon the conditions in solution. At low acidity, nitrous anhydride (N_2O_3) is the effective nitrosating agent. At higher acidity an equilibrium is set up with either $H_2NO_2^+$ or NO^+ (nitrosonium ion). At moderate acidities, in the presence of halide or pseudohalide ions (X^-), NOX is formed in solution and this acts as the nitrosating agent.

1.2 The nitrous anhydride (N_2O_3) mechanism

In the course of their studies on diazotisation reactions of primary aromatic amines in dilute acid solution, Hantzsch and Schumann[1] expressed their results in terms of a second order rate equation (1.1). However, later work on nitrosation reactions of

$$\text{Rate} = k\,[Ar\,NH_3^+]\,[HNO_2] \qquad 1.1$$

ammonia[2] and other aliphatic amines[3] and some deamination[2] reactions was found to be consistent with third order kinetics as expressed in equation 1.2. There were in the early literature[4], many arguments

$$\text{Rate} = k\,[\text{Amine}]\,[HNO_2]^2 \qquad 1.2$$

and different mechanistic ideas put forward. The position was rationalised by Hammett[5] who suggested that the third order kinetics could be attributed to reactions occurring via nitrous anhydride. His results were interpreted in terms of Scheme 1.1. Further experiments by Hughes[6,7] and co-workers have provided support for the above

$$2HNO_2 \overset{K(\text{fast})}{\rightleftharpoons} N_2O_3 + H_2O$$

$$ArNH_2 + N_2O_3 \xrightarrow{\text{slow}} Ar\overset{+}{N}H_2NO + NO_2^-$$

$$\downarrow \text{ fast}$$

$$ArN_2^+$$

Scheme 1.1

mechanism and have achieved rate limiting N_2O_3 formation for very reactive amines at very low acidities (0.002M), consistent with rate

$$\text{Rate} = k\,[HNO_2]^2 \qquad 1.3$$

equation 1.3. O^{18} exchange[8] between nitrous acid and water has provided further support for intermediate N_2O_3 formation.

Until recently, the generally accepted value for the equilibrium constant for nitrous anhydride formation ($K = \frac{[N_2O_3]}{[HNO_2]^2}$) was 0.20 l mol^{-1} [9,10] in water at 25°C. It has now been redetermined as 3.03×10^{-3} l mol^{-1} [11]. Although both values have been measured spectrophotometrically, the extinction coefficient of N_2O_3 as determined by the later work is in agreement with that measured by pulse radiolysis[12]. It has been suggested that the large discrepancy in the two equilibrium constant values is probably due to the fact that the earlier values were affected by the high acidity of the medium used for the determinations. The new value has enabled the redetermination[13] of the bimolecular rate constants for the reaction of a number of amines with N_2O_3. The results show that the reaction of N_2O_3 with amines is diffusion controlled[14] and therefore explains the earlier observed constancy[15] in the k values (equation 1.2) over a wide range of basicity of these amines. It also seems likely[16] that N_2O_3 is comparable in reactivity to nitrosyl halides.

1.3 Nitrosation by $H_2NO_2^+$ or NO^+

In fairly strong acid solutions, the active nitrosating species is believed to be $H_2NO_2^+$ (nitrous acidium ion) or NO^+ (nitrosonium ion). Early kinetic studies by Hughes[17] and co-workers and Larkworthy[18] on the acid catalysed mechanism of diazotisation

reactions was interpreted in terms of scheme 1.2 with the formation of $H_2NO_2^+$ as the active nitrosating species. There is however no

$$HNO_2 + H^+ \overset{\text{fast}}{\rightleftharpoons} H_2NO_2^+$$

$$ArNH_2 + H_2NO_2^+ \overset{\text{slow}}{\longrightarrow} ArNH_2NO^+ \overset{\text{fast}}{\longrightarrow} ArN_2^+$$

Scheme 1.2

spectroscopic evidence[19] for this ion, in contrast to that for the nitrosonium ion which has been detected spectroscopically in very strong[19,20] acid solutions. Stedman[21] *et al.* have argued against formation of NO^+ in weak acidic solutions from their O^{18} exchange experiments between azide and nitrite ions. However, later work[22] on the nitrosation of hydrogen peroxide has provided some kinetic evidence which was interpreted in terms of rate limiting NO^+ formation. The experimental results were consistent with a mechanism as underlined in scheme 1.3.

$$H^+ + HNO_2 \underset{\text{fast}}{\overset{K}{\rightleftharpoons}} H_2NO_2^+$$

$$H_2NO_2^+ \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} NO^+ + H_2O$$

$$NO^+ + H_2O_2 \xrightarrow{k_2} HOONO + H^+$$

Scheme 1.3

At high $[H_2O_2]$, $k_2[H_2O_2] >> k_{-1}[H_2O]$ and formation of NO^+ is rate determining. Use of high concentration of hydrogen peroxide to effect transition from first to zero order kinetics has been criticised[16], since this behaviour could also be attributed to a medium effect.

Williams and co-workers[23,24] have observed a similar transition from first order to zero order kinetics in the course of their studies on the nitrosation of alcohols (equation 1.4).

$$ROH + HNO_2 \rightleftharpoons RONO + H_2O \qquad 1.4$$

They have however argued against rate limiting NO^+ formation since different alcohols yield different limiting rates and have interpreted their results in terms of a medium effect. Some recent theoretical calculations[25,26] on the protonated form of nitrous acid, support $\overset{+}{O}N{-}{-}H_2O$ (hydrated NO^+ species) as the effective nitrosating agent in weak acid solutions. It has also been recently reported[27] that in dilute acidic solutions of acetonitrile there is direct evidence for rate limiting formation of NO^+ from both alkyl nitrite and nitrous acid. The authors have observed a zero order kinetic dependence of the reaction on the concentration of substrate (alcohols and thioglycolic acid) and kinetically identified NO^+ as the effective nitrosating species in this solvent.

Whatever the effective nitrosating species, it appears that protonation of nitrous acid is necessary for all nitrosation reactions and for all possible substrates (S), the general rate equation for reaction with $H_2NO_2^+$ or NO^+ is expressed by equation 1.5.

$$\text{Rate} = k[S]\,[HNO_2]\,[H^+] \qquad 1.5$$

A comprehensive account of a number of these reactions has been presented by Williams[16] and by Ridd[14] in recent reviews. A k value (equation 1.5) of *ca.* 7×10^3 $l^2\ mol^{-2}\ s^{-1}$ is considered[14] to be the diffusion controlled limit for reactions of neutral substrates with $H_2NO_2^+$ / NO^+. For anionic substrates the k values are much higher as expected from electrostatic considerations and has indeed been found so for the thiocyanate ion[28] $\approx$ 11700 $l^2\ mol^{-2}\ s^{-1}$,

18000 l^2 mol^{-2} s^{-1} and 11800 l^2 mol^{-2} s^{-1} for thiosulphate[29] and benzenesulphinate[30] ions respectively and $\approx 4 \times 10^5$ l^2 mol^{-2} s^{-1} for enolate ions[31].

The first reported[32] pK_a value for the dissociation of nitrous acid is 3.35 at 25°C which has been measured conductometrically. Later, many other values have been reported. However, the most reliable one is that measured thermodynamically by Lumme[33] *et al* which is 3.148 at zero ionic strength.

1.4 Nitrosyl chloride and Nitrosyl bromide as nitrosating agents

At moderate acidities ($\approx$ 0.1M), solutions of nitrous acid when treated with halide ions (X^-) give rise to formation of low equilibrium concentrations of nitrosyl halides (NOX). First evidence[34] for involvement of nitrosyl halides in nitrosation reactions came from kinetic studies of diazotisation. Schmid[35,36] elucidated the kinetic form of this catalysis for diazotisation of amines with a rate expressed as in equation 1.6. and Hammett[5]

$$\text{Rate} = k[ArNH_2]\,[H^+]\,[HNO_2]\,[X^-] \qquad 1.6$$

$$X^- = Cl^-,\ Br^-$$

pointed out that this corresponds to equation 1.7 and proposed a mechanistic scheme (1.4).

$$\text{Rate} = k[ArNH_2]\,[NOX] \qquad 1.7$$

$$HNO_2 + X^- + H^+ \underset{\text{fast } k_2}{\overset{k_1}{\rightleftharpoons}} NOX + H_2O$$

$$NOX + ArNH_2 \xrightarrow[k]{\text{slow}} ArNH_2NO^+ \xrightarrow{\text{fast}} ArN_2^+$$

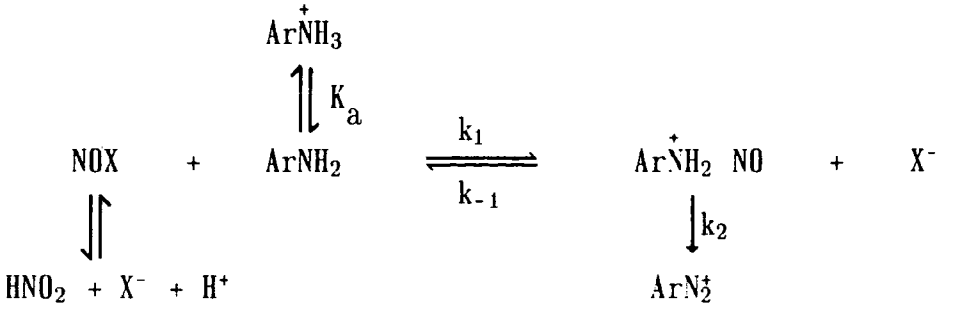
Scheme 1.4

The equilibrium constants (K_{NOX}) for the formation of NOCl and NOBr have been determined independently (by spectroscopic methods) in water at 25^0C as 1.14×10^{-3} [37] and 5.1×10^{-2} [38] $l^2\ mol^{-2}$ respectively. Iodide ions are also known[39] to catalyze nitrosation reactions, but iodine formation has prevented the determination of K_{NOI}. By using large concentrations of highly reactive substrates, it has been possible to achieve conditions where the first stage of scheme 1.4 could be made rate determining, so that rate of formation of NOCl[40] (k_1 = 975 $l^2\ mol^{-2}\ s^{-1}$ at 0^0C for reaction with azide ions) and NOBr[39] (k_1 = 1170 $l^2\ mol^{-2}\ s^{-1}$ for reaction with amines) could be measured. More recently, Williams[41] *et al* have found that for reactive thiols (N-acetyl cysteine, thioglycolic acid, mercaptosuccinic acid) at sufficiently high concentration of the substrate, nitrosation by NOX becomes so rapid as to allow the formation of NOX to be rate limiting. They have derived rate constants for NOX formation and its hydrolysis (k_1 and k_2 respectively in scheme 1.4) which are in reasonable agreement with each other for the three substrates studied. Also, the calculated equilibrium constants for NOX formation using the above determined k_1 and k_2 values, agree well with the literature values which were measured directly.

The activation energies and rate coefficients for the reaction of nitrosyl halides with amines approach the values expected for an encounter controlled reaction[42] ($k \approx 10^{10}\ l^2\ mol^{-2}\ s^{-1}$ and $E_{act} \approx 20$ kJ mol^{-1}).

For diazotisation reactions of NOCl and NOBr with aniline derivatives in methanol[43], it was found that plots of the first order rate constant. k_0 (defined by $d[ArN_2^+] / dt = k_0[HNO_2]$) against

[HCl] or [HBr] were curved. The kinetic measurements were interpreted in terms of scheme 1.5 where the initial N-nitrosation



Scheme 1.5

step was reversible and k_0 was given by equation 1.8 where K_a is the acid dissociation constant for $ArNH_3^+$ and $[A]_T$ is the total substrate concentration $\approx [ArNH_3^+]$.

$$k_0 = \frac{k_1\ k_2\ K_{NOX}\ K_a\ [X^-]\ [A]_T}{k_{-1}\ [X^-] + k_2} \qquad 1.8$$

$$(k_0)^{-1} = \left(k_1\ K_{NOX}\ K_a\ [X^-]\ [A]_T\right)^{-1} + k_{-1}/k_1 k_2 K_{NOX} K_a [A]_T \qquad 1.9$$

Plots of $(k_0)^{-1}$ vs $[X]^{-1}$ (equation 1.9) were found to be linear and values of k_1 and ratios of k_{-1}/k_2 could be obtained from these plots. Similar initial reversible N-nitrosation has also been observed for some diazotisation reactions in water[44]. The rate constants (k_1) show that as expected nitrosyl chloride is more reactive than nitrosyl bromide towards all substituted anilines studied. With the more basic amines, the rate constants level off as they approach the diffusion controlled limit.

Catalysis by chloride and bromide has also been observed in a large number of reactions involving O;[16,23] S;[16,45] and C[46] nitrosation

and very recently, molecular orbital calculations[47] have enabled the identification of the structural features involved in NOCl nitrosation.

1.5 Nitrosation by nitrosyl thiocyanate and S-nitrosothiouronium ion

Thiocyanate and thiourea catalysis in nitrosation reactions has been observed[45] in a number of cases and as in the case of chloride and bromide ion catalysis, is interpreted in terms of intermediate formation of nitrosyl thiocyanate and S-nitrosothiouronium ions.

$$SCN^- + H^+ + HNO_2 \underset{k_2}{\overset{k_1}{\rightleftharpoons}} NOSCN + H_2O \qquad 1.10$$

$$(NH_2)_2CS + H^+ + HNO_2 \underset{k_2}{\overset{k_1}{\rightleftharpoons}} (NH_2)_2\overset{+}{C}SNO + H_2O \qquad 1.11$$

The equilibrium constants for their formation have been measured as 32 l^2 mol^{-2} (at 20^0C)[48] and 5000 l^2 mol^{-2} (at 25^0C)[49] respectively. Al-Mallah[49] *et al* have also measured the rates of the forward (k_1 = 6960 l^2 mol^{-2} s^{-1} at 25^0C) and reverse reactions of nitrous acid with thiourea (equation 1.11). The larger values of the equilibrium constants K_{NOSCN} and $K_{(NH_2)_2\overset{+}{C}SNO}$ in comparison to K_{NOCl} and K_{NOBr}, makes thiocyanate and thiourea catalysis much more pronounced than that by chloride or bromide. Williams and co-workers have measured values of rate constants for reactions of aniline[24] and morpholine[50] with NOBr, NOSCN, and $(NH_2)_2\overset{+}{C}SNO$. From their results and also by taking into account the reactions of a large number of other substrates with the above NOX species, a general trend in reactivity is established[16] as NOCl > NOBr > NOSCN > $(NH_2)_2\overset{+}{C}SNO$ and catalysis by thiourea > thiocyanate > bromide >

chloride. This reactivity order can be explained in terms of the electronegativity of the halogens. The NO-X bond in NOCl will be much more polarised, hence more electrophilic than the corresponding NOBr or NOSCN bonds, owing to the greater electronegativity of the chlorine atom, thus making it more reactive. However the overall catalytic efficiency of the added nucleophile (X^-) is governed by the K_{NOX} values and the greater catalytic effect of thiocyanate in comparison to chloride or bromide ions is attributed to the larger value of K_{NOSCN}.

For very reactive substrates (aniline[8]; azide ion;[40] hydrazoic[28] acid, thioglycolic[41] acid) rate limiting NOSCN formation consistent with a rate equation 1.12 has been observed.

$$\text{Rate} = k\,[H^+]\,[HNO_2]\,[SCN^-] \qquad 1.12$$

k values of $\approx 1500\ l^2\ mol^{-2}\ s^{-1}$ at 0^0C for aniline and azide ion, and $\approx 11000\ l^2\ mol^{-2}\ s^{-1}$ at 25^0C for hydrazoic and thioglycolic acids are close to those obtained for reactions at encounter between a positively charged nitrosating species and an anion.

Thiocyanate[51] and thiourea[52] are also known to catalyse denitrosation reactions of nitrosamines. Nitrosyl thiocyanate or the S-nitrosothiouronium ion is formed respectively (equation 1.13) which is removed by means of a nitrite trap.

$$\overset{+}{\text{PhNH}}(\text{Me})\text{NO} + \text{SCN}^- \,/\!/\, (\text{NH}_2)_2\,\text{CS} \rightleftharpoons \text{PhNHMe} + \text{NOSCN} \,/\!/\, (\text{NH}_2)_2\,\overset{+}{\text{C}}\text{SNO}$$

$$\text{NOSCN} \xrightarrow{\text{nitrite trap}} \text{removed}$$

(1.13)

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CHAPTER 2

Enolisation, halogenation, and nitrosation of carbonyl compounds

2.1 INTRODUCTION:

Nitrosation reactions of carbonyl compounds have been known since Victor Meyer performed the reaction of β-keto esters with nitrous acid. The reaction is quite general for all carbonyl compounds and can be represented by equation 2.1. The products are usually the

$$RCOCHR'R'' \xrightarrow[HNO_2]{H^+} RCOCR'R'' \xrightarrow{\text{if } R'=H} R\text{-}COCR'' \qquad 2.1$$

(RCOCR'R'': NO; R-COCR'': NOH)

nitroso ketone — oxime

nitroso ketones which tautomerize to the more stable oximes. These reactions are very useful synthetically but until recently there had been little investigation into their mechanisms.

In acid solutions, these reactions have been considered to involve the reaction of the nitrosating agent with the enol form of the carbonyl compounds. This is by analogy with other electrophilic addition reactions like halogenation, racemisation and isotope exchange.

2.2 KETO-ENOL TAUTOMERISM

Enolisation is an example of prototropic rearrangement[1] in which a proton is transferred from a carbon to a hetero atom. This phenomenon which is commonly observed with ketones, β-keto esters and acids, diketones and malonic esters can be expressed by equation 2.2.

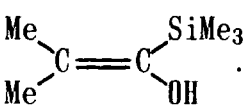
$$—\overset{|}{\underset{H}{C}}—\overset{|}{C}=O \rightleftharpoons —\overset{|}{C}=\overset{|}{C}—OH \qquad 2.2$$

keto form — enol form

In simple carbonyl compounds the equilibrium is usually shifted towards the keto form. However, several factors influence the direction of the equilibrium. For instance, hydrogen bonding in acetylacetone (equation 2.3) and electrostatic repulsion between the carbonyl groups in the keto form of 1,2-diketones usually favour the equilibrium towards the enol form.

(2.3)

Keto $\rightleftharpoons$ enol tautomerism has been extensively studied and has been the subject of a number of earlier reviews[2,3,4] which dealt primarily with factors which affect the equilibration of the tautomers. However, since the attempts of Fuson[5,6] to prepare exclusively the enol tautomer by introducing some bulky mesityl groups at one or both ends of the enolic C=C double bond, there now exists a large number of kinetically and thermodynamically stable enols. Hart[6] has presented a comprehensive rewiew of isolation and characterisation of a number of such kinetically stable enols. Most of the reactions for the generation of the enol involve methods that retard or prevent the proton transfer which convert it to keto. Photochemical[7] and thermal[8] methods (used for the synthesis of vinyl alcohol in the gas phase) have been particularly useful. Some simple fluorinated enols like pentafluoroacetone ($CF_2{=}C(OH)—CF_3$) have been prepared[6] and are very stable. Fusons work was later extended by Rappoport[9] and co-workers who isolated the first stable α-silyl enol,

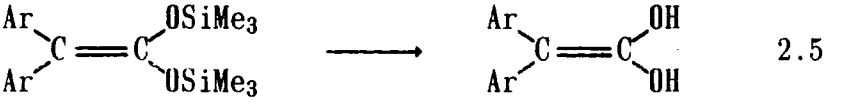


. They have further synthesised and studied spectral

properties of a range of 1-aryl 2,2-dimesityl ethenols[10] prepared by the reaction of a Grignard reagent with dimesityl ketene (equation 2.4).

$$Mes_2\ C{=}{=}C{=}{=}O \xrightarrow[2.\ H^+\ /\ H_2O]{1.\ ArMgBr/THF} Mes_2\ C{=}{=}C(OH)Ar \qquad 2.4$$

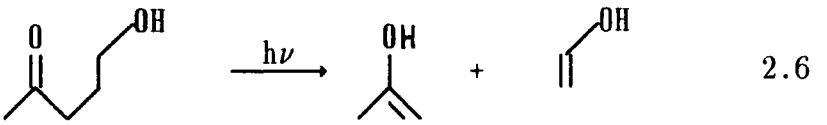
They have found that in the aromatic series, the stability of the enol increases with increase in the bulk of the α-aryl group whereas in the α-alipatic substituted series[11], stability decreases along the series H > Me > Et > i-Pr > t-Bu. From the results of their extensive studies they conclude, that the greater stabilisation of the enol is mainly due to the destabilisation of the keto form by electron withdrawing α-aryl substituents. Also, a combination of polar, resonance and H-bonding effects is not sufficient to account for the intrinsic stability of some enols, but steric effects also play an important role in contributing to their stability. The introduction of bulky groups to stabilise the enol has also found application in the synthesis of the first kinetically stable acid and ester enols[12] from silylated ketene acetals (equation 2.5) by introducing a pentamethyl phenyl group.



2.5

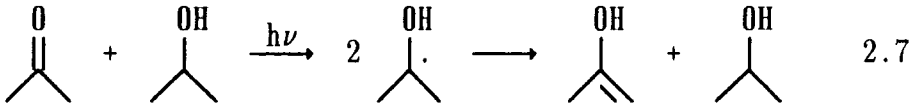
Ar = Me_5C_6 (2,3,4,5,6-pentamethyl phenyl)Enols have also been generated in aqueous solution (under conditions where the kinetics of their reactions may be measured accurately) by flash photolysis of the appropriate ketone precursors. Kresge[13] *et al* and Capon[14] have used

this method to prepare enols of acetone, acetophenone and isobutyraldehyde, and more recently, vinyl alcohol[15] (equation 2.6). Capon has characterised the enols by either I.R., N.M.R., U.V. spectroscopy or by ClDNP. The techniquehas also been used by Weedon[16]



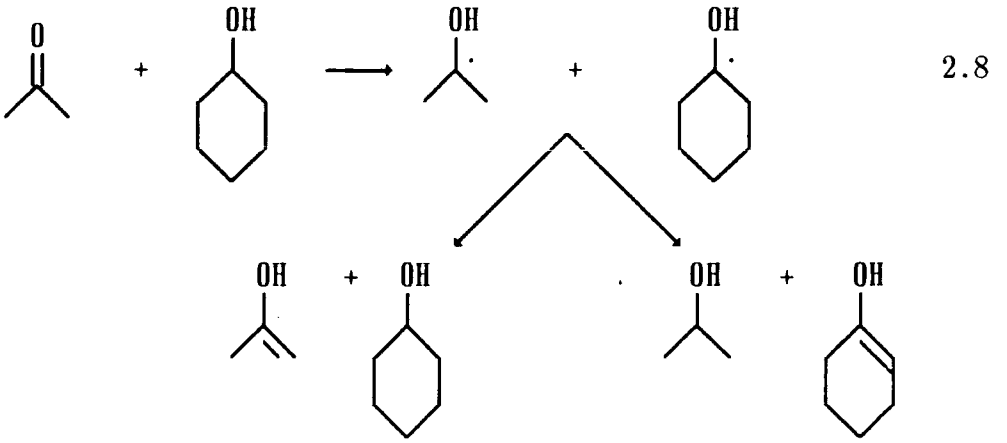
2.6

to produce a series of dienolates of β-alkyl α-β unsaturated ketones and measure their rates of reketonization in aqueous basic solution. Very recently Kresge and co-workers report[17] the generation of an enol by another new method which involves photo-oxidation of alcohols by carbonyl compounds to produce ketyl radicals which further disproportionate to the enol (equation 2.7). Flash photolysis of acetone and cyclohexanol produces two transients which decay at



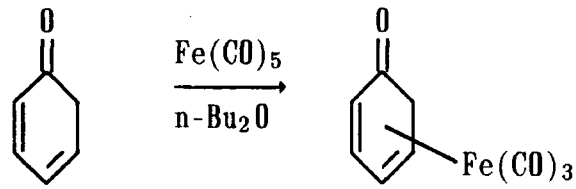
2.7

different rates and have been identified as their respective enols (equation 2.8).



2.8

Some of the techniques which are used to prepare stable forms of enols have been used[6] to stabilise the keto form of some compounds like phenols, for which the enol form is usually the predominant tautomer. Complexation with metals has stabilised both enol and keto forms of phenols, as in the conjugated tautomer of phenol[18] which is stabilised as the iron-tricarbonyl complex (equation 2.9).



2.9

One of the most important aspects of the keto $\rightleftharpoons$ enol tautomerism has been the measurement of the enol content in the equilibrium. From as early as 1912, there have been attempts[19] to measure the keto-enol equilibrium constants (K_e) by physical, chemical, and spectroscopic methods. The halogen titration[19] method was very much in use in early years. Different groups[20] of workers have modified this original method of Meyer but their results differed from each other and were not in agreement with the later developed indirect techniques.

Detailed investigations have been carried out by Guthrie using three different indirect approaches. A thermodynamic approach[21,22]based on the determination of Gibbs free energy for enol ether formation, a kinetic approach[23] in which the enol content was estimated as the ratio of the rate constant for acid catalysed enolisation of the carbonyl compound and acid-catalysed hydrolysis of the corresponding methyl enol ether, and the third[24] was based on

determination of dissociation constants of the enol and keto forms. Although these methods led to concordant results and also enabled determination of the equilibrium constant for a number of keto-enol systems, they have been critisized by Dubois[25,26] *et al* especially on the ground that it was assumed that rate constants for enol ketonization are equal to those for enol ether hydrolysis. These authors have proposed another approach based on kinetic measurements of acid catalysed halogenation of ketones at low halogen concentration, when the enolisation step is rate determining. The values of K_e so obtained are much less than those obtained by halogen titration methods and are in fair agreement with some results obtained by Guthrie.

The important drawback of this method is that it is still an indirect method and is based on the assumption that halogenation occurs on encounter with molecular halogens.

N.M.R. spectroscopy[27] is also a powerful tool in measuring the K_e values, but it has limitations in detecting too high or low enol content. Recently, Moriyasu[28] *et al* have reported the measurement of K_e values of some β-dicarbonyl compounds by high performance liquid chromatography. Kresge[29] and co-workers have developed a new and direct method which is based on the kinetic studies of base catalysed ketonization of the enol (generated by flash photolysis) to the more reactive enolate ion (equation 2.10). From the analysis of the

$$\begin{array}{ccccc} RC(OH)=CH_2 + OH^- & \overset{K}{\rightleftharpoons} & RC(O^-)=CH_2 + H_2O & & \\ & & \downarrow k & & \\ & & RC(O)CH_3 + OH^- & & \end{array} \qquad 2.10$$

kinetic data, the equilibrium constant (K) and rate contant (k) can

be determined which are related to the acid dissociation constants of the enol (K_a^E) and the keto form (K_a^K) respectively by equations 2.11 and 2.12. The ratio K_a^E / K_a^K = the keto-enol equilibrium constant (K_e)

$$K_a^E = K \times K_w \qquad 2.11$$

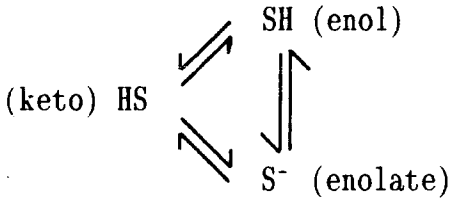
$$K_a^K = k_{OH}^E \; K_w \; / \; k \qquad 2.12$$

K_w = self ionisation constant of water

k_{OH}^E = specific rate for hydroxide catalysed enolisation of the carbonyl compound.

The authors have determined the K_e values of acetone, acetophenone, butanone and a few other carbonyl compounds. K_e values for sterically crowded polyaryl substituted enols (Fuson enols) and acenaphthols have been measured in non-aqueous solvents by Rappoports[30] linear free energy correlation between K_e values for stable β-β dimesityl and unstable β-β unsubstituted α-enols. The plot is for measuring pK_e values for simple enols which cannot be measured easily.

The keto form of carbonyl compounds can be in equilibrium with either the enol or its corresponding enolate ion (scheme 2.1) depending on the value of the acidity constants for enols ($K_{SH}^{S^-}$).



Scheme 2.1

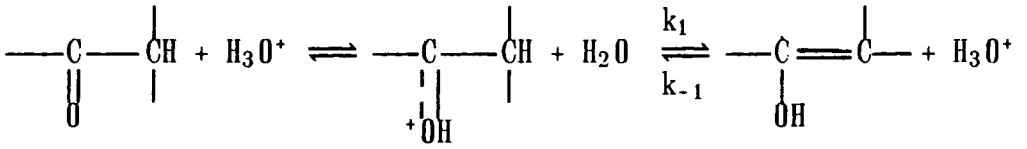
Initially these values were determined[20] by halogen titration methods, but the values are doubtful as the equilibrium constants (K_e) are questionable. A comprehensive account of a number of other methods

which have enabled measurement of the $K_{SH}^{S^-}$ values , has been presented by Toullec[31]. Recently, Haspra[32] *et al* have developed a straightforward method in which the initial absorbances of the transient enol (produced by the Norrish II photoelimination of ketone precursors) is dependent upon the pH, leading to a sigmoid titration curve (when absorbance values are plotted as a function of pH). The inflection point of the curve gives the $pK_{SH}^{S^-}$ value. This method has also been used by Kresge[29] *et al* for determination of $pK_{SH}^{S^-}$ of acetone and by far appears to be the most effective method.

Guthrie[24] has also estimated values for $pK_{HS}^{S^-}$ (i.e. dissociation constant for the keto form of the carbonyl compound as a carbon acid) by the help of equation 2.13. The method has been applied to a series of p-substituted acetophenones.

$$pK_{HS}^{S^-} = pK_{SH}^{S^-} - \log K_{HS}^{S^-} \qquad 2.13$$

A comprehensive account of the thermodynamic and stereochemical aspects of this tautomerism has been reviewed by Toullec[31]. The generally accepted mechanism for acid-catalysed enolisation is given[33] by equation 2.14, where there is an initial rapid formation of



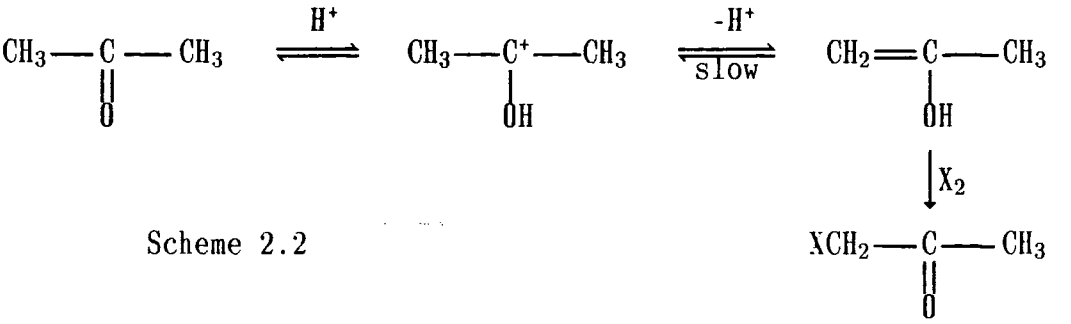
(equation 2.14)

the hydroxycarbonium ion followed by α-H^+ elimination in presence of a base (water in a strong acid). This is similar to a Pedersen[34] type mechanism. Work on solvent and CH-CD kinetic isotope effects by different groups of workers[25,35,36] has independently supported the above mechanism.

2.3 Halogenation of carbonyl compounds

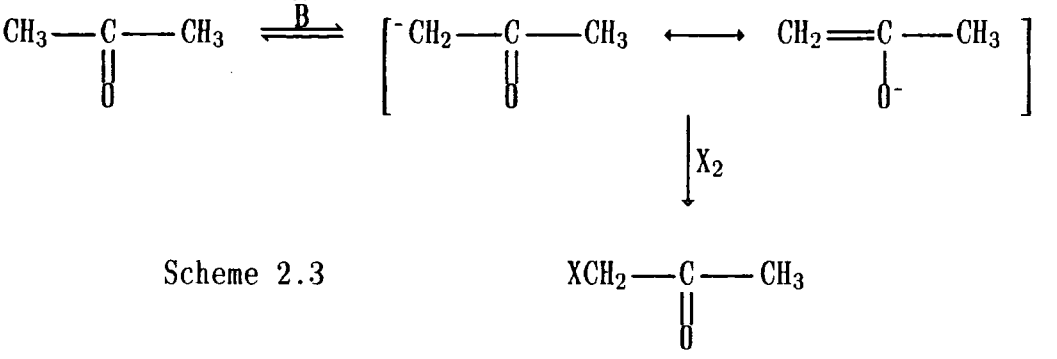
It has been generally assumed[37] until recently (without any evidence), that the mechanism of nitrosation of carbonyl compounds is similar to that of halogenation. In contrast to the former, the mechanisms of halogenation reactions have been extensively studied since the pioneering work of Lapworth[38] who showed that the rate of halogenation of acetone was independent of the nature or concentration of the halogen, and was subject to catalysis by both acids and bases. He proposed schemes 2.2 and 2.3 for both reactions.

Acid catalysis:



Scheme 2.2

Base catalysis:



Scheme 2.3

In acid catalysis the intermediate attacked is the enol, which undergoes an S_E2' rearrangement to the product. In base catalysis reaction occurs via the more reactive enolate ion. Later, detailed studies of these reactions involving a number of substrates were

performed by Bell[40] and co-workers. Their work on acid catalysed reactions has shown that the most commonly observed kinetic form for a reaction involving molecular halogen is given by equation 2.15.

$$\frac{-d[\text{halogen}]}{dt} = k\ [\text{ketone}]\ [H^+] \qquad 2.15.$$

For the chlorination of acetone, they proposed a scheme as in 2.4. Their results were consistent with an observed rate constant as

$$SH + H^+ \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} HS + H^+$$

$$HS + Cl_2 \xrightarrow{k_2} SCl + H^+ + Cl^-$$

Scheme 2.4

(SH and HS are keto and enol forms respectively, of the compound.) expressed in equation 2.16.

$$k = \frac{k_2\ k_1\ [H^+]\ [Cl_2]}{k_{-1}\ [H^+] + k_2\ [Cl_2]} \qquad 2.16$$

At high halogen concentration, $k = k_1\ [H^+]$, and the reaction is zero order in halogen (i.e. it becomes independent of the concentration and nature of the halogen, thus supporting the observation of Lapworth), implying that the slow rate limiting step of the reaction is the formation of the enol or the enolate ion, which then subsequently reacts with the halogen more rapidly than reverting to ketone. However, at low halogen concentration, the kinetic form changes to equation 2.17.

$$\frac{-d\ [\text{halogen}]}{dt} = k\ [\text{ketone}]\ [X_2] \qquad 2.17$$

and, from equation 2.16

$$k = k_2 K_e [Cl_2] \quad \left(\text{because } K_e = \frac{k_1}{k_{-1}}\right) \quad 2.18$$

and the rate of reaction has a first order dependence on concentration of halogen (equation 2.18), and the reaction of the halogen with the enol form is the slow rate limiting step.

Using low halogen concentration and the values of the keto-enol equilibrium constant (K_e), the actual rate constants for halogenation of a number of carbonyl compounds have been determined. However, the uncertainty[24,25] in the K_e values casts doubt on these rate coefficients, as reported earlier. In studying the chlorination[39] and bromination[40,41] of acetone it was found that in contrast to bromination, the rate constant for chlorination ($k = 7.3 \times 10^5$ l mol^{-1} s^{-1}) did not vary with concentration of chloride ion, suggesting that Cl_2 and Cl_3^- react at similar rates.
For bromination, analysis of the variation yielded rate constants for reaction of Br_2 ($k = 1.03 \times 10^7$ l mol^{-1} s^{-1}) and Br_3^- ion ($k' = 2.8 \times 10^6$ l mol^{-1} s^{-1}). It was therefore concluded without any explanation that for halogenation, bromine is more reactive than chlorine. Later work of Dubois and Toullec[25] has shown on the contrary, that the reactivity of an enol to the halogens is similar, suggesting that reactions occur at encounter and the previous work of Bell and co-workers is in error, because of the use of unnecessarily high halogen concentrations. Recently, the mechanisms of chlorination of some alicyclic ketones in carbon tetrachloride[42] and that of acetone using trichloroisocyanuric acid as the chlorinating agent[43], have been kinetically examined. The zero order dependence of the reaction on

halogen concentration is again consistent with rate limiting enolisation.

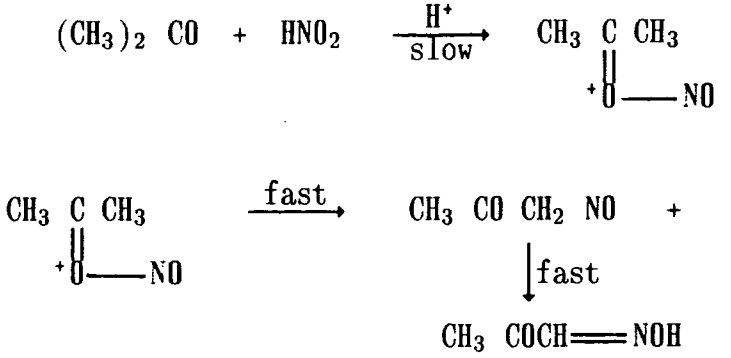
Reactions of carbonyl compounds where the enol is the bulk component, have also been studied[44]. The rate constants obtained in these cases should be much more precise, as the uncertainty arising from the keto-enol equilibrium constant values is avoided. Compounds with known enol acid dissociation constant values ($pK_{SH}^{S^-}$) have been studied, and it was found that for some enols the reaction rate was independent of acidity over the range pH 1-3, implying that the rate of halogenation is independent of whether the bulk of substrate exists as enol or enolate. This is interpreted in terms of an encounter reaction of enol and enolate with the halogenating agent. However, the low values of the rate constants $\approx 10^6$ l mol^{-1} s^{-1} (much less than that for encounter) and the fact that for some compounds like diethyl malonate[40] and methylmethanetricarboxylate[44], halogenation reaction with the enolate ion occurs at encounter, but not with the enol, questions the validity of the above explanation.

Base catalysed halogenation of a number of carbonyl compounds has also been studied[45,46]. The mechanism has been shown kinetically[47,48] to involve attack by hypohalite ion on the enolate ion. Rate determining enolate formation has made possible the determination of rate constants for base catalysed enolisation.

2.4 Nitrosation of carbonyl compounds.

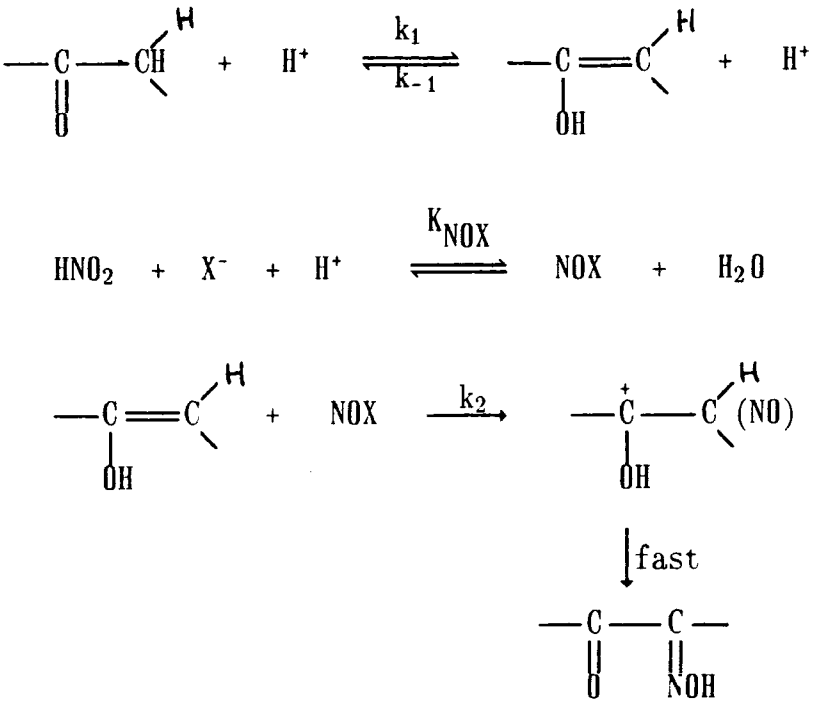
In spite of the synthetic importance[49] of these reactions, until recently, the only reported mechanistic work on nitrosation of carbonyl compounds was that of acetone. This investigation has argued against electrophilic attack of nitrosating agent on the enol form (as

in halogenation). It was reported that the rate of nitrosation of acetone is *ca.* 7 times faster than rate of enolisation under the same experimental conditions, and a mechanism was proposed which involved attack of the carbonyl oxygen atom by the nitrosating agent, followed by an internal rearrangememt of the nitroso group to the adjacent carbon atom (scheme 2.5).



scheme 2.5

Williams[51,52] *et al* have indicated that the above work is in error because a third order rate constant has been compared to a second order rate constant, leading to an incorrect estimation of the reactivity ratio (nitrosation : enolisation). Their more recent experimental work has in fact shown that nitrosation is not faster than enolisation under conditions employed by Singer and Vamplew. Williams and co-workers have studied the mechanism of nitrosation of acetone (Ac), ethylmethylketone (EMK), 1,3-dichloroacetone (DCA), and acetylacetone (AcAc). For their reactions with Ac, EMK, and DCA in presence of nucleophilic catalysts (Br^-, Cl^-, SCN^-) they observed a zero order dependence of the reaction on $[HNO_2]$ when the nucleophile concentration was quite high. However, with very low [nucleophile] the reaction order changed from zero to first. They have interpreted their results in terms of scheme 2.6 where nitrosation proceeds via the enol tautomer.



scheme 2.6

At high concentration of nucleophile (X^-), $k_2 K_{NOX}[HNO_2][X^-][H^+] >> k_{-1}[H^+]$ and the rate which is governed by acid catalysed enolisation is expressed as in equation 2.19. Whereas at low concentration of X^-

$$\text{Rate} = k_1 [\text{ketone}] [H^+] \qquad 2.19$$

the other limiting condition is achieved, when attack of the nitrosating species (NOX) on the enol becomes rate limiting (equation 2.20). The situation is therefore analagous to the halogenation of carbonyl compounds. The rate constants for enolisation

$$\text{Rate} = k_2 [\text{ketone}] [NOX] \qquad 2.20$$
$$= k_2 K_{NOX} [H^+] [HNO_2] [X^-] [\text{ketone}]$$

K_{NOX} = equilibrium constant for the formation of NOX.

(equation 2.19). compare well with those obtained from halogenation and isotope exchange kinetics.

The kinetic behaviour of DCA in presence of high [nucleophile] was similar to that of Ac and EMK, except that there was an initial fast reaction which was not zero order in $[HNO_2]$. It was however first order in [DCA] and was not acid catalysed. From the amount of nitrous acid consumed for this initial part of the reaction, the authors have estimated the keto-enol equilibrium constant (K_e = 3.2×10^{-3}) and the rate constant for enolisation ($k_e = 3.2 \times 10^{-6}$ s^{-1}) which compares with those derived by Guthrie[24] ($K_e = 1 \times 10^{-2}$) and Bell[40] ($k_e = 3.2 \times 10^{-6}$ s^{-1}) respectively. At lower concentration of X^- it was not possible to achieve a complete change from zero to first order kinetics. The authors have analysed the kinetic data for mixed zero and first order reactions by using an approach suggested by Dubois[26] *et al* and have obtained rate constants for both enolisation (equation 2.19) and nitrosation (equation 2.20).

For AcAc there was no direct evidence that the reaction occurred via the enol form as it was not possible to achieve rate limiting enolisation, even in the presence of high nucleophilic catalyst concentration, but by analogy with the other ketones it was proposed to proceed via the enol. For reactions in the absence of nucleophilic catalysts, for Ac and EMK the reaction rate was found to be proportional to $[HNO_2]^2$ which was interpreted in terms of reactions via N_2O_3. Whereas for AcAc and DCA the reactions were first order in both $[HNO_2]$ and [ketone], indicating nitrosation via $H_2NO_2^+/NO^+$. This behaviour has been interpreted in terms of the reactivity of the enol. Due to the presence of the additional electron withdrawing groups -COMe and Cl in AcAc and DCA respectively, their enols are much less reactive and hence react preferentially with the more reactive positively charged electrophile $H_2NO_2^+/NO^+$, whilst for the

more reactive enols of Ac and EMK, N_2O_3 pathway is favoured. The results of the derived rate rate constants for enolisation and for attack of NOX (for reactions in the presence of X^-) and $H_2NO_2^+/NO^+$ or N_2O_3 (for uncatalysed reactions) are presented in table 2.1. Owing to the uncertainty over the K_e values for Ac, where a number of values have been reported, the authors have based their results on those presented by Guthrie[24] and more recently by Kresge[29] *et al.* It is clear from the results that the trend in reactivity NOCl > NOBr > NOSCN, now well established in nitrosation, is followed and the reactivity trend of enols EMK ≈ Ac > AcAc > DCA is much as expected.

TABLE 2.1

	Acetone	Ethyl methyl ketone	Acetyl acetone	1,3-dichloro acetone
k_e	3.8×10^{-5}	4.9×10^{-5}	-	3.2×10^{-6}
K_{NOCl}	1.4×10^{8} [a] 1.5×10^{9} [b]	4.6×10^{9}	1.0×10^{5}	1.2×10^{4} [c] 3.8×10^{4} [d]
K_{NOBr}	7.0×10^{7} [a] 7.4×10^{8} [b]	3.8×10^{9}	1.4×10^{4}	2.8×10^{3} [c] 8.8×10^{3} [d]
K_{NOSCN}	-	3.0×10^{8}	500	-
k_{TU}	-	-	38	-
$K_{N_2O_3}$	1.2×10^{9} [a] 1.3×10^{10} [b]	2.5×10^{9}	-	-
$K_{NO_+} k_{NO_+}$	-	-	36 $l^2mol^{-2}s^1$	2.4 [c] 7.5 [d] $l^2mol^{-2}s^{-1}$

[a] Using $K_e = 6.3 \times 10^{-8}$. [b] Using $K_e = 6.0 \times 10^{-9}$.

[c] Using $K_e = 1.0 \times 10^{-2}$. [d] Using $K_e = 3.2 \times 10^{-3}$.

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CHAPTER 3

Nitrosation of Ethylacetoacetate

3.1 INTRODUCTION

Ethylacetoacetate (EAA) has been extensively studied[1], especially during the development of the concept of tautomerism. The equilibrium (equation 3.1) in this compound is greatly in favour of the keto form (I) as there are no factors contributing to the stabilisation of the

$$CH_3\ CO\ CH_2\ CO_2\ C_2H_5 \underset{}{\overset{K_e}{\rightleftharpoons}} CH_3\ C(OH)=CH\ CO_2\ C_2H_5 \qquad 3.1$$

(I) (II)

enol form (II). It has however been possible to isolate both the keto and enol forms[2]. The equilibrium constant for enolisation (K_e) has been measured in a number of solvents[1]. In water its value, determined[3] by spectroscopic methods is reported as 5.02×10^{-3}. The nitrosation reactions of β-keto esters are well known[4] and have been much used synthetically in the preparation of α-oximino acids, esters and ketones since Victor Meyer first prepared[5] ethyl α-oximino acetate from ethyl acetoacetate. In view of the synthetic importance of these reactions, the mechanistic study of nitrosation[6,7] of carbonyl compounds has been further extended in this work to esters like ethylacetoacetate and the results of the kinetic investigations in acidic solutions and in presence of added nucleophiles (chloride, bromide and thiocyanate ions) are reported.

The reaction was monitored spectrophotometrically at 25^0C, at 370nm wavelength, by following the disappearance of the absorbance due to nitrous acid. All the experimental runs were carried out in 20% dioxan - water mixture because of the very low solubility of EAA in water and, its concentration was in large excess over that of nitrous acid.

3.2 Uncatalysed reactions

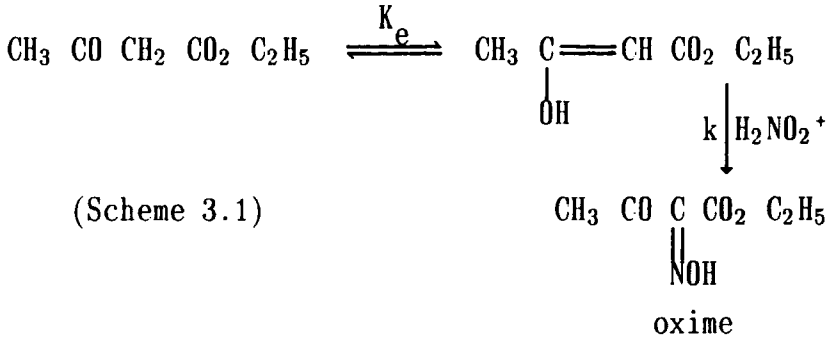
Reactions were studied by varying concentrations of either acid ($HClO_4$) or EAA, keeping that of the other constant. The kinetic runs showed good first order behaviour with respect to nitrous acid and the variation of the observed rate constant (k_0) with acid and EAA concentrations is given in table 3.1 and figure 3.1.

Table 3.1: Dependence of k_0 upon [acid] and [EAA]

$[NaNO_2] = 0.01M$

10^2 [Acid] / M	10 [EAA] / M	10^3 k_0 / s^{-1}
4.2	2.5	2.20
9.4	2.5	4.88
14.5	2.5	7.50
19.7	2.5	9.96
15.5	1.0	3.04
15.5	2.0	5.80
15.5	3.0	9.27
15.5	4.0	11.6

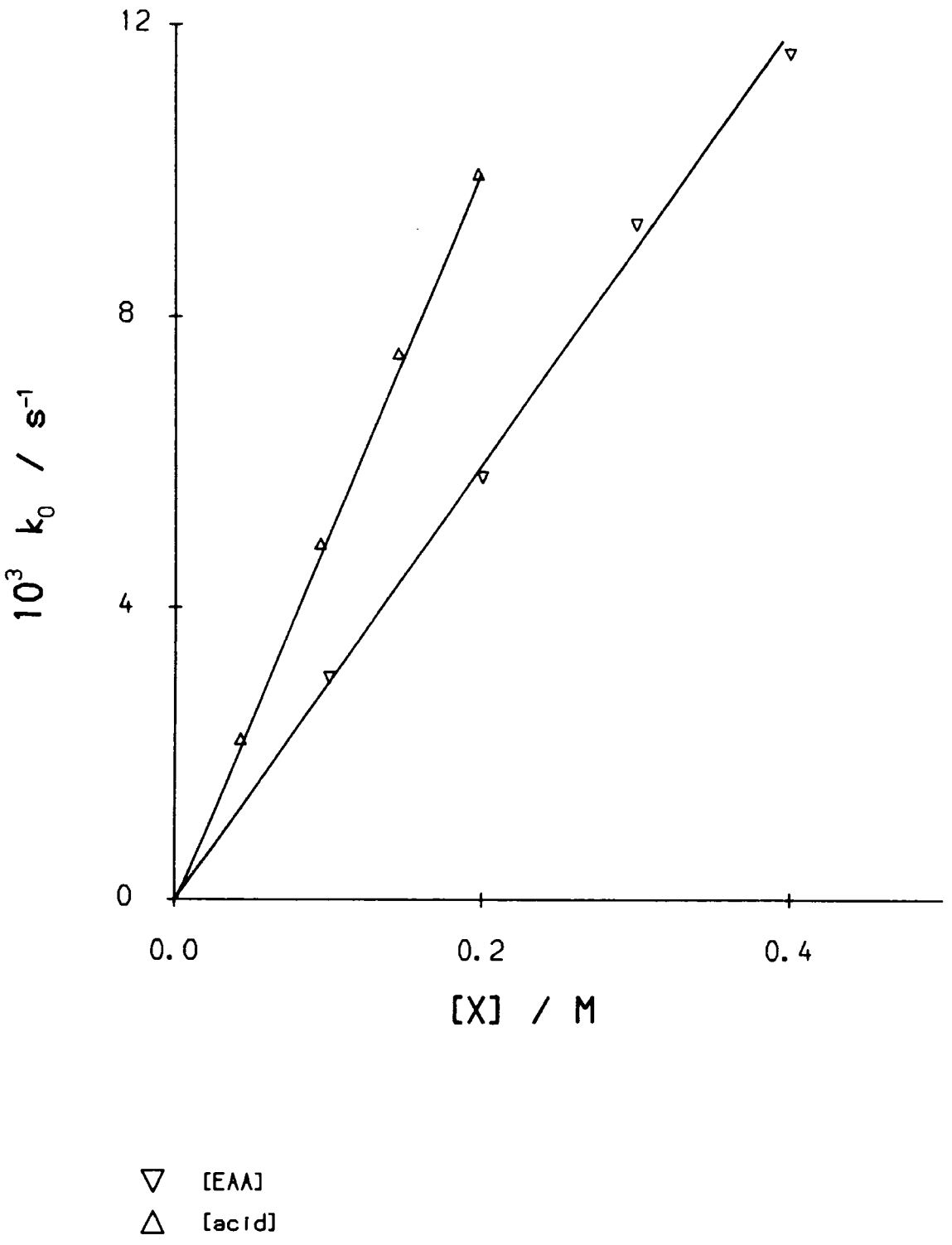
The plots of k_0 vs [acid] and also of k_0 vs [EAA] show that the reaction has a first order dependence on the concentrations of both acid and EAA and the results are consistent with a scheme (3.1) as outlined below.



(Scheme 3.1)

Figure 3.1

Variation of k_0 with [acid] and [EAA]



The rate expression expected for scheme 3.1 (when the reaction of the enol is rate limiting) is given by equation 3.2 where k_0 is the observed first order rate constant defined by equation 3.4.

$$\text{Rate} = k\,[H^+]\,[HNO_2]\,[\text{enol}] \qquad 3.2$$

$$= k_0\,[HNO_2] \qquad 3.3$$

$$\frac{-d\,[HNO_2]}{dt} = k_0\,[HNO_2] \qquad 3.4$$

The total concentration of EAA ($[EAA]_T$) is the sum of the concentrations of enol and keto forms as expressed in equation 3.5.

$$[EAA]_T = [\text{enol}] + [\text{keto}] \qquad 3.5$$

$$\text{but} \quad K_e = \frac{[\text{enol}]}{[\text{keto}]}$$

Ke is the equilibrium constant for enolisation.

$$\text{therefore} \quad [EAA]_T = [\text{enol}]\,(K_e+1 \,/\, K_e) \qquad 3.6$$

From equations 3.2, 3.3 and 3.6

$$k_0 = k\,[H^+]\,[EAA]_T\,(K_e \,/\, 1 + K_e) \qquad 3.7$$

The K_e value for EAA in aqueous solution has been reported as 5.02×10^{-3}. We have tried to measure this value in 20% dioxan-water mixture by N.M.R. spectroscopy, but only minute traces of enol could be detected. The enol content here is probably similar to that in water (0.5% enol) which is also too low to be detected by N.M.R. and in our calculations we have used the K_e value for aqueous solution.

So, from plots of k_0 vs [acid] and [EAA]

Slope = $k[EAA]_T$ (K_e / 1+K_e) or $k[H^+]$ (K_e / 1 + K_e) respectively. The k values so calculated and shown in table 3.2 are in very good agreement with each other.

Table 3.2: Values of slopes and rate constants from plots of k_0 vs [acid] and [EAA]

Variation of	10^2 slope / l $mol^{-1}s^{-1}$	k / $l^2mol^{-2}s^{-1}$
Acid concentration	4.96	40.0
EAA concentration	2.93	38.0

3.3 Nucleophile catalysed reactions

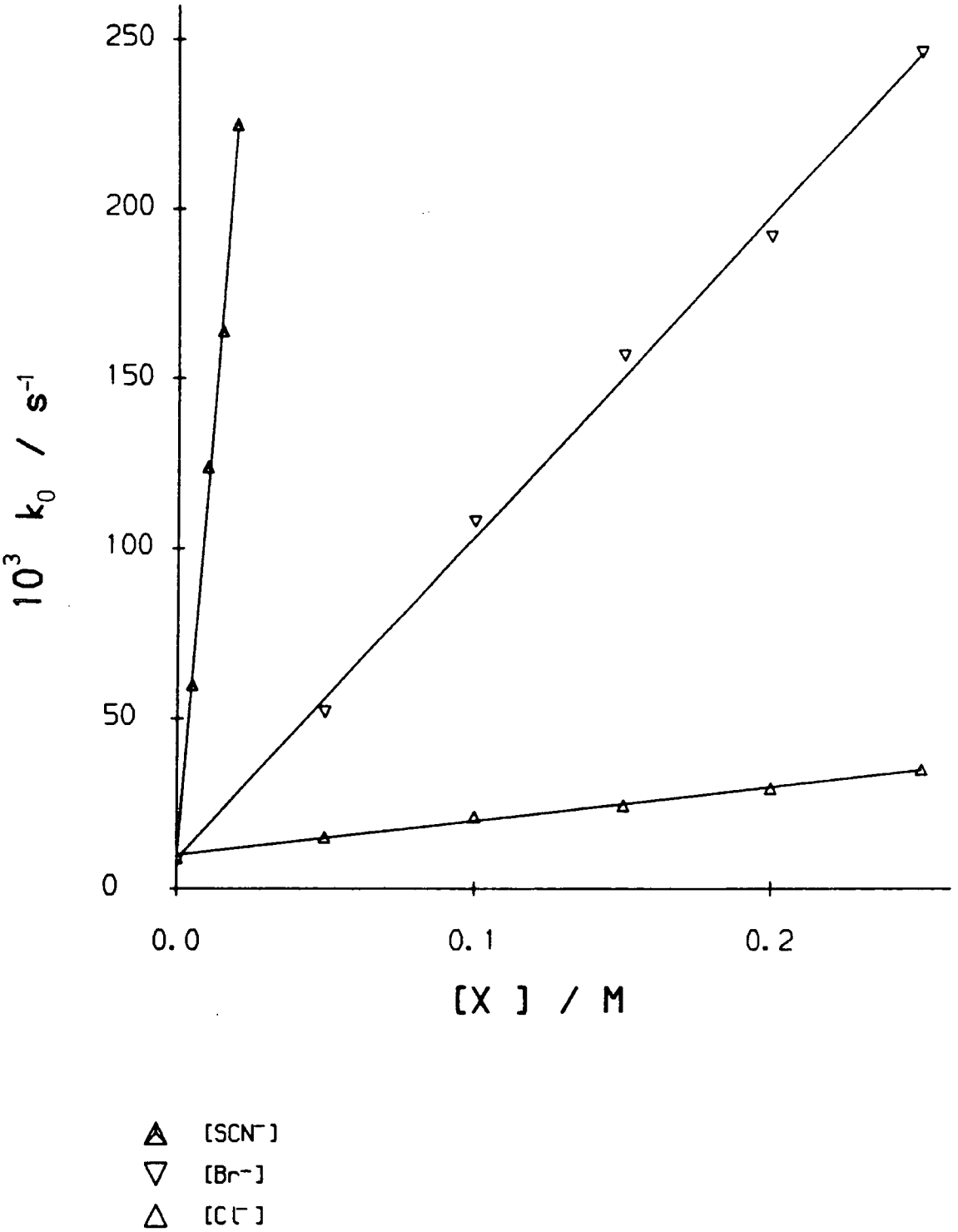
Nitrosation of EAA appeared to be significantly catalysed by added chloride, bromide and thiocyanate (X^-) ions. The results of the kinetic runs, all of which showed good first order behaviour with respect to nitrous acid, are given in table 3.3 and figure 3.2.

Table 3.3: Variation of k_0 with [X^-] (X^- = Cl^-, Br^-, SCN^-)
[acid] = 0.211M, $[EAA]_T$ = 0.25M, $[NaNO_2]$ = 4.5 x 10^{-3}M

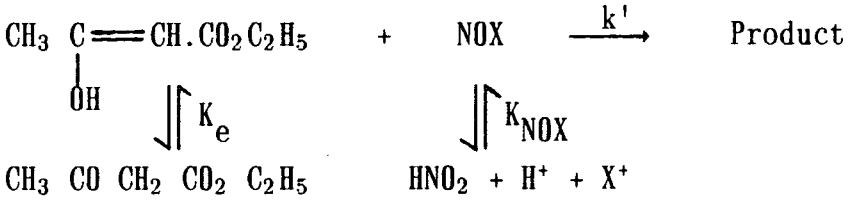
$10^2[Cl^-]$ (M)	10^4k_0 (s^{-1})	$10^2[Br^-]$ (M)	10^3k_0 (s^{-1})	$10^3[SCN^-]$ (M)	10^3k_0 (s^{-1})
0	93	0	8.2	0	9
5	152	5	52	5	60
10	212	10	108	10	124
15	245	15	157	15	164
20	296	20	192	20	225
25	352	25	246		

Figure 3.2

Nucleophilic catalysis for the nitrosation of EAA



The positive intercept in figure 3.2 represents the uncatalysed reaction. The above results are readily interpreted in terms of a mechanism as outlined in scheme 3.2 and the overall rate constant expressed as in equation 3.8.



Scheme 3.2

$$\text{Rate} = \underbrace{k'[\text{enol}][\text{NOX}]}_{\text{catalysed reaction}} + \underbrace{k[\text{enol}][H^+][HNO_2]}_{\text{uncatalysed reaction}} = k_0[HNO_2] \qquad 3.8$$

$$\text{but from equation 3.6,} \quad [\text{enol}] = [\text{EAA}]_T \, (K_e \,/\, 1+K_e)$$

$$\text{and} \quad [\text{NOX}] = K_{NOX}\,[H^+][HNO_2][X^-]$$

Substituting the above in equation 3.8, the expression for k_0 is given by equation 3.9

$$k_0 = (k + k'\,K_{NOX}\,[X^-]\,)\,[H^+]\,[\text{EAA}]_T\,(K_e \,/\, 1+K_e) \qquad 3.9$$

and from the plot of k_0 vs $[X^-]$,

$$\text{slope} = k'\,K_{NOX}\,[H^+]\,[\text{EAA}]_T\,(K_e \,/\, 1+K_e)$$

$$\text{and intercept} = k\,[H^+]\,[\text{EAA}]_T\,(K_e \,/\, 1+K_e)$$

Using the literature values of K_{NOX}, the rate constants (k and k')

calculated from the above expressions for slope and intercept are given in table 3.4.

Table 3.4: Values of slopes and intercepts of plots of k_0 vs $[X^-]$ and the derived k and k'

X^-	10 slope ($l\ mol^{-1}s^{-1}$)	10^3 intercept (s^{-1})	k ($l^2mol^{-2}s^{-1}$)	k' ($l\ mol^{-1}s^{-1}$)
chloride	1.01	9.87	37.6	3.5×10^5
bromide	9.63	8.47	32.3	7.1×10^4
thiocyanate	107.20	9.20	35.0	1.27×10^3

The values of the rate constant (k) in table 3.4 obtained from the intercepts of plots of k_0 vs $[X^-]$ are approximately constant and agree well with those obtained for the uncatalysed reactions (table 3.2).

The concentration of EAA was varied in the presence of fixed concentration of nucleophiles (X^-) and acid. The results of the variation in the presence of bromide ion are presented in table 3.5.

Table 3.5: Variation of k_0 with [EAA]

$[acid] = 1.8 \times 10^{-1}$ M
$[NaBr] = 1.5 \times 10^{-1}$ M
$[NaNO_2] = 2 \times 10^{-3}$ M

10^2 [EAA] / M	$10^2\ k_0$ / s^{-1}
6.30	2.30
12.60	5.30
18.90	7.50
25.20	9.70

The plot of k_0 vs [EAA] is linear, passing through the origin and from equation 3.9, the expression for the slope of the plot of k_0 vs [EAA] is given by equation 3.10. The value of the slope so calculated (4.9×10^{-1}) agrees well with that measured (4.1×10^{-1}).

$$\text{slope} = (k + k' K_{NOX} [X^-]) [H^+] (K_e / 1+K_e) \qquad 3.10$$

This provides support for the consistency in the k and k' values determined experimentally.

3.4 Discussion

From the kinetic results, there is no direct evidence that nitrosation of EAA proceeds via its enol tautomer. This is unlike the situation encountered in nitrosation[7] of some other carbonyl compounds like acetone (Ac), ethyl methyl ketone (EMK) and 1,3-dichloroacetone (DCA), where in the presence of high nucleophile concentrations the rate of the reaction of the enol form with the NOX species became substantially faster than the ketonisation of the enol, thus achieving rate limiting enolisation and providing direct evidence for the involvement of the enol tautomer in nitrosation. For EAA however, it was not possible to achieve this limit experimentally, a situation resembling the nitrosation of acetylacetone (AcAc). This is probably due to the fact that both of these enols have a reduced reactivity due to the presence of the electron withdrawing groups (-COMe / $-CO_2Et$).

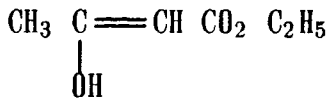
For the uncatalysed reaction, the observed first order dependence of the reaction on the concentration of nitrous acid implies that the reaction proceeds via $H_2NO_2^+$ / NO^+ thus supporting the

observation by Williams[7] and co-workers that the more reactive enols (Ac and EMK) react preferentially with N_2O_3 while for the less reactive enols, reaction via $H_2NO_2^+$ / NO^+ is preferred. The value of the third order rate constant (k) as determined in this experiment compares with that of AcAc (table 3.6) suggesting that the reactivities of the two enols is similar.

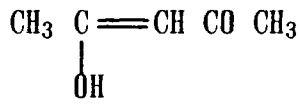
Table 3.6: Values of the third order rate constants for nitrosation of EAA and AcAc

Ketone	k / l^2 mol^{-2} s^{-1}
EAA	39
AcAc	36

This can be explained by taking into account the structural similarities of their enols (EAA III, AcAc IV), the only difference



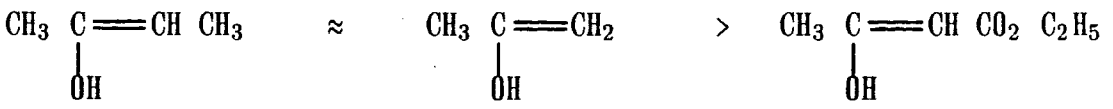
(III)



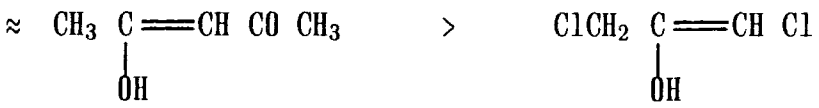
(IV)

being the nature of the electron withdrawing group ($-CO_2\ C_2H_5$ instead of -COMe) which however is not expected to extend any significant effect on their reactivities. These values of k are as predicted much below that expected for a diffusion controlled[8] reaction between $H_2NO_2^+$ / NO^+ and neutral substrates. For the catalysed reactions, rate constants for attack of NOX on the enol form of EAA are in agreement with the established[9] reactivity sequence NOCl > NOBr > NOSCN. Again the rate constants are very similar to those obtained for AcAc and are *ca.* 10 times greater than those for DCA (table 2.1) but are much less

than the values for Ac and EMK whose reactions with NOX are diffusion controlled thus reflecting the activating effect of the -OH substituent in these enols. A comparison of the rate constants obtained for EAA, with those in table 2.1 show that for each nitrosating agent the enol reactivity trend is
EMK ≈ Ac > EAA ≈ AcAc > DCA (as shown in the sequence below)



Ethyl methyl ketone (EMK) Acetone (Ac) Ethyl acetoacetate (EAA)



Acetyl acetone (AcAc) 1,3-dichloroacetone (DCA)

The mechanism of the well known nitrosation reaction of EAA has now been established.

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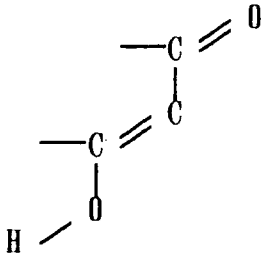
CHAPTER 4

Nitrosation of Dimedone (5,5-dimethyl cyclohexa-1,3-dione)

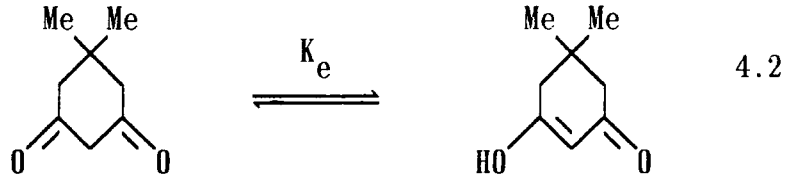
4.1 Introduction

Dimedone and other 1,3-diketones are compounds which are well known to have a high enol content[1]. This has been attributed to the greater stabilisation of the enolic structure relative to the diketo form, by the fact that the enols are held in a trans co-planar arrangement (4.1) in which the oxygen-oxygen repulsion is at a



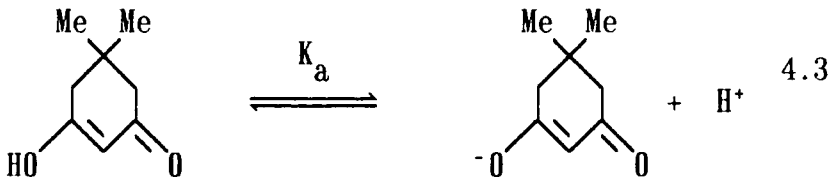
4.1

minimum and resonance stabilisation is maximum. The equilibrium constant for enolisation of dimedone (equation 4.2) has been determined[2] as 13.3 in aqueous solution.



4.2

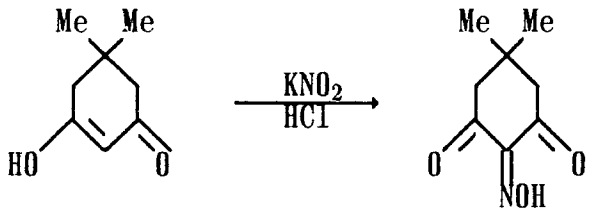
A study[3] of the acid dissociation constants (pK_a) of a series of 1,3-cyclohexanediones has shown that these compounds as a class are relatively strong acids. The pK_a value of dimedone (equation 4.3) is reported[4] as 5.2 (K_a = 6.3 x 10^{-6}).



4.3

Dimedone has been nitrosated[5,6] in 99% yield by using potassium nitrite and hydrochloric acid. The product is the keto oxime

(equation 4.4) which is very heat sensitive and decomposes readily.



4.4

The aim of the work described in this chapter was to investigate the mechanism of nitrosation of a carbonyl compound which existed overwhelmingly in the enol form.

All the kinetic experiments were carried out at 25^0C in water under pseudo first order conditions with a large excess of dimedone over HNO_2. The reaction was followed at 320 nm by following the increase in absorbance due to product formation. In all kinetic experiments [$NaNO_2$] was maintained as 1.74×10^{-4} M.

4.2 Uncatalysed reactions

All kinetic runs showed good first order behaviour with respect to nitrous acid concentration. The variation of the observed first order rate constant (k_0) with [acid] and [dimedone] are shown in table 4.1, figure 4.1, and table 4.2 respectively. A plot of k_0 vs [$HClO_4$] (figure 4.1) is linear with a significant positive intercept. This behaviour can be explained if it is assumed that reaction occurs via both the neutral enol and the enolate ion as shown in scheme 4.1. The overall reaction rate is given by equation 4.5 where [E] and [E^-] are concentrations of enol and enolate forms respectively and k_1, k_2 are the rate constants for their attack respectively by $H_2NO_2^+$ / NO^+.

Table 4.1: Variation of k_0 with $[HClO_4]$

[dimedone] = 9×10^{-3} M

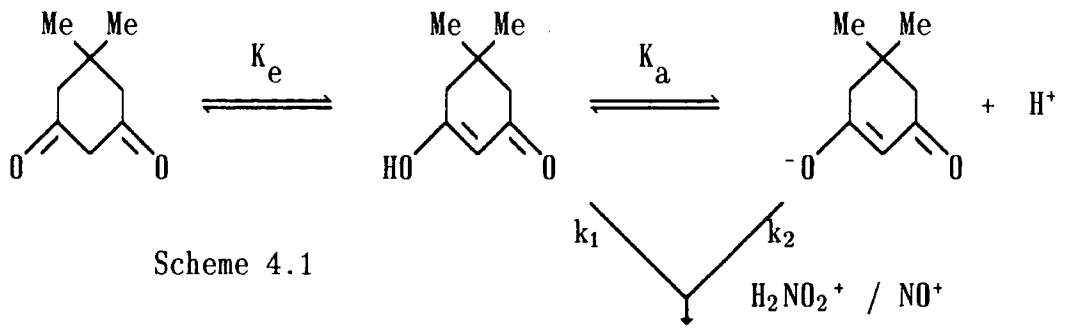
10^2 $[HClO_4]$ / M	10^2 k_0 / s^{-1}
2.5	5.8
5.1	9.2
7.6	12.4
10.0	16.3
12.7	20.5
15.2	23.2
17.7	27.1

Table 4.2: Variation of k_0 with [dimedone]

$[HClO_4] = 5.2 \times 10^{-2}$ M

10^3 [dimedone] / M	10^2 k_0 / s^{-1}
2.95	3.2
4.20	4.6
5.90	6.1
7.56	7.7
9.20	9.6

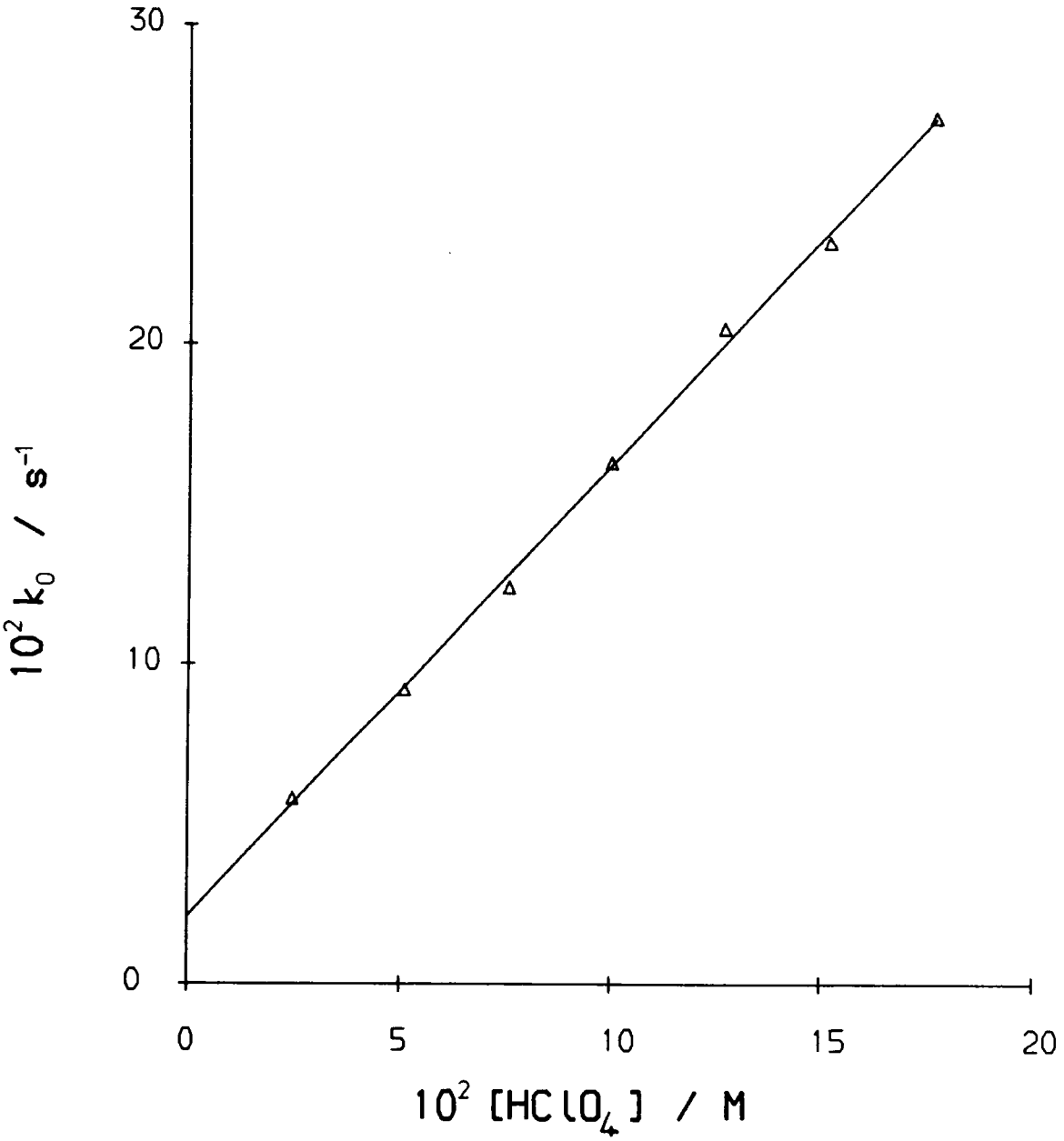
$$\text{Rate} = k_1 [HNO_2] [H^+] [E] + k_2 [HNO_2] [H^+] [E^-] \qquad 4.5$$



Scheme 4.1

Figure 4.1

Variation of k_0 with $[HClO_4]$



By analogy with equation 3.7 of chapter 3.

$$([E] + [E^-]) = [\text{dimedone}]_T \, (K_e / 1+K_e) \qquad 4.6$$

$[\text{dimedone}]_T$ = total concentration of dimedone.

and $[E^-] = ([E] \, K_a) / [H^+]$

$$\text{therefore, Rate} = \left(k_1 + \frac{k_2 \, K_a}{[H^+]}\right) [E] \, [H^+] \, [HNO_2] \qquad 4.7$$

But from equation 4.6 $\quad [E] \left(1 + \dfrac{K_a}{[H^+]}\right) = [\text{dimedone}]_T \, (K_e / 1+K_e)$

and rate = $k_0 \, [HNO_2]$

$$\text{Therefore} \quad k_0 = (k_1 \, [H^+] + k_2 \, K_a) \frac{[\text{dimedone}]_T \, [H^+]}{(K_a + [H^+])} \, (K_e / 1+K_e) \qquad 4.8$$

K_a is the acid dissociation constant of dimedone and K_e is its equilibrium constant for enolisation. When $[H^+] >> K_a$ (a condition which applies throughout all the experiments done) the expression for k_0 (equation 4.8) reduces to equation 4.9. This equation predicts

$$k_0 = (k_1 \, [H^+] + k_2 \, K_a) \, [\text{dimedone}]_T \, (K_e / 1+K_e) \qquad 4.9$$

that a plot of k_0 vs $[H^+]$ should be linear with a positive intercept and positive slope. Figure 4.1 is an example of a typical plot. In this plot the slope represents $\{k_1 \, [\text{dimedone}]_T \, (K_e / 1+K_e)\}$ and the intercept $\{k_2 \, K_a \, [\text{dimedone}]_T \, (K_e / 1+K_e)\}$. The values of k_1 and k_2 calculated from the expressions for slope and intercept are as given below.

$$k_1 = 168 \; l^2 \; mol^{-2} \; s^{-1}$$

$$k_2 = 3.9 \times 10^5 \; l^2 \; mol^{-2} \; s^{-1}$$

For a plot of k_0 vs $[\text{dimedone}]_T$ (equation 4.9) the slope is given by equation 4.10. The calculated slope (10.3 l mol^{-1} s^{-1}) from this

expression (4.10) using the above determined k_1 and k_2 values

$$\text{slope} = (k_1\ [H^+] + k_2\ K_a)\ (K_e\ /\ 1+K_e) \qquad 4.10$$

agrees very well with that measured (10.45 l mol^{-1} s^{-1}) from a plot of k_0 vs $[\text{dimedone}]_T$. This indicates that the values of k_1 and k_2 determined experimentally are internally consistent.

4.3 Nucleophile catalysed reactions

Reactions were studied in presence of added chloride, bromide and thiocyanate ions. The results of the variation of k_0 with [nucleophile] are presented in tables 4.3, 4.4, 4.5 respectively and in figure 4.2.

Table 4.3: Variation of k_0 with [chloride]

$[HClO_4] = 1.01 \times 10^{-1}$ M, $[\text{dimedone}] = 3.2 \times 10^{-3}$ M

$[Cl^-]$ / M	$10^2\ k_0$ / s^{-1}
0	5.3
0.04	8.2
0.1	11.7
0.16	15.7
0.22	19.6

Table 4.4: Variation of k_0 with [bromide]

$[HClO_4] = 5.1 \times 10^{-2}$ M, $[\text{dimedone}] = 3.2 \times 10^{-3}$ M

$[Br^-]$ / M	$10^2\ k_0$ / s^{-1}
0	3.7
0.02	14.0
0.05	30.7
0.08	46.4
0.11	61.2

Figure 4.2

Nucleophilic catalysis for nitrosation of dimedone

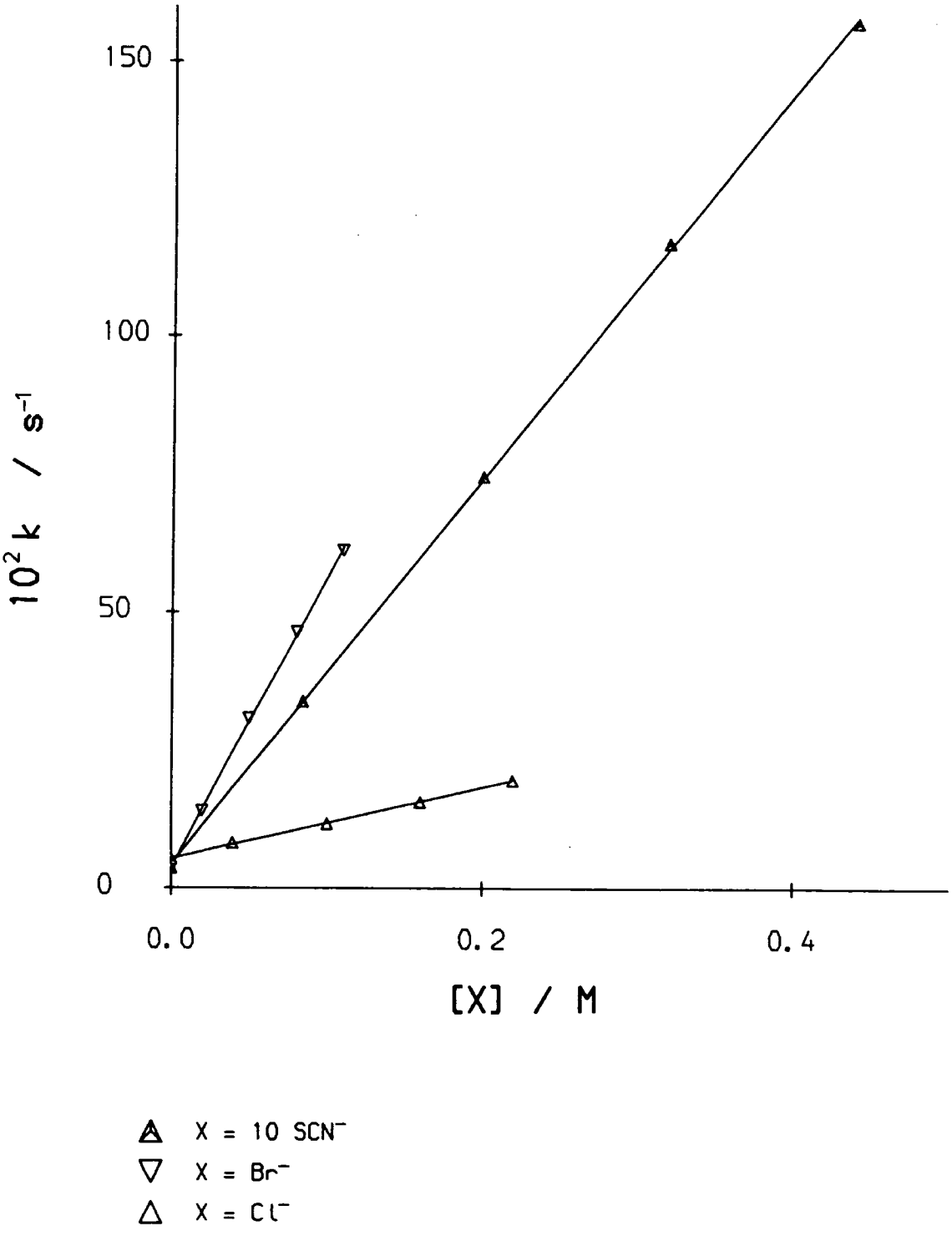
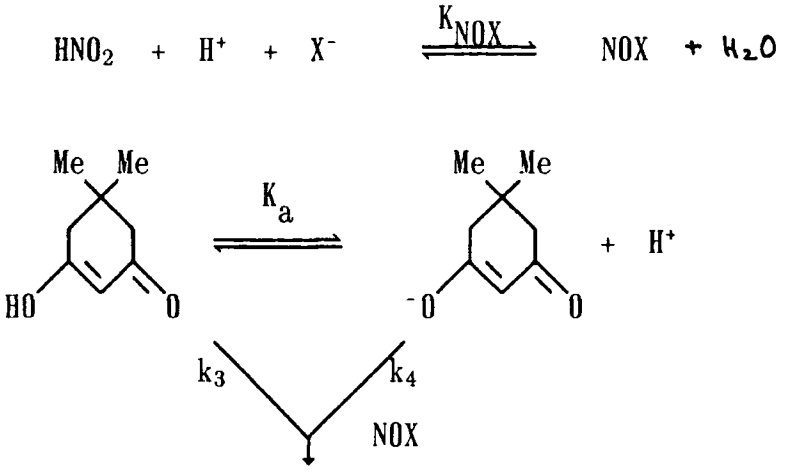


Table 4.5: Variation of k_0 with [thiocyanate]

$[HClO_4] = 5.1 \times 10^{-2}$ M, [dimedone] = 3.2×10^{-3} M

$10^4[SCN^-]$ / M	10^2 k_0 / s^{-1}
0	3.7
8.4	33.8
20	74.6
32	117
44	157

As for the uncatalysed reactions, here also the reaction could proceed via both enol and enolate forms with a possible mechanism as outlined in scheme 4.2.



scheme 4.2

The overall rate constant is as expressed in equation 4.11 where k_3 and k_4 represent rate constants for attack of enol and enolate respectively by the NOX species.

$$\text{Rate} = k_3 [E] [NOX] + k_4 [E^-] [NOX] + \text{uncatalysed rate} \qquad 4.11$$

$$= k_0 [HNO_2]$$

From equation 4.6, $[E]\left(1 + \frac{K_a}{[H^+]}\right) = [\text{dimedone}]_T \, (K_e / 1+K_e)$ and $[NOX] = K_{NOX} [H^+] [HNO_2] [X^-]$, where K_{NOX} is the equilibrium constant for formation of NOX.

Rate =

$$(k_3\ [H^+] + k_4\ K_a)\ K_{NOX}\ [H^+][HNO_2][X^-][\text{dimedone}]_T\ (K_e/1+K_e)(1/K_a+[H^+])$$

+ uncatalysed rate

By combining rates for uncatalysed (equation 4.7) and catalysed reactions the expression for k_0 is given by equation 4.12.

$$k_0 = \{(k_1[H^+]+k_2\ K_a)+(k_3[H^+]+k_4\ K_a)\ K_{NOX}\ [X^-]\}\ [\text{dimedone}]_T\ (K_e/1+K_e)$$

when $[H^+] >> K_a$ 4.12

So plots of k_0 vs $[H^+]$ should be linear with a

$$\text{slope} = (k_1 + k_3\ K_{NOX}\ [X^-])\ [\text{dimedone}]_T\ (K_e\ /\ 1+K_e) \quad 4.13$$

$$\text{and intercept} = (k_2 + k_4\ K_{NOX}\ [X^-])\ K_a\ [\text{dimedone}]_T\ (K_e\ /\ 1+K_e) \quad 4.14$$

In order to measure the values of k_3 and k_4 using this method, it is necessary to measure the rate constants for nitrosation of dimedone over a range of acid concentrations in presence of fixed concentrations of different nucleophiles. Tables 4.6, 4.7, 4.8 and figure 4.3 show the variation of k_0 with $[H^+]$ in presence of Cl^-, Br^- and SCN^-.

Table 4.6: Variation of k_0 with $[HClO_4]$ in presence of chloride.

$[Cl^-] = 1 \times 10^{-1}$ M, [dimedone] = 6×10^{-3} M

10^2 $[HClO_4]$ / M	10^2 k_0 /s^{-1}
5.1	12.6
7.6	17.6
10.1	23.3
12.7	27.9
15.2	33.2

Figure 4.3

Variation of k_0 with [acid] in presence of X
(X = Cl^-, Br^-, SCN^-)

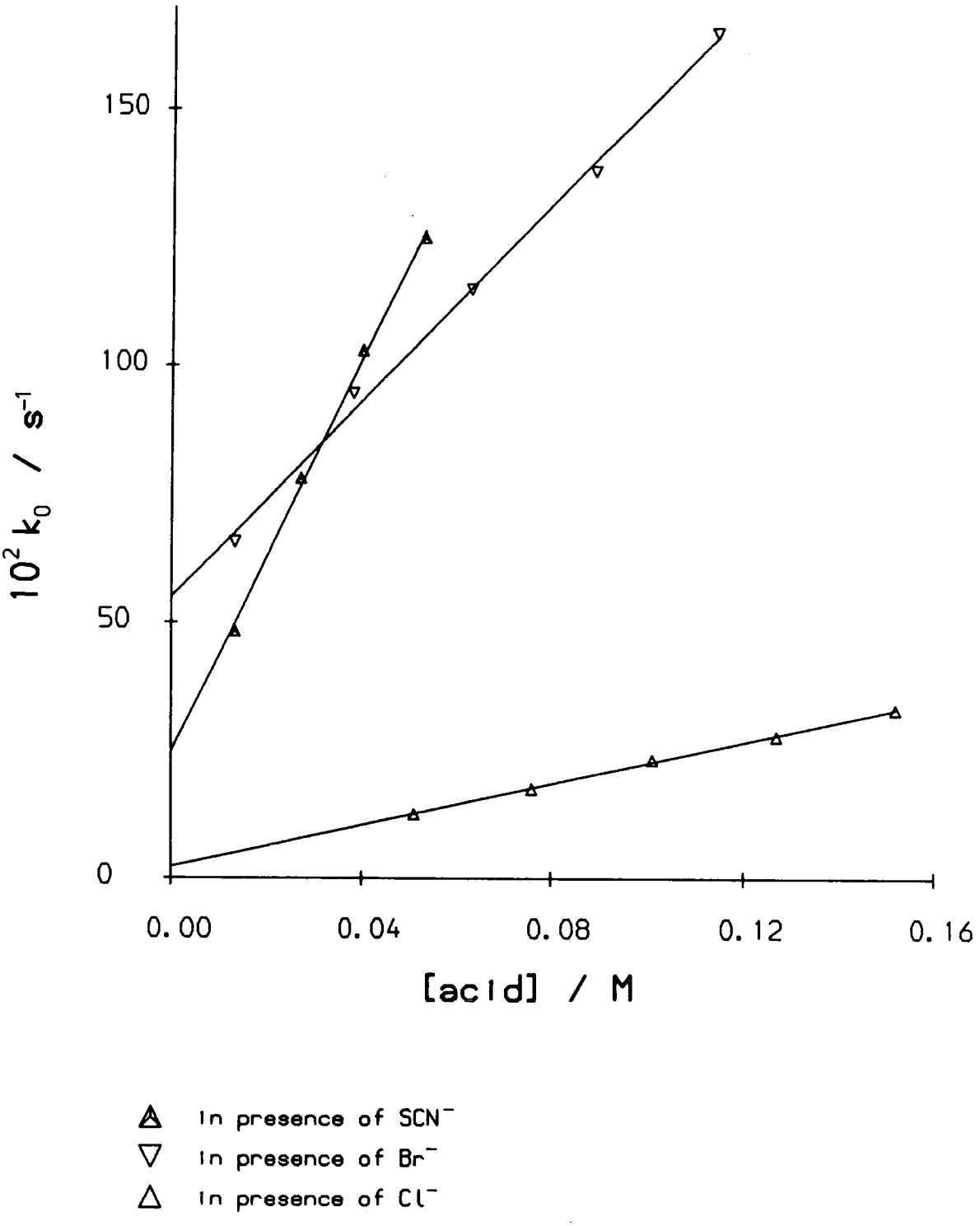


Table 4.7: Variation of k_0 with $[HClO_4]$ in presence of bromide.
$[Br^-] = 1 \times 10^{-1}$ M, [dimedone] = 6×10^{-3} M

10^2 $[HClO_4]$ / M	10^2 k_0 /s^{-1}
1.3	65.6
3.8	94.6
6.3	115
8.9	138
11.4	165

Table 4.8 Variation of k_0 with $[HClO_4]$ in presence of thiocyanate.
$[SCN^-] = 3 \times 10^{-3}$ M, [dimedone] = 3.9×10^{-3} M

10^2 $[HClO_4]$ / M	10^2 k_0 /s^{-1}
1.3	48.4
2.7	78.1
4.0	103
5.3	125

The measured slopes and intercepts from these plots and the calculated k_3 and k_4 values are shown in table 4.9

Table 4.9: Values for slopes and intercepts for plot of k_0 vs $[H^+]$ and corresponding k_3 and k_4 values for the reactions of NOCl, NOBr, and NOSCN with E and E^-.

nucleophile	slope $l\ mol^{-1}s^{-1}$	intercept s^{-1}	k_3 $l\ mol^{-1}s^{-1}$	k_4 $l\ mol^{-1}s^{-1}$
chloride	2.0	2.3×10^{-2}	1.8×10^6	2.3×10^9
bromide	9.6	5.5×10^{-1}	3.0×10^5	3.0×10^9
thiocyanate	20.2	2.3×10^{-1}	5.6×10^4	9.8×10^7

The measured slopes and intercepts from plots of k_0 vs $[X^-]$ (figure 4.2) are compared in table 4.10 with those calculated from the expressions 4.15 and 4.16 (derived from equation 4.12), using the k_1,

k_2, k_3 and k_4 values determined in this work.

$$\text{slope} = (k_3\,[H^+] + k_4\,K_a)\,K_{NOX}\,[\text{dimedone}]_T\,(K_e / 1+K_e) \qquad 4.15$$

$$\text{intercept} = (k_1\,[H^+] + k_2\,K_a)\,[\text{dimedone}]_T\,(K_e / 1+K_e) \qquad 4.16$$

Table 4.10: Calculated and observed slopes and intercepts for plots of k_0 vs $[X^-]$

X^-	slope / l $mol^{-1}s^{-1}$	intercept / s^{-1}	
Cl^-	0.644	5.4×10^{-2}	observed
	0.639	5.8×10^{-2}	calculated
Br^-	5.26	3.8×10^{-2}	observed
	5.19	3.3×10^{-2}	calculated
SCN^-	348	4.3×10^{-2}	observed
	357	3.5×10^{-2}	calculated

The agreement between the two sets of results is excellent, thus providing support for the consistency in the values of k_1, k_2, k_3 and k_4. A further support for this consistency was obtained by varying the concentration of dimedone at fixed concentrations of bromide and acid. The results are presented in table 4.13.

Table 4.11: Variation of k_0 with [dimedone]
$[HClO_4] = 7.6 \times 10^{-2}$ M, $[NaBr] = 5 \times 10^{-2}$ M

10^3 [dimedone] / M	10 k_0 / s^{-1}
3.6	4.3
6.0	7.3
8.4	10.1
10.8	12.9

From equation 4.12 the expression for the slope of plot of k_0 vs [dimedone] is given by equation 4.17 and the calculated value of the

$$\text{slope} = \{k_1[H^+] + k_2K_a + k_3K_{NOX}[H^+][X^-] + k_4K_aK_{NOX}[X^-]\} (K_e / 1+K_e) \quad (4.17)$$

slope (122 l $mol^{-1}s^{-1}$) agreed very well with that measured (120 l $mol^{-1}s^{-1}$) from plot of k_0 vs [dimedone].

4.4 Discussion

The results of the kinetic analysis are consistent with reaction via two forms, the neutral enol form and the enolate ion. The fraction of the reaction proceeding via each form is obviously dependent on the overall acid concentration. As expected, the enolate is the more reactive species. The values of the third order rate constants (Rate = $k[S][HNO_2][H^+]$, for any general substrate S) are 168 and 3.9×10^5 l^2 mol^{-2} s^{-1} respectively for reaction via enol and enolate. The generally accepted upper limits for the rate constant (k) representing diffusion controlled reactions are *ca* 7×10^3 l^2 mol^{-2} s^{-1} (for neutral substrates)[7] and *ca* 1.1×10^4 l^2 mol^{-2} s^{-1} (for negatively charged substrates)[8,9]. The results obtained in this study therefore suggest that the reaction of the enol is not diffusion controlled (although it is not far removed from the limit). However, the value of the rate constant for reaction of the enolate ion ($k_2 = 3.9 \times 10^5$ l^2 mol^{-2} s^{-1}) is much greater than the predicted limit (1.1×10^4 l^2 mol^{-2} s^{-1}) which has been observed for nitrosation of thiocyanate[8] and benzenesulphinate anions[9]. From equation 4.8, it is clear that the values of the rate constants are very much dependent on the pK_a and K_e values, both of which have been determined by

indirect methods and any error in them would be reflected in the rate constant values. For halogenation[10] of enolates also, the measured rate constants were 10^2 times greater than those predicted for encounter processes, the authors have however not offered any explanation for this. By analogy with halogenation reactions and taking into consideration the uncertainty over the pK_a and K_e values, it is still reasonable to assume that the enolate ion is very reactive towards nitrosation and its reactivity is comparable to thiocyanate and benzenesulphinate ions.

For reactions in presence of nucleophilic catalysts the rate constants for reaction of enol (k_3) and enolate ion (k_4) with the NOX species show again that the enolate ion is the more reactive species by *ca* 10^3 - 10^4. The well established reactivity trend NOCl > NOBr > NOSCN also applies to nitrosation of dimedone. For the more reactive enolate ion, the k_4 values for attack by NOCl and NOBr are very close together and also close to the calculated[7] encounter controlled limit (7×10^9 l mol^{-1} s^{-1}) for such processes, implying that the reactions occur at encounter.

The high reactivity of the enol and enolate ion towards nitrosation, coupled with the irreversibility of the reactions suggest that dimedone and other such related enols have potential use as nitrite traps for denitrosation reactions to remove nitrous acid quantitatively and rapidly.

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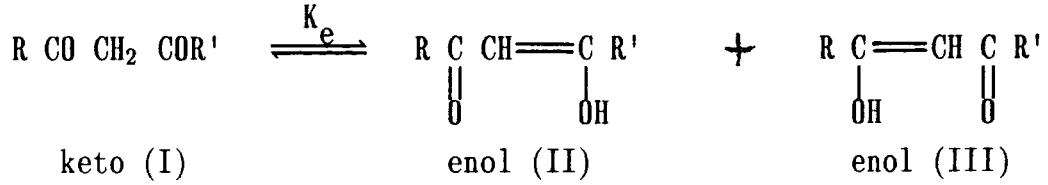
CHAPTER 5

Nitrosation of Trifluoroacetylacetone

(1,1,1-trifluoropentane-2,4-dione)

5.1 INTRODUCTION

β-diketones and their fluoro derivatives have been much used synthetically[1] for the preparation[2] of a number of transitional metal derivatives. The effect of the fluorine substituents on the chemical reactivity of fluoro β-diketones has prompted many physical chemical studies. The compounds are also very good chelating agents[3]. However, most of their study[4] has been mainly concerned with the kinetics and mechanism of their reactions with metal ions in water and in organic solvents. These compounds exist as keto and enol tautomers (equation 5.1) and the keto : enol ratio is highly solvent dependent. In polar media the keto form predominates, whilst in less polar solvents the enol form is the main component.



(5.1)

This tautomerism of β-dicarbonyls has been studied by the conventional bromine titration method[5] and also by N.M.R. spectroscopy[6]. In non-polar solvents, the effect of the highly electronegative perfluoromethyl group in compounds like trifluoracetylacetone (TFA) and hexafluoroacetylacetone (HFA) is to increase the percentage of the enol tautomer. In these solvents it is form II which predominates. Burdett and Rogers[7] suggest that the high enol content is a result of electron withdrawal from the region of the α-proton. Also, in the enol tautomer the electronegative group in the α-position is further

from the carbonyl group thus reducing the electrostatic repulsions. In water however, it is not known what enol is formed or in what proportion.

The kinetics and mechanistic aspects of the nitrosation of some β-dicarbonyl compounds have recently been investigated both in aqueous[8] and non-aqueous (acetonitrile)[9] media. In this chapter the results for the nitrosation of trifluoroacetylacetone (R = CF_3, R' = CH_3) in water are presented. The equilibrium constant for enolisation (K_e) of TFA in water (equation 5.1) has been reported[5] as 0.011. The compound is more acidic than acetylacetone (AcAc), owing to the substitution by fluorine which is highly electron withdrawing and increases the acidity of the methylene hydrogen. This is strongly reflected in their pK_a values (AcAc = 9.8, TFA = 6.7).

All the kinetic experiments were carried out at 25^{0}C in water with an excess of TFA over HNO_2. The reaction was followed at 240 nm by following the increase in absorbance due to product formation. Throughout the experiment the ionic strength was maintained as 1.0 ($NaClO_4$) and [$NaNO_2$] = 3 x 10^{-4} M.

5.2 Uncatalysed reactions

The kinetic runs were all first order with respect to nitrous acid concentration. The reaction was studied by varying the concentration of both acid and TFA, keeping that of the other constant. The variation of k_0 (the observed first order rate constant) with [acid] and [TFA] is shown in table 5.1, figure 5.1 and table 5.2 respectively.

Table 5.1: Variation of k_0 with $[HClO_4]$
$[TFA] = 2 \times 10^{-2}$ M

$[HClO_4]$ / M	10^3 k_0 / s^{-1}
0.1	1.67
0.2	2.85
0.3	3.65
0.4	4.66
0.5	5.80

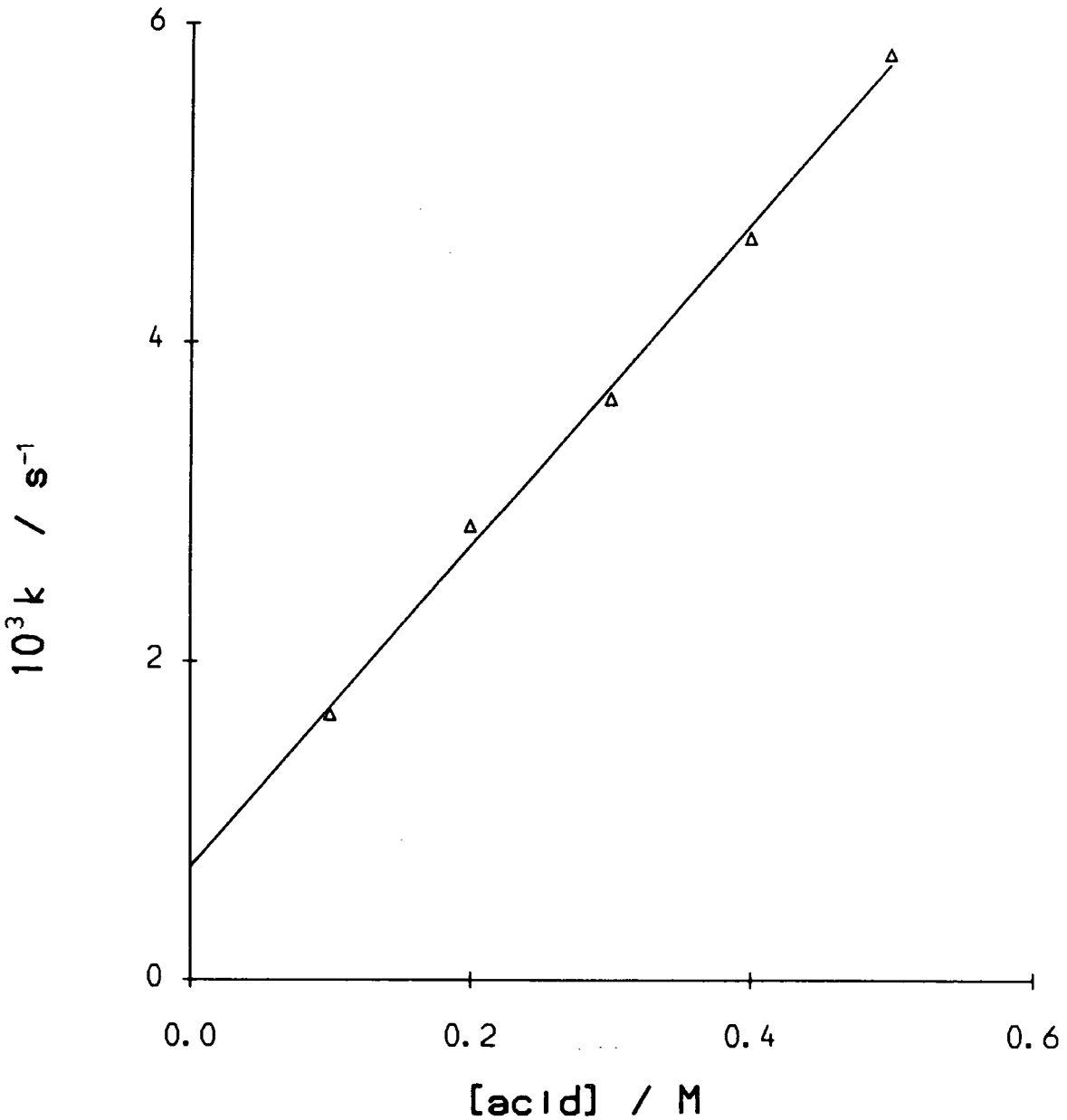
Table 5.2: Variation of k_0 with [TFA]
$[HClO_4] = 0.5$ M

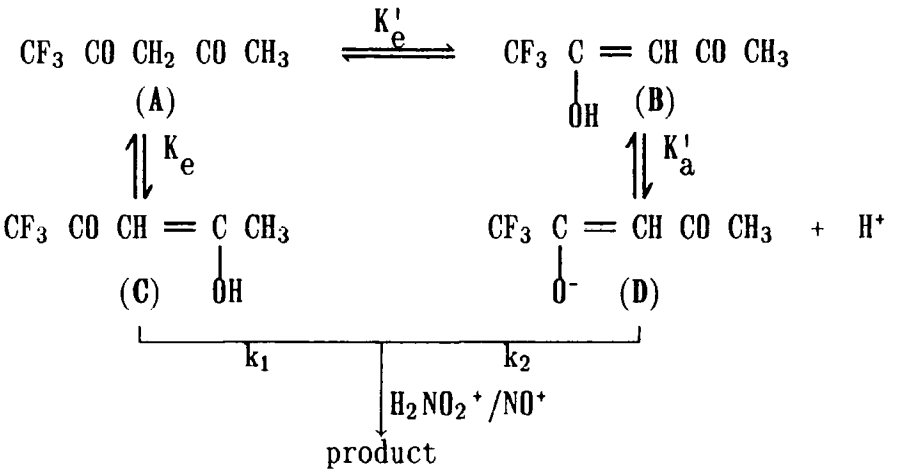
10^3 [TFA] / M	10^3 k_0 / s^{-1}
5.0	1.47
10.0	2.85
15.0	4.60
20.0	5.80
25.0	7.50

The plot of k_0 vs $[HClO_4]$ (figure 5.1) is linear and as in the case of dimedone (chapter 4, figure 4.1), there is a significant positive intercept. This situation is consistent with a situation where reaction takes place via both neutral enol and the enolate ion. A reasonable scheme for such a reaction is shown in scheme 5.1.In TFA, both enol forms B and C are possible. However in water, it is form C which is expected to predominate as, in the enol form B the influence of the highly electron withdrawing CF_3 group is likely to destabilise the enol form by reducing the extent of intramolecular hydrogen bonding. However the enolate ion is more likely to arise from B, because of the proximity of the acid strengthening CF_3 group.

Figure 5.1

Variation of k_0 with [acid]





Scheme 5.1

The rate expression corresponding to scheme 5.1 can then be expressed in terms of equation 5.2 where k_1 and k_2 are rate constants for attack by $H_2NO_2^+$/ NO^+ on enol and enolate respectively

$$\text{Rate} = k_1\ [HNO_2][H^+][C] + k_2\ [HNO_2][H^+][D] = k_0\ [HNO_2] \qquad 5.2$$

$$= \left(k_1\ K_e\ [A] + k_2\ \frac{[B]}{[H^+]}\ K_a'\right)\ [H^+]\ [HNO_2] = k_0\ [HNO_2]$$

As K_e is small $[A] \simeq [TFA]_{Total}$ and $[B] = K_e'\ [A]$

$$\text{therefore}\quad k_0 = (k_1\ K_e\ [H^+] + k_2\ K_e'\ K_a')\ [TFA]_T \qquad 5.3$$

$$= (k_1\ K_e\ [H^+] + k_2\ K_a)\ [TFA]_T \qquad 5.4$$

K_a is the apparent acid dissociation constant of TFA

and $K_a = K_a'\ K_e' = 3.16 \times 10^{-7}$.

From equation 5.4, a plot of k_0 vs $[H^+]$ should be linear with a positive slope and intercept, where the slope is $k_1\ K_e\ [TFA]_T$ and intercept is $k_2\ K_a\ [TFA]_T$. From these expressions the values of k_1

and k_2 were determined as

$$k_1 = 46\ l^2\ mol^{-2}\ s^{-1}$$

$$k_2 = 1.1 \times 10^5\ l^2\ mol^{-2}\ s^{-1}$$

A calculated value of 0.29 l mol^{-1} s^{-1} was obtained for the slope of k_0 vs $[TFA]_T$ using equation 5.4 and the above calculated values of k_1 and k_2. This value compares very well with the measured value of slope (0.30 l mol^{-1} s^{-1}) obtained from the plot of k_0 vs $[TFA]_T$. This indicates that the values of k_1 and k_2 determined experimentally are internally consistent.

5.3 Nucleophile catalysed reactions

The effect of added chloride, bromide and thiocyanate ions on the nitrosation reaction of TFA was examined. The results of the variation of k_0 (the observed rate constant) with concentration of added nucleophile is given in tables 5.3, 5.4 and 5.5 respectively and in figure 5.2. As for the uncatalysed reactions, there is again the possibility of attack of both enol and enolate ion by the nitrosating species NOX. A possible mechanism is as outlined in scheme 5.2.

Table 5.3: Variation of k_0 with $[Cl^-]$
$[HClO_4]$ = 0.2 M, [TFA] = 2×10^{-2} M

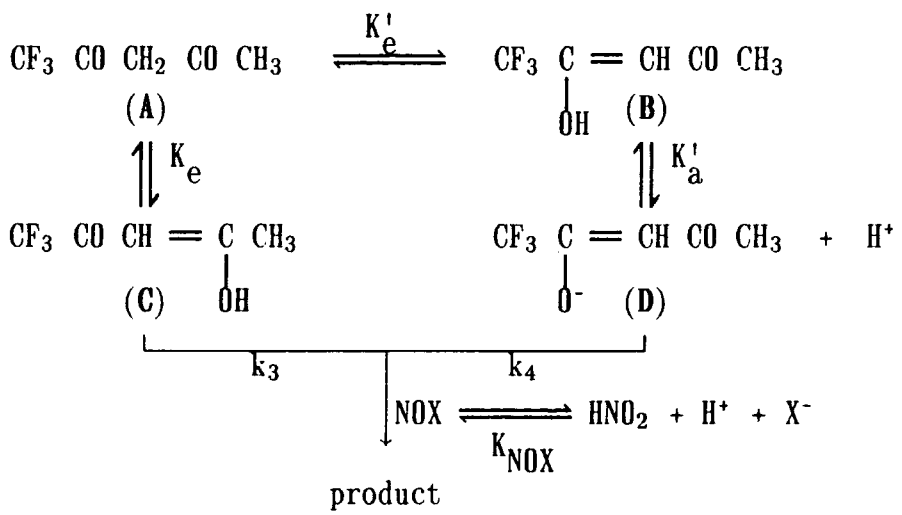
$[Cl^-]$ / M	$10^3\ k_0$ / s^{-1}
0	2.40
0.1	3.80
0.2	5.26
0.3	6.75
0.4	7.77
0.5	9.16

Table 5.4: Variation of k_0 with $[Br^-]$
$[HClO_4]$ = 0.277 M, [TFA] = 2 x 10^{-2} M

$10^2[Br^-]$ / M	10^3 k_0 / s^{-1}
0	3.65
5.0	25.9
10.0	43.9
15.0	64.9
20.0	80.4

Table 5.5: Variation of k_0 with $[SCN^-]$
$[HClO_4]$ = 0.2 M, [TFA] = 1 x 10^{-2} M

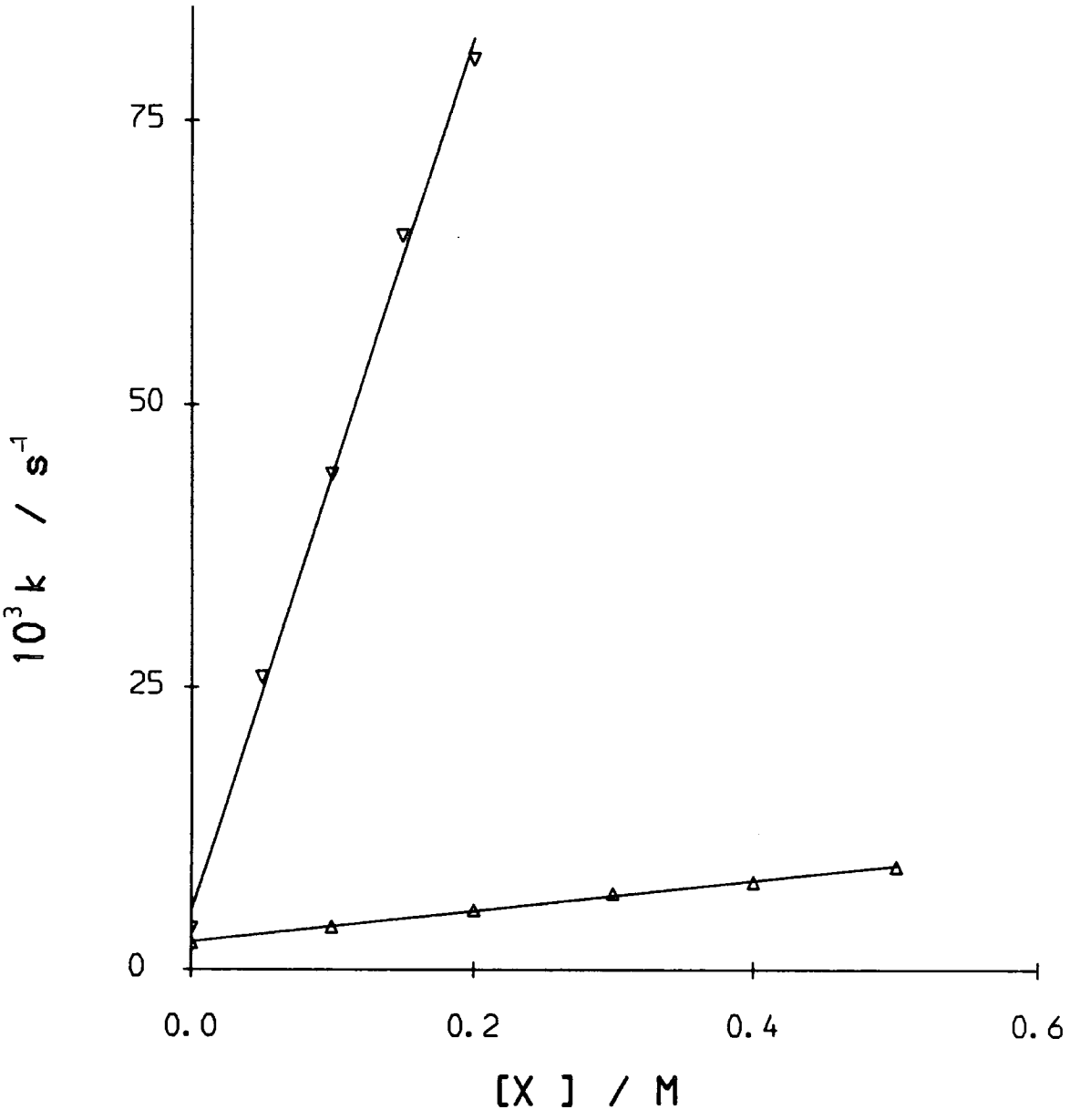
$10^4[SCN^-]$ / M	10^3 k_0 / s^{-1}
0	1.40
4.20	8.00
8.40	12.9
12.60	18.4
16.80	23.0
21.0	30.1



Scheme 5.2

Figure 5.2

Nucleophilic catalysis for nitrosation of TFA



The overall rate expression can be given by equation 5.5 where k_3 and k_4 are the rate constants for attack of enol and enolate ion respectively by the NOX species.

$$\text{Rate} = k_3[C][NOX] + k_4[D][NOX] + \begin{matrix}\text{uncatalysed}\\ \text{component}\end{matrix} = k_0[HNO_2] \qquad 5.5$$

$$= \left(k_3 K_e [A] + k_4 \frac{[B]}{[H^+]} K_a'\right) K_{NOX} [X^-] [H^+] [HNO_2] + \begin{matrix}\text{uncatalysed}\\ \text{component}\end{matrix} \qquad 5.6$$

$$= k_0 [HNO_2]$$

but, $[A] = [TFA]_T$ and $[B] = [A]K_e'$, also $K_e' K_a' = K_a$
substituting the above in equation 5.6 and combining both rates for uncatalysed (equation 5.2) and catalysed reactions, the expression for k_0 is given by equation 5.7. where K_{NOX} is the equilibrium constant for formation of NOX.

$$k_0 = (k_3 K_e [H^+] + k_4 K_a) K_{NOX} [X^-] [TFA]_T + (k_1 K_e [H^+] + k_2 K_a) [TFA]_T \qquad 5.7$$

So plots of k_0 vs $[H^+]$ should be linear with

$$\text{slope} = (k_1 + k_3 K_{NOX} [X^-]) K_e [TFA]_T$$

$$\text{and intercept} = (k_2 + k_4 K_{NOX} [X^-]) K_a [TFA]_T$$

In order to measure the values of k_3 and k_4, it is necessary to measure the rate constants for nitrosation of TFA over a range of acid concentrations in presence of fixed nucleophile concentration. Tables 5.6, 5.7 and 5.8 show the variation of k_0 with $[H^+]$ in presence of Cl^-, Br^- and SCN^- respectively.

Table 5.6: Variation of k_0 with $[HClO_4]$ in presence of Cl^-
$[Cl^-] = 0.4$ M, $[TFA] = 2 \times 10^{-2}$ M

$[HClO_4]$ / M	10^3 k_0 / s^{-1}
0.1	5.86
0.2	7.77
0.3	8.93
0.4	10.06
0.5	11.80

Table 5.7: Variation of k_0 with $[HClO_4]$ in presence of Br^-
$[Br^-] = 0.2$ M, $[TFA] = 2 \times 10^{-2}$ M

10^2 $[HClO_4]$ / M	10^2 k_0 / s^{-1}
9.3	6.42
18.5	7.21
27.7	7.90
37.0	8.43

Table 5.8: Variation of k_0 with $[HClO_4]$ in presence of SCN^-
$[SCN^-] = 1.05 \times 10^{-3}$ M, $[TFA] = 1 \times 10^{-2}$ M

$[HClO_4]$ / M	10^2 k_0 / s^{-1}
0.1	1.38
0.2	1.55
0.3	1.66
0.4	1.88
0.5	2.21

The linear plots of k_0 vs $[H^+]$ (figure 5.3) with significant positive intercepts are again consistent with reaction of NOX with both the enol and the enolate ion. The measured slopes and intercepts of these plots and the calculated k_3 and k_4 values are shown in table 5.9.

Figure 5.3

Variation of k_0 with [acid] in presence of nucleophile

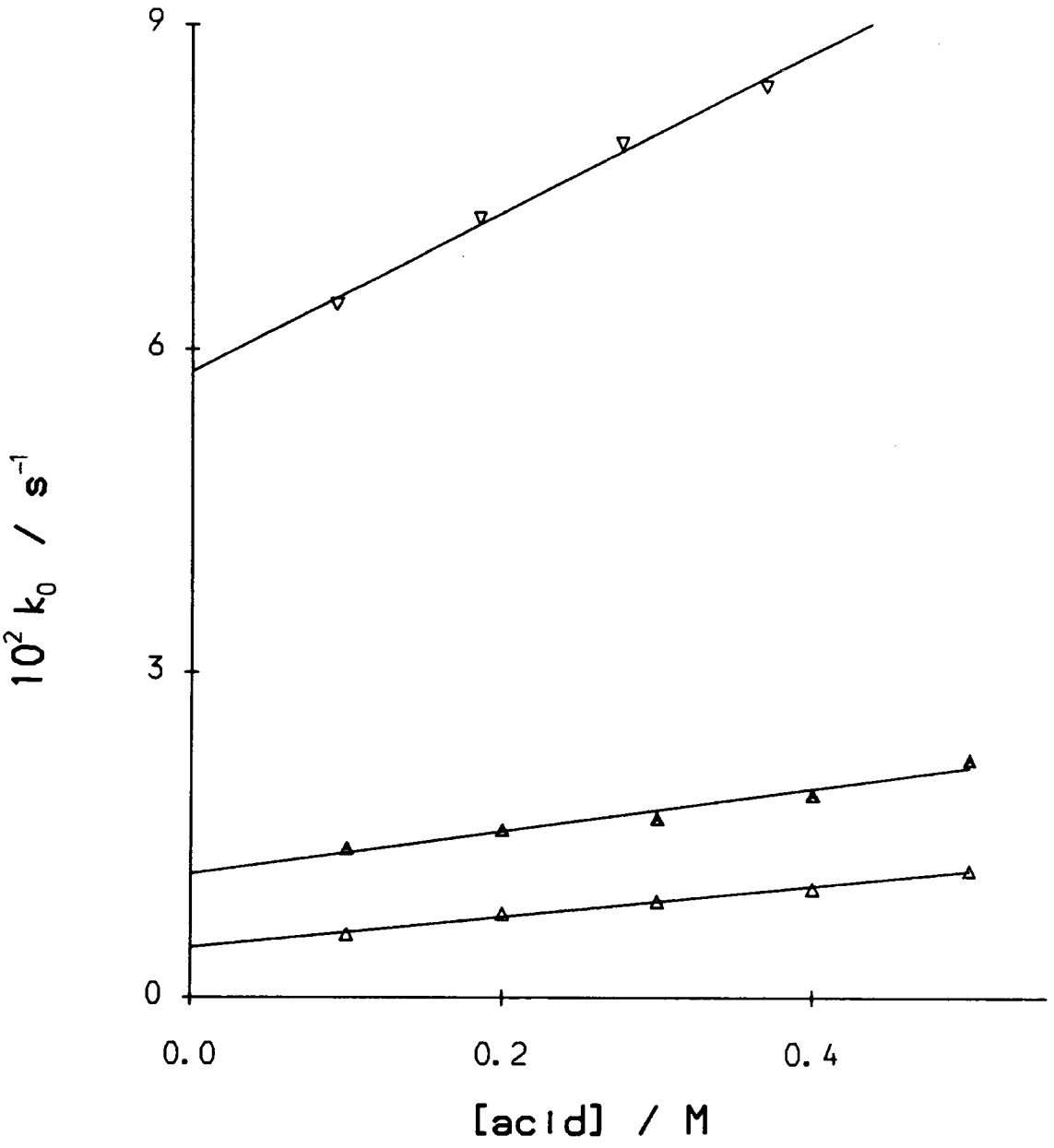


Table 5.9: Values for slopes and intercepts for plots of k_0 vs $[H^+]$ and corresponding k_3 and k_4 values for the reactions of NOCl, NOBr, and NOSCN with enol and enolate.

nucleophile	slope $l\ mol^{-1}s^{-1}$	intercept s^{-1}	k_3 $l\ mol^{-1}s^{-1}$	k_4 $l\ mol^{-1}s^{-1}$
chloride	1.53×10^{-2}	4.5×10^{-3}	4.2×10^{4}	1.4×10^{9}
bromide	6.3×10^{-2}	6.0×10^{-2}	2.3×10^{4}	9.2×10^{8}
thiocyanate	1.54×10^{-2}	1.22×10^{-2}	3.1×10^{3}	1.2×10^{8}

Table 5.10 compares the values of the measured slopes and intercepts of plots of k_0 vs $[X^-]$ with those calculated from expression 5.7 using the k_1, k_2, k_3 and k_4 values as determined in this work.

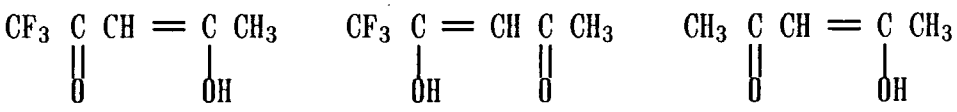
Table 5.10: Calculated and observed slopes and intercepts for plots of k_0 vs $[X^-]$

X^-	slope / $l\ mol^{-1}s^{-1}$	intercept / s^{-1}	
Cl^-	0.013	2.58×10^{-3}	observed
	0.012	2.72×10^{-3}	calculated
Br^-	0.38	5.5×10^{-3}	observed
	0.37	3.5×10^{-3}	calculated
SCN^-	13.23	1.83×10^{-3}	observed
	14.30	1.36×10^{-3}	calculated

The fact that the calculated and experimentally determined values of slopes and intercepts are so similar, shows that the values of k_1, k_2, k_3 and k_4 determined are internally consistent.

5.4 Discussion

The results of the kinetic experiments show, that nitrosation of TFA proceeds via both neutral enol form and the enolate ion. The situation is analogous to that encountered in acetonitrile medium[9] where it has also been experimentally shown that both forms (enol and enolate) of TFA participate in nitrosation. In aqueous media it is the enol form IV which is more likely to be attacked by the



(IV) (V) (VI)

nitrosating agent (i.e. undergo electrophilic attack), rather than the enol form V where the electron withdrawimg effect of the CF_3 group is expected to have a large deactivating effect on the enol towards electrophilic susbtitution. This then makes the enol form IV structurally similar to that of acetylacetone VI and their reactivities are expected to be rather similar, although it is expected that TFA would be somewhat less reactive since the CF_3 CO group is more electron withdrawing than the CH_3 CO group. The rate constants for the nitrosation of TFA by $H_2NO_2^+$/ NO^+ and NOX species (X^- = Cl^-,Br^-,SCN^-) are compared in table 5.11 with those of AcAc[8]. The reason for the slight discrepancy in the rate constant values is not clear, but it is worth pointing out that these values are crucially dependent on the corresponding K_e value, which may be in error. While the more acidic trifluoro compound (pK_a 6.7) undergoes nitrosation via both neutral enol and enolate ion, in AcAc (pK_a 9.8) the enol is the only reactive species. The structural similarities

of the enols are also reflected in their similar rate constant values (table 5.11). In the present study, as expected, the enolate is more reactive than the enol. In presence of nucleophilic catalysts, the reaction of the enolate ion with NOCl, NOBr and NOSCN are close to the encounter controlled limit[10] (7×10^9 l mol^{-1} s^{-1}). For the enol, the established[11] reactivity trend NOCl > NOBr > NOSCN is followed. For reactions of $H_2NO_2^+$/ NO^+ with any general substrate S, (rate = $k [H^+][HNO_2][S]$) rate constant values[10,12,13] of 7×10^3 and 1.1×10^4 l^2 mol^{-2} s^{-1} are considered as diffusion limits for such reactions with neutral and negatively charged substrates respectively. While the reaction of the enol of TFA (k_1 = 46 l^2 mol^{-2} s^{-1}) does not occur at encounter, the rate constant for attack of enolate (k_2 = 1.1×10^5 l^2 mol^{-2} s^{-1}) is *ca* 10 times greater than the above predicted limit. The value is however comparable to the reaction of the enolate of dimedone (k_2 = 4×10^5 l^2 mol^{-2} s^{-1}). For both substrates, the only explanation that can be offered for this is the probable uncertainty over the K_e and pK_a values, which would affect the rate constants. Similar values, in excess of the calculated limit have also been noted for the halogenation reaction of enolates[14]. Table 5.12 shows the effect of fluorine substitution on the trend of reactivity of β-dicarbonyl compounds towards nitrosation in aqueous and acetonitrile[9] media.

Table 5.12: Reactivity trend in nitrosation of β-dicarbonyl compounds

Compound	pK_a[5]	Reaction in aqueous medium	Reaction in acetonitrile medium[9]
AcAc	9.8	via enol only	via enol only
TFA	6.7	via enol and enolate ion	via enol and enolate ion
HFA	4.6	-	via enolate ion only

Table 5.11: Comparison of rate constants (l $mol^{-1}s^{-1}$ except where stated) for nitrosation of TFA and AcAc

	ENOL				ENOLATE			
Reactant	$k_{H_2NO_2^+}$	k_{NOCl}	k_{NOBr}	k_{NOSCN}	$k_{H_2NO_2^+}$	k_{NOCl}	k_{NOBr}	k_{NOSCN}
TFA	45 ($l^2mol^{-2}s^{-1}$)	4.2×10^4	2.3×10^4	3.1×10^3	1.1×10^5 ($l^2mol^{-2}s^{-1}$)	1.4×10^9	9.2×10^8	1.2×10^8
AcAc	36 ($l^2mol^{-2}s^{-1}$)	1.0×10^5	1.4×10^4	5.0×10^2	—	—	—	—

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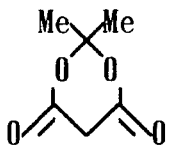
CHAPTER 6

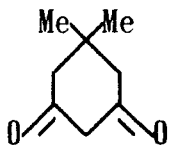
Nitrosation of Meldrum's Acid
(2,2-dimethyl 1,3-dioxane 4,6-dione)

6.1 Introduction

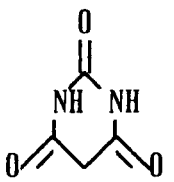
Since its discovery[1] in 1908 Meldrums acid (M.acid) has been extensively studied[2] and used, especially in organic synthesis. The properties of this compound (I) are related to those of other cyclic 1,3-diones like dimedone (II) and barbituric acid (III). M.acid is



I

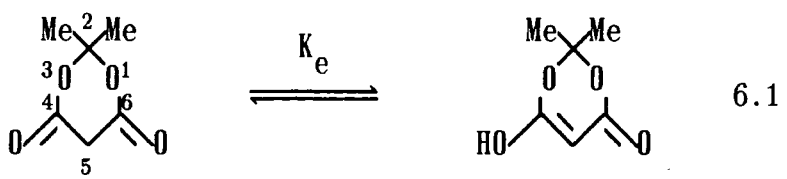


II



III

characterised by an unusually high acidity (pK_a = 4.83)[3] which is comparable to that of acetic acid. The explanation for this facile proton loss lies in the stability of the resultant anion in which the π orbitals are rigidly held in an ideal configuration for overlap. M.acid however differs significantly from dimedone in its tautomeric properties. While the former exists predominantly in the keto form, dimedone is highly enolic. The equilibrium constant for enolisation of M.acid in aqueous solution (equation 6.1) has been reported[4] as 4.05×10^{-3}. The chemistry of this compound is dominated by its



6.1

susceptibility to nucleophilic attack at positions 4 and 6 and electrophilic attack at position 5. Under acidic or basic conditions it undergoes hydrolysis[1] to malonic acid. The nitrosation of M.acid by aqueous sodium nitrite gives the oxime (equation 6.2) which has

6.2

been isolated as an unstable yellow solid[5,6]. In this chapter, the results of the detailed kinetic investigation into the mechanism of its nitrosation in aqueous medium in the absence and presence of nucleophilic catalysts (Cl^-, Br^-, SCN^- and $CS(NH_2)_2$) are presented.

All the kinetic experiments were carried out at 25^0C in water under pseudo first order conditions with excess of M.acid over nitrous acid. The reaction was followed spectrophotometrically at 320 nm, by noting the increase in absorbance due to product formation. The $[NaNO_2]$ was 1.14×10^{-3} M for all the kinetic runs.

6.2 Uncatalysed reactions

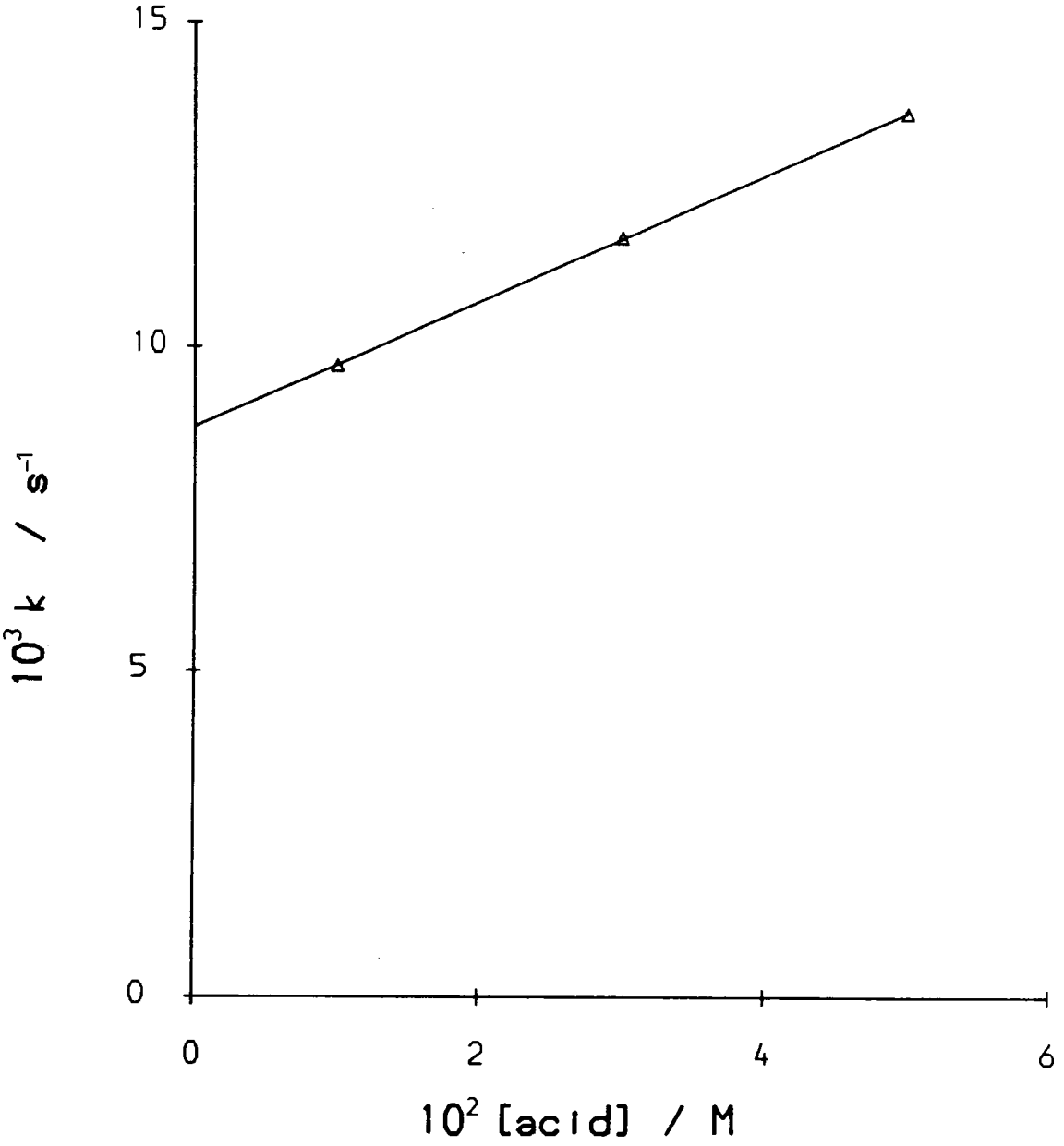
The kinetics of the nitrosation of M.acid was complicated by the fact that different rate laws were obtained in different acid ranges. (a) In the acid range 0.01 - 0.05 M, the reaction was first order with respect to nitrous acid and was catalysed by acid, as can be seen from the variation of k_0 (the observed rate constant) with $[HClO_4]$ (table 6.1 and figure 6.1).

Table 6.1: Variation of k_0 with $[HClO_4]$
[M.acid] = 0.029 M

10^2 $[HClO_4]$ / M	10^3 k_0 / s^{-1}
1.0	9.72
3.0	11.70
5.0	13.60

Figure 6.1

Variation of k_0 with [acid]



(b) At acidities above 0.05 M, the overall reaction had a mixed order dependence on $[HNO_2]$. In the region of acidity 0.06 - 1.5 M, the kinetic runs showed an initial zero order component followed by a first order reaction and there was no significant acid catalysis.

(c) At very high acidities, > 2 M, the reaction pattern changed from mixed (zero and first) to first order dependence on $[HNO_2]$.

6.3 Nucleophile catalysed reactions

Nitrosation of M.acid appeared to be significantly catalysed by added chloride, bromide, thiocyanate ions and thiourea. The reactions were all first order in $[HNO_2]$ and were quite fast and followed by stopped flow spectrophotometry. Tables and figures 6.2 and 6.3 show the variation of k_0 with concentration of Cl^-, Br^- and SCN^-, $CS(NH_2)_2$ respectively.

Table 6.2: Variation of k_0 with $[Cl^-]$ and $[Br^-]$
$[HClO_4]$ = 0.116 M, [M.acid] = 0.032 M

10^2 $[Cl^-]$ / M	10^2 k_0 / s^{-1}	10^2 $[Br^-]$ / M	k_0 / s^{-1}
5.0	6.0	5.0	1.43
10.0	9.2	10.0	2.61
15.0	11.6	15.0	3.98
20.0	13.6	20.0	5.23
25.0	15.8	25.0	6.30
30.0	18.2		

Table 6.3: Variation of k_0 with $[SCN^-]$ and $[CS(NH_2)_2]$
$[HClO_4]$ = 0.116 M, [M.acid] = 0.0284 M

10^3 $[SCN^-]$ / M	k_0 / s^{-1}	10^4 $[CS(NH_2)_2]$ / M	10 k_0 / s^{-1}
2.54	3.30	1.92	1.65
5.10	5.85	4.80	3.85
7.63	8.91	8.64	6.31
10.0	11.80	12.50	8.78
12.7	14.44	16.30	11.0
		20.20	14.5

The plots of k_0 vs $[X^-]$ (figures 6.2 and 6.3) are all linear with a positive intercept representing the uncatalysed reaction.

The variation of k_0 with concentration of acid in presence of nucleophile was also examined. The results are presented in tables 6.4, 6.5, 6.6 and 6.7.

Table 6.4: Variation of k_0 with [acid]
$[Cl^-]$ = 0.25 M, [M.acid] = 0.032 M

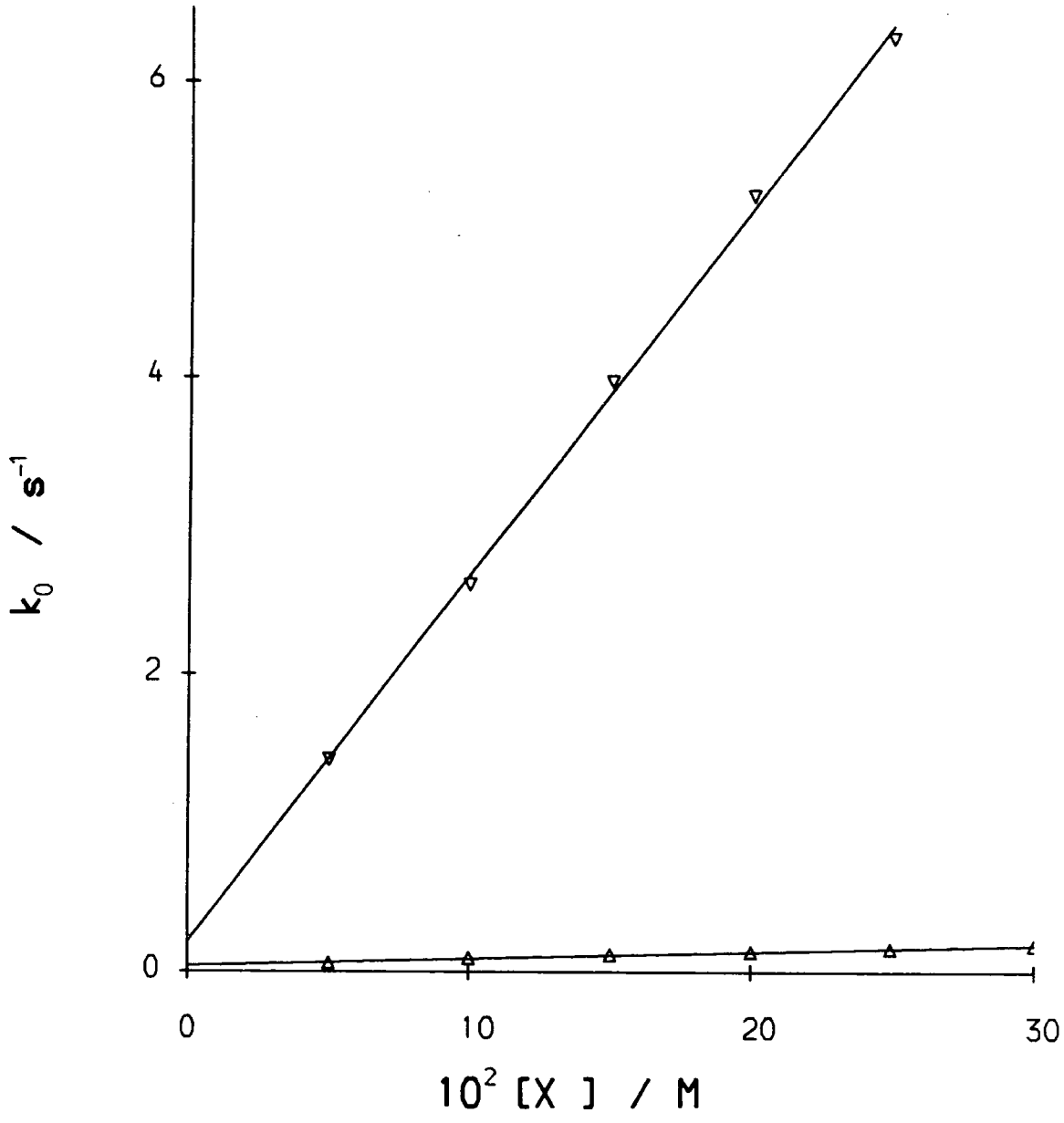
10 $[HClO_4]$ / M	10 k_0 / s^{-1}
1.16	1.58
2.31	1.56
3.45	1.58

Table 6.5: Variation of k_0 with [acid]
$[Br^-]$ = 0.15 M, [M.acid] = 0.015 M

10^2 $[HClO_4]$ / M	k_0 / s^{-1}
6.9	2.055
11.6	2.018
16.2	2.055
20.8	2.099
30.1	2.155

Figure 6.2

Variation of k_0 with $[Cl^-]$ and $[Br^-]$

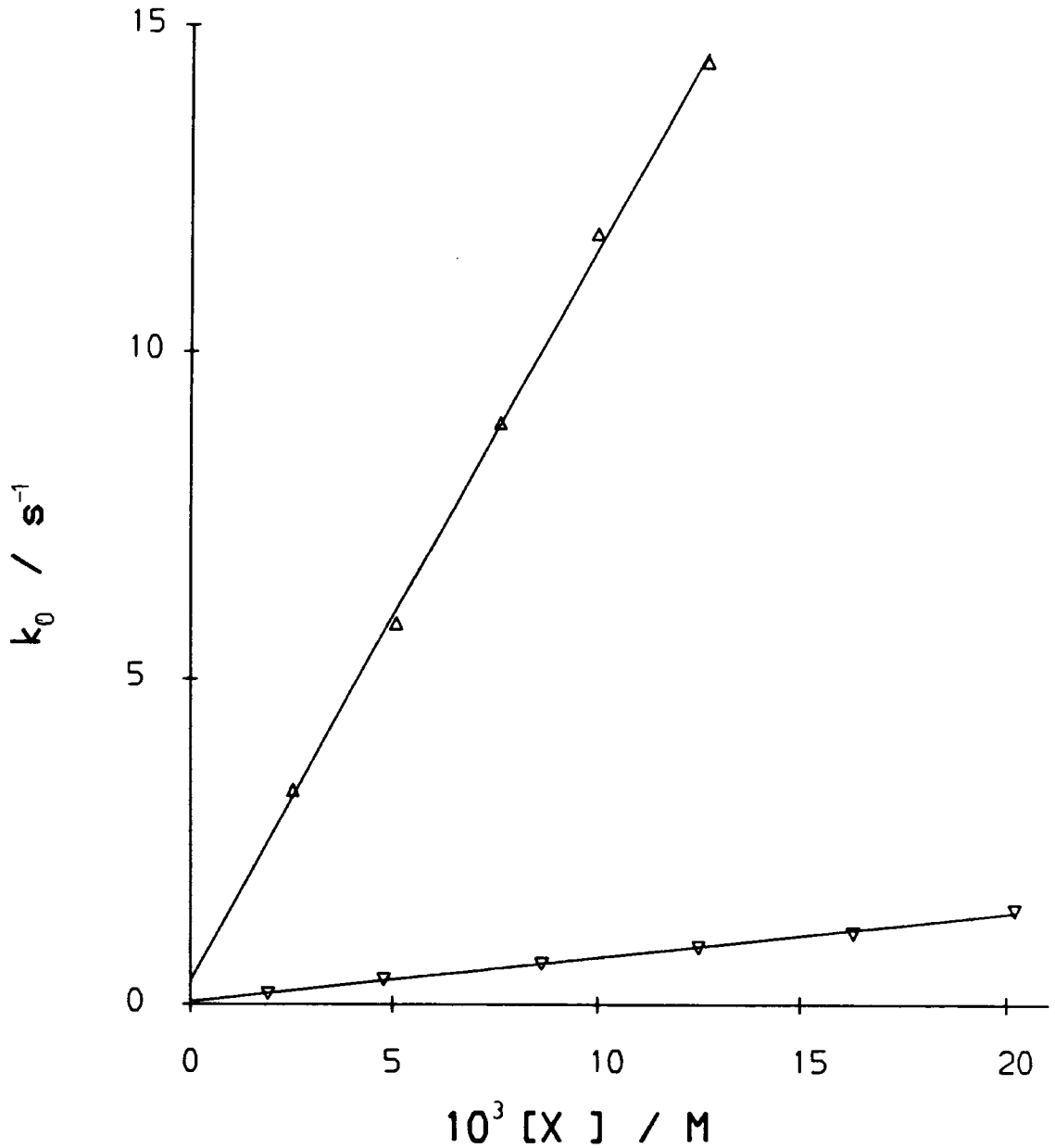


▽ X = Br^-

△ X = Cl^-

Figure 6.3

Variation of k_0 with $[SCN^-]$ and $[CS(NH_2)_2]$



▽ X = 10 $CS(NH_2)_2$

△ X = SCN^-

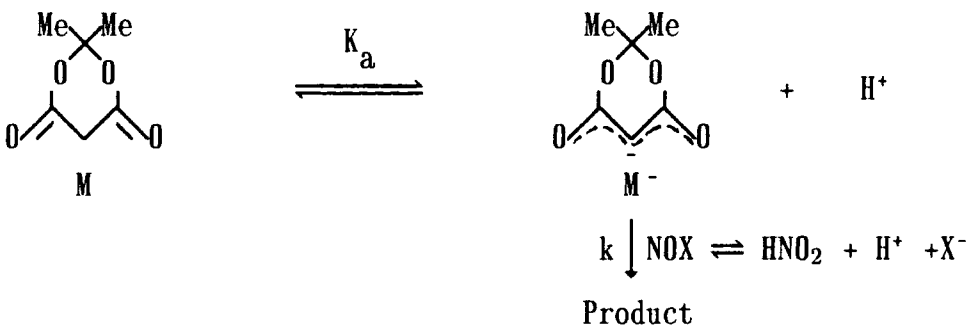
Table 6.6: Variation of k_0 with [acid]
$[SCN^-] = 2.5 \times 10^{-3}$ M, [M.acid] = 0.0168 M

10^2 [$HClO_4$] / M	k_0 / s^{-1}
3	1.01
6	1.62
9	2.01
12	2.43
14	2.74

Table 6.7: Variation of k_0 with [acid]
$[CS(NH_2)_2] = 4.8 \times 10^{-4}$ M, [M.acid] = 0.0254 M

10^2 [$HClO_4$] / M	10 k_0 / s^{-1}
4.6	1.65
8.1	2.89
11.6	3.75
18.5	5.56
25.0	7.18

Tables 6.4 and 6.5 show that there is no variation of k_0 with [acid] in the acidity region 0.07 - 0.35 M. This indicates that there is reaction only via the anion as interpreted in scheme 6.1. The rate



Scheme 6.1

expression for such a scheme is given by equation 6.3.

$$\text{Rate} = k\,[M^-]\,[NOX] = k_0\,[HNO_2] \qquad 6.3$$

$$\text{but } [M^-] = \frac{[M]\,[K_a]}{[H^+]} \quad \text{and } [NOX] = K_{NOX}[H^+]\,[HNO_2]\,[X^-]$$

$$\text{therefore Rate} = k\,K_{NOX}[X^-]\,[H^+]\,[HNO_2]\,[M]\,\frac{K_a}{[H^+]} = k_0\,[HNO_2] \qquad 6.4$$

$$\text{and } k_0 = k\,K_{NOX}\,[X^-]\,[M]\,K_a \qquad 6.5$$

From equation 6.5, for a plot of k_0 vs $[X^-]$ slope = $k\,K_{NOX}[M]\,K_a$. The values of slopes for a plot of k_0 vs $[X^-]$ (X^- = Cl^- and Br^-) and the corresponding k values are given in table 6.8

Table 6.8: Values of the slopes for k_0 vs $[X^-]$ and corresponding k values

X^-	slope ($l\ mol^{-1}s^{-1}$)	k ($l\ mol^{-1}s^{-1}$)
Cl^-	0.47	9.1×10^8
Br^-	24.6	1.0×10^9

Table 6.9 gives the values of k_0 as obtained from the constancy with [acid] and the corresponding k values calculated from equation 6.5.

Table 6.9: Values of k_0 and k (for variation of k_0 with acid in presence of X^-)

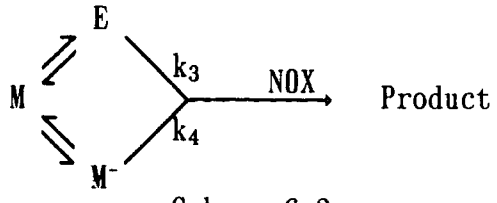
X^-	k_0 (s^{-1})	k ($l\ mol^{-1}s^{-1}$)
Cl^-	0.158	1.2×10^9
Br^-	2.05	1.2×10^9

The variation of [M.acid] in presence of Br^- is given in table 6.10. From the plot of k_0 vs [M.acid], slope = k $[X^-]$ K_{NOX} K_a. The calculated value of the rate constant, k = 1.13 x 10^9 l $mol^{-1}s^{-1}$ agrees very well with those calculated from plots of k_0 vs $[X^-]$ and from the constancy with acid. This provides support for the proposed mechanistic scheme (scheme 6.1).

Table 6.10: Variation of k_0 with [M.acid]
$[Br^-]$ = 0.1 M, $[HClO_4]$ = 0.125 M

10^3 [M.acid] / M	k_0 / s^{-1}
9.4	0.710
18.8	1.67
28.2	2.55
37.6	3.34

Reactions in presence of SCN^- and $CS(NH_2)_2$ show that the reactions are acid catalysed, as seen from the variation of k_0 with [acid] (tables 6.6 and 6.7 respectively and figure 6.4). This situation may again represent reaction via both enol and enolate ion (scheme 6.2), where M, E, M^- represent M.acid, its enol form and the enolate ion respectively.

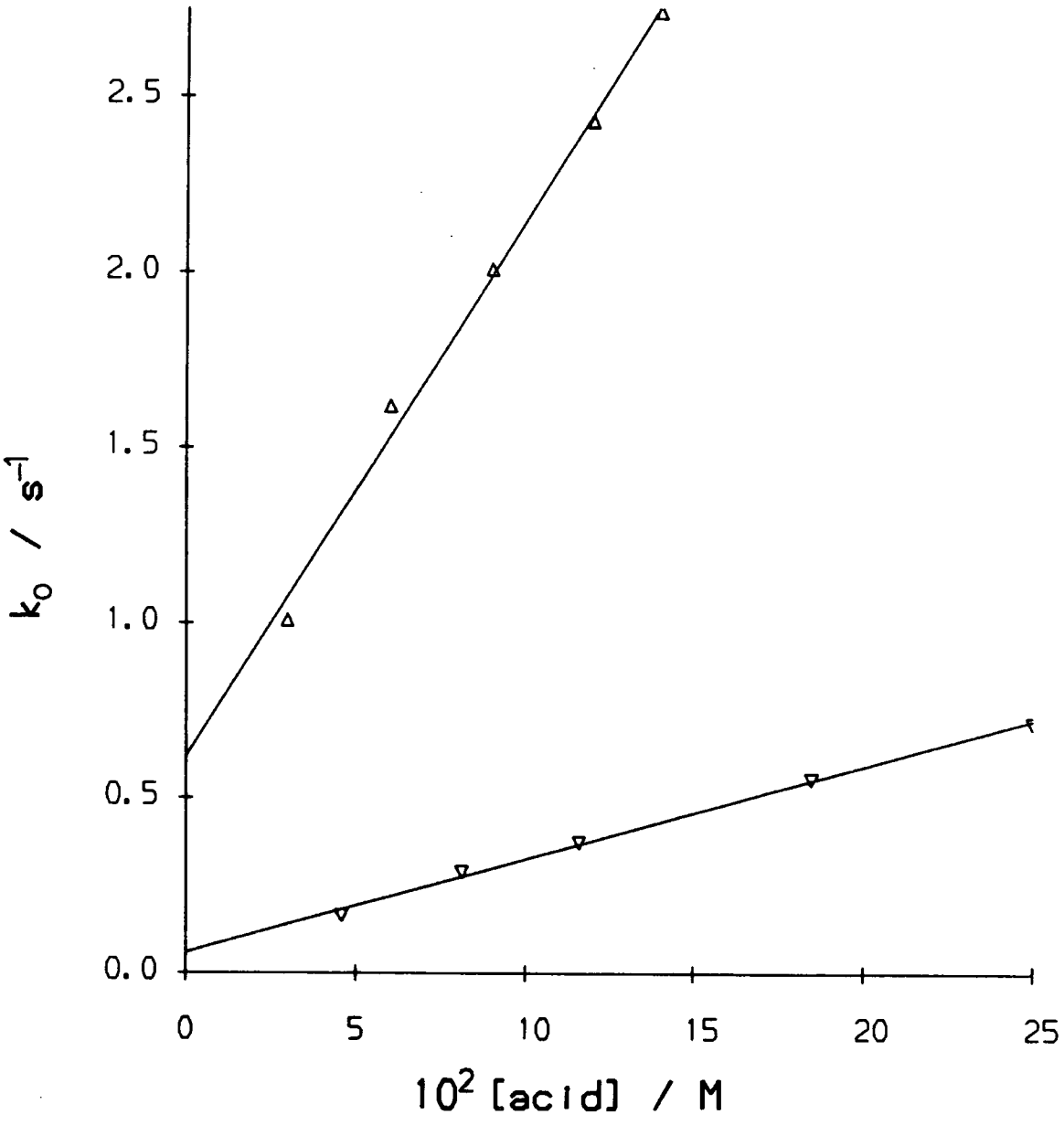


Scheme 6.2

The overall rate constant can be expressed in terms of equation 6.6 and k_0 by equation 6.7 (by analogy to reactions of trifluoroacetylacetone representing a similar situation).

Figure 6.4

Variation of k_0 with [acid] in presence of SCN^- and $CS(NH_2)_2$



▽ In presence of $CS(NH_2)_2$

△ In presence of SCN^-

$$\text{Rate} = k_3\,[E][NOX] + k_4\,[M^-]\,[NOX] + \text{uncatalysed reaction}$$
$$= k_0\,[HNO_2] \qquad 6.6$$

$$k_0 = (k_3K_e[H^+] + k_4K_a)K_{NOX}[X^-][M.acid]_T + (k_1K_e[H^+] + k_2K_a)[M.acid]_T \qquad (6.7)$$

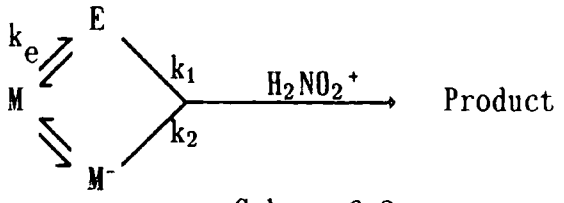
In order to measure the values of k_3 and k_4 (the rate constants for attack of NOX on the enol and enolate ion resectively), it is necessary to know the values of k_1 and k_2 (the corresponding rate constants for the uncatalysed reactions). However, the complicated kinetics for the uncatalysed reactions prevents the measurement of k_1 and k_2 and hence the k_3 and k_4 values.

6.4 Discussion

The kinetic results of the nitrosation of M.acid are consistent with reaction involving either the neutral enol or the enolate ion or a combination of both reactions. M.acid is a very strong acid (pK_a 4.76) and its anion is therefore expected to be very reactive towards electrophilic attack. Williams *et al*[7] have established that nitrosation of malononitrile in acid solution proceeds via the carbanion. The malononitrile carbanion is a very reactive species and its reaction with NOX (X^- = Cl^-, Br^-, SCN^- and $CS(NH_2)_2$) are all encounter controlled. From our experimental data there is evidence that reactions in presence of Cl^- and Br^- proceeded via the anion only. It was possible to analyse the kinetic data and determine the rate constants for attack of the NOX species on the anion. The reactions were found to be diffusion controlled.

Nucleophilic catalysis by SCN^- and $CS(NH_2)_2$ was also very pronounced. In this case however, The reaction appeared to involve attack on both enol and enolate ion. The individual rate constants for the reactions could not be determined and hence it is not possible to comment on the general mechanistic features of the reactions involving these NOX species. It may well be that the selectivity may be related to the well known[8] lower reactivity of NOSCN and $\overset{+}{N}OSC(NH_2)_2$ than NOBr and NOCl.

For the uncatalysed reactions, the results may be interpreted in terms of scheme 6.3



Scheme 6.3

M.acid can exist either as its enol (E) or its anion (M^-). At lower acidities, the linear plot of k_0 vs [acid] with a significant positive intercept clearly indicates reaction via both E and M^- with rate limiting attack of these species by $H_2NO_2^+$ (as reaction is first order in $[HNO_2]$). The overall rate can be expressed in terms of the rate constants k_1 and k_2 for attack of $H_2NO_2^+$ on E and M^- respectively by equation 6.8.

$$\text{Rate} = k_1[E][H^+][HNO_2] + k_2[M^-][H^+][HNO_2] = k_0\,[HNO_2] \qquad 6.8$$

$$\text{but } [E] = K_e[\text{M.acid}]_T \text{ and } [M^-] = (K_a\,[\text{M.acid}]_T) \,/\, [H^+]$$

$$\text{therefore } k_0 = (k_1\,K_e\,[H^+] + k_2\,K_a)\,[\text{M.acid}]_T \qquad 6.9$$

At high acidities (>2 M), the equilibrium ($M \rightleftharpoons M^- + H^+$) probably shifts towards M and hence towards E and the reaction involves rate limiting attack by $H_2NO_2^+$ on enol only.

At intermediate acidities, the tendency towards a zero order reaction (although not fully zero order) strongly suggests that enolisation ($M \longrightarrow M^-$ or $M \longrightarrow E$) is rate limiting to some extent. The absence of any significant acid catalysis implies that enolisation is not acid catalysed. The situation is analagous to that encountered in the nitrosation 1,3-dichloroacetone[9] where enolisation is not acid catalysed and also, the reaction is mixed zero and first order. The mechanism of enolisation is believed to involve proton abstraction by a water molecule from the non-protonated form of the ketone. However, the simple scheme (scheme 6.3) does not quantitatively explain the three different mechanistic patterns. It must be a little more complicated and further work may be helpful. Although our kinetic experiments do not provide a complete explanation of the mechanistic details of the nitrosation of M.acid the gross features appear to be quite clear. Further work in this area is desirable.

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CHAPTER 7

Experimental Details

7.1 Experimental techniques used.

Both UV-Visible and stopped flow spectrophotometry were used for the determination of rate constants in this study.

7.1.1 UV-Visible spectrophotometry

Rate measurements for nitrosation of ethylacetoacetate, 1,1,1-trifluoropentane-2,4-dione, and Meldrum's acid were carried out by this technique using either Perkin Elmer Lambda 3 or Philips PU8720 spectrophotometers.

Stock solutions were made up in water (20% dioxan for ethylacetoacetate) from which two solutions, one containing sodium nitrite and the other containing the substrate, acid and appropriate nucleophile (where necessary) were thermostatted in a water bath at 25^0C. The required amount of $NaNO_2$ solution was added to a solution containing all the other reagents (total volume *ca* 25 ml) and after rapid mixing, a portion of the reaction mixture was transferred to a 1 cm pathlength quartz cell and placed in a thermostatted cell holder of the spectrophotometer. An identical cell containing the solvent was used as the reference. The reaction was monitored by following the change in absorbance at a particular wavelength as a function of time.

7.1.2 Stopped-flow spectrophotometry

Conventional UV-Visible spectrophotometry is not suitable for measuring reaction rates when the half-life of the reaction is less than 5-10 seconds. Instead stopped-flow spectrophotometry may be used. This technique enables measurement of reaction rates with half-lives between one millisecond and several seconds. The

nitrosation of dimedone and catalysed reactions of ethylacetoacetate and Meldrum's acid were studied by this method.

In this technique, two solutions (one normally being sodium nitrite and the other containg all the other components of the reaction) are stored in reservoirs and from there enter two identical syringes. A single piston drives the two syringes so that equal volumes of each solution are mixed. On mixing, the concentration of each reactant present is halved. The reaction solution then flows into a third syringe. On filling, the plunger of this syringe is forced against a stop which halts the flow and at the same time presses the trigger which starts the monitoring of the reaction (figure 7.1).

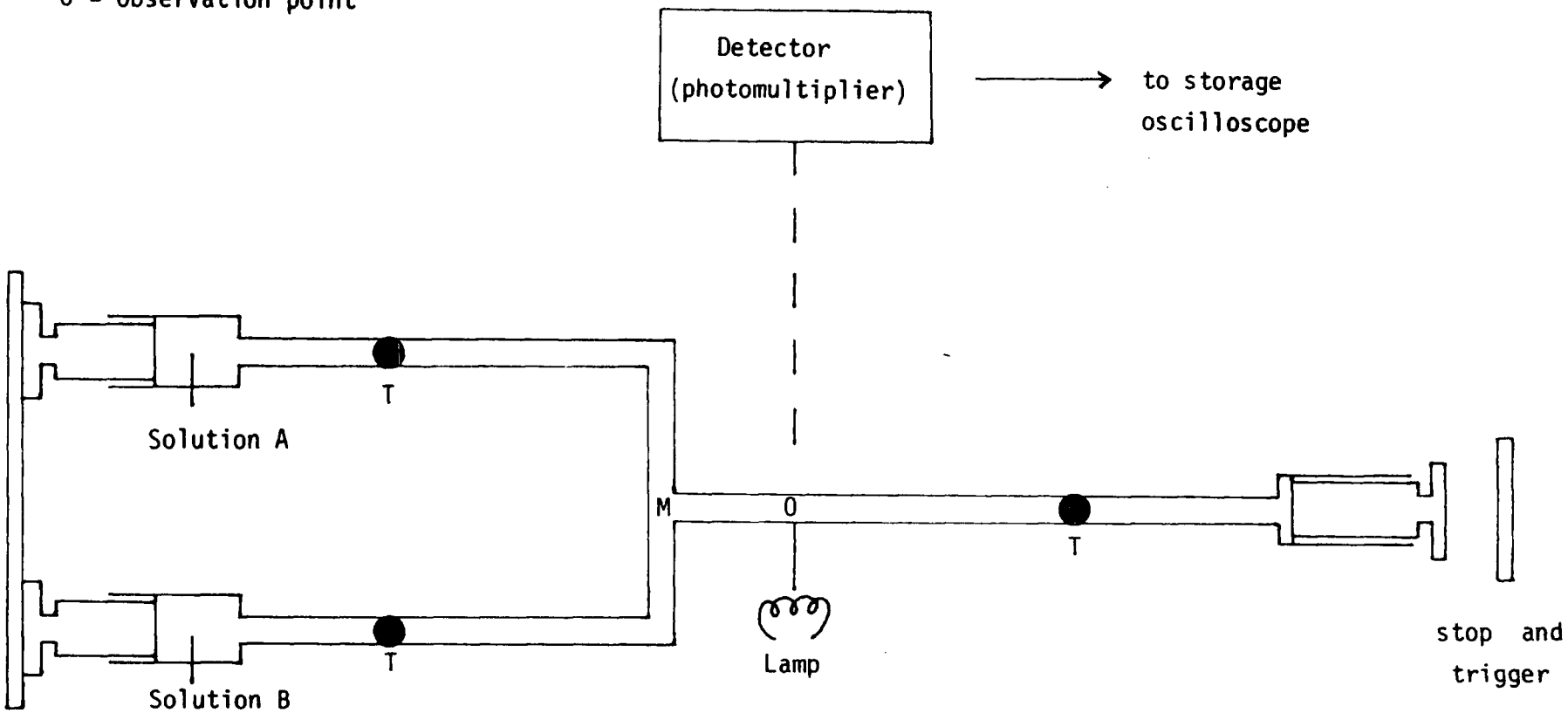
The reaction is followed by a beam of monochromatic light which passes through the cell. The intensity of the beam is converted to an electrical signal and amplified by a photomultiplier, giving typically minus five to minus eight volts for the light intensity with no absorbing species in the cell. If this signal were to be used, the change in voltage due to the reaction proceeding would appear as a very small voltage change superimposed on the photomultiplier's standing output voltage, so an equal but opposite voltage is added to this standing voltage (biasing) allowing amplification by the recording equipment of the voltage change only. With non-absorbing solution at the observation point the final voltage is zero and any voltage change observed results from the progression of the reaction. The voltage changes were recorded and analysed (to give the rate constants) by an Apple IIe microcomputer, fitted with a fast analogue to digital converter, and running a kinetics analysis program supplied by "HITECH".

Figure 7.1 : Schematic Diagram of a Stopped-Flow Spectrophotometer

T = three way taps

M = mixing point

O = observation point



7.2 Chemical reagents used

All the carbonyl compounds studied were commercially available. Ethylacetoacetate was distilled under reduced pressure and the middle fraction of the distillate was used. Dimedone and Meldrum's acid were further purified by recrystallisation from water. 1,1,1-trifluoropentane-2,4-dione was of an analytical grade and was not purified further. Commercially available dioxan was used. The inorganic reagents $NaNO_2$, NaCl, NaBr, $NaSCN.2H_2O$, $CS(NH_2)_2$ and $NaClO_4$ were all of AR grade and were used as supplied commercially. Perchloric acid solutions were prepared by dilution of 60-62% $HClO_4$ and standardised against standard sodium hydroxide solutions using phenolphthalein indicator. Stock solutions of $NaNO_2$ were prepared fresh daily.

7.3 Determination of the observed rate constants.

As stated previously, all the experiments were performed under first order conditions, and the reactions were followed by monitoring the rate of disappearance of the reactant present in the lowest concentration, or appearance of the product, with time. The relationship between concentration and absorbance is given by the Beer-Lambert law and is simply: $A = \epsilon Cl$, where A is the absorbance, ϵ the molar extinction coefficient, C the concentration and l the pathlength. For a first order reaction $R \longrightarrow P$, where R = reactant and P = product, $[P]_t = [R]_0 - [R]_t$, where $[P]_t$ is the concentration of P at time t = t and $[R]_0$ is the concentration of R at time t = 0. The expression for the observed first order rate constant k_0 is given by equation 7.1

$$k_0 = \frac{1}{t} \ln \frac{[R]_0}{[R]_t} \qquad 7.1$$

Using the Beer-Lambert law the aborbance at time t = 0 may be defined as $A_0 = \epsilon_R [R]_0$, if the pathlength of the cell is assumed to be 1 cm.

Similarly, $A_t = \epsilon_R [R]_t + \epsilon_P [P]_t$

substituting for $[P]_t$

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

$$A_\infty = \epsilon_P [P]_\infty = \epsilon_P [R]_0 \quad \text{since } [P]_\infty = [R]_0$$

subtracting

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

$$[R]_t = \frac{(A_t - A_\infty)}{(\epsilon_R - \epsilon_P)}$$

similarly,

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

$$[R]_0 = \frac{(A_0 - A_\infty)}{(\epsilon_R - \epsilon_P)}$$

Substituting into equation 7.1

$$k_0 = \frac{1}{t} \ln \frac{(A_0 - A_\infty)}{(A_t - A_\infty)} \qquad 7.2$$

Thus an instantaneous value of k_0 at time t = t may be obtained from equation 7.2.

Since $\ln(A_t - A_\infty) = -k_0 t + \ln(A_0 - A_\infty)$, from equation 7.2, a plot of $\ln(A_t - A_\infty)$ vs t should be linear with a slope of $-k_0$. The infinity value A_∞, was determined after a period of ten half-lives.

The disappearance or appearance of absorbance, depending on the reaction, was generally followed for at least two half-lives.

For experiments carried out using the stopped-flow technique the value of k_0 was determined using the "HITECH" kinetics program. This program initially calculates a value for k_0 from the slope of a calculated plot of $\ln(V_t - V_\infty)$ vs time, then optimises this value iteratively, using a non-linear regression analysis thus removing some of the error inherent in using linear regression methods. Owing to the errors in measuring fast reactions, the value of k_0 quoted for these reactions is the mean of at least five separate determinations. Some examples from actual kinetic runs are given below:

Example 1: Nitrosation of ethylacetoacetate (EAA):

The rate measurements were made on the Perkin Elmer Lambda 3 spectrophotometer at 25^0C by following the absorbance due to the disappearance of nitrous acid. A typical kinetic run is shown in table 7.1.

Table 7.1: Typical kinetic run for nitrosation of EAA

[EAA] = 0.2 M, $[NaNO_2]$ = 0.01 M, $[HClO_4]$ = 0.155 M

A_t	t / s	10^3 k_0 / s^{-1}
0.523	0	-
0.425	40	5.95
0.350	80	5.85
0.293	120	5.72
0.245	160	5.73
0.205	200	5.80
0.175	240	5.80
0.156	280	5.62
0.06	∞	-

$k_0 = 5.78 \times 10^{-3} \pm 9.73 \times 10^{-5}$ s^{-1}

The individual rate constants at each time interval have been calculated by using equation 7.2. These values are not normally calculated but have been shown here to give an impression of the error involved in a kinetic run.

Example 2: Nitrosation of 1,1,1-trifluoropentane-2,4,-dione (TFA)

Rate measurements were carried out at 25^0C using a Philips PU8720 spectrophotometer. The absorbance change due to formation of the product was monitored at 240 nm wavelength. Table 7.2 shows a typical kinetic run.

Table 7.2: A typical kinetic run for chloride ion catalysis of TFA

[chloride] = 0.4 M [TFA] = 2×10^{-2} M
$[HClO_4]$ = 0.2 M $[NaNO_2] = 3 \times 10^{-4}$ M

A_t	t / s	$10^3 k_0$ / s^{-1}
0.630	0	-
0.729	30	7.40
0.811	60	7.55
0.873	90	7.55
0.923	120	7.42
0.962	150	7.35
0.994	180	7.32
1.020	210	7.32
1.041	240	7.31
1.127	∞	-

$k_0 = 7.4 \times 10^{-3} \pm 9.91 \times 10^{-5}$ s^{-1}

Example 3: Nitrosation of Meldrum's acid (M.acid)

Rate measurements were made either on the Perkin Elmer Lambda 3 or the stopped-flow spectrophotometer (for reactions in presence of nucleophilic catalysts). A typical first order run on the Lambda 3 is shown in table 7.3.

Table 7.3: Typical kinetic run for nitrosation of M.acid
[M.acid] = 0.029 M, $[NaNO_2]$ = 1.14 x 10^{-3} M, $[HClO_4]$ = 0.01 M

A_t	t / s	10^3 k_0 / s^{-1}
0.072	0	-
0.106	20	9.30
0.135	40	9.46
0.158	60	9.37
0.178	80	9.44
0.194	100	9.42
0.208	120	9.50
0.272	∞	-

$k_0 = 9.42 \times 10^{-3} \pm 7.09 \times 10^{-5}$ s^{-1}

APPENDIX

Colloquia, lectures and seminars organised by the Department of Chemistry and Durham University Chemical Society during the period 1987-1988 (* denotes lectures attended).

Prof. R.H. Ottewill (Bristol) January 22, 1987
Colloid Science, A Challenging Subject *

Dr. W. Clegg (Newcastle upon Tyne) January 28, 1987
Carboxylate Complexes of Zinc; Charting a Structural Jungle

Prof. A. Thomson (East Anglia) February 4, 1987
Metallo Proteins and Magneto Optics

Dr. P. Hubberstey (Nottingham) February 5, 1987
Demonstration Lecture on various aspects of Alkali Metal Chemistry *

Dr. T. Shepherd (Durham) February 11, 1987
Pteridine Natural Products; Synthesis and Use in Chemotherapy

Dr. P.J. Rodgers (ICI Billingham) February 12, 1987
Industrial Polymers from Bacteria *

Prof. E.H. Wong (New Hampshire, USA) February 17, 1987
Symmetrical Shapes from Molecules to Art and Nature

Dr. M. Jarman (Institute of Cancer Research) February 19, 1987
The Design of Anti-Cancer Drugs *

Dr. R. Newman (Oxford) March 4, 1987
Change and Decay: A Carbon-13 CP/MAS NMR Study of Humification and Coalification Processes

Prof. S.V. Ley (Imperial College) March 5, 1987
Fact and Fantasy in Organic Synthesis *

Prof. G.G. Bordwell (N.E. University, USA) March 9, 1987
Carbon Anions, Radicals, Radical Anions and Radical Cations

Dr. R.D. Cannon (East Anglia) March 11, 1987
Electron Transfer in Polynuclear Complexes *

Dr. E.M. Goodger (Cranfield Inst. of Tech.) March 12, 1987
Alternative Fuels for Transport *

Prof. R.F. Hudson (Kent) March 17, 1987
Aspects of Organophosphorus Chemistry

Prof. R.F. Hudson (Kent) March 18, 1987
Homolytic Rearrangements of Free Radical Stability

Dr. R. Bartsch (Sussex) May 6, 1987
Low Coordinated Phosphorus Compounds

Dr. M. Harmer (ICI Chem. & Polymer Group) May 7, 1987
The Role of Organometallics in Advanced Materials

Prof. S. Pasynkiewicz (Tech. Univ., Warsaw) May 11, 1987
Thermal Decomposition of Methyl Copper and its Reactions with Tri-alkyl Aluminium

Dr. M. Blackburn (Sheffield) May 17, 1987
Phosphonates as Analogues of Biological Phosphate Esters

Prof. S.M. Roberts (Exeter) June 24, 1987
Synthesis of Novel Antiviral Agents *

Dr. C. Krespan (E.I. DuPont de Nemours) June 26, 1987
Nickel (0) and Iron (0) as Reagents in Organofluorine Chemistry

Dr. M.J. Winter (Sheffield) October 15, 1987
Pyrotechnics (Demonstration Lecture) *

Prof. J.W. Gray (Hull) October 22, 1987
Liquid Crystals and their Applications *

Mrs. S. van Rose (Geological Museum) October 12, 1987
Chemistry of Volcanoes *

Dr. A.R. Butler (St. Andrews) November 5, 1987
Chinese Alchemy *

Prof. D. Seebach (E.T.H. Zurich) November 12, 1987
From Synthetic Methods to Mechanistic Insight *

Dr. D.H. Williams (Cambridge) November 26, 1987
Molecular Recognition

Dr. J. Howard (ICI Wilton) December 3, 1987
Chemistry of Non-equilibrium Processes *

Dr. C.J. Ludman (Durham) December 10, 1987
Explosives

Mr. R.M. Swart (ICI) December 16, 1987
The Interaction of Chemicals with Lipid Bilayers

Prof. P.G. Sammes (Smith, Kline and French) December 19, 1987
Chemical Aspects of Drug Development *

Dr. F. Palmer (Nottingham) January 21, 1988
Luminescence (Demonstation Lecture) *

Dr. A. Cairns-Smith (Glasgow) January 28, 1988
Clay Minerals and the Origin of Life *

Prof. J.J. Turner (Nottingham) February 11, 1988
Catching Organometallic Intermediates

Dr. K. Borer (Durham, UDIRL) February 18, 1988
The Brighton Bomb - A Forensic Science View *

Prof. A. Underhill (Bangor) February 25, 1988
Molecular Electronics

Prof. W.A.G. Graham (Alberta, Canada) March 3, 1988
Rh and Ir Complexes in the Activation of C-H Bonds

Prof. H.F. Koch (Ithaca College, USA) March 7, 1988
Does the E2 Mechanism Occur in Solution *

Prof. M.P. Hartshorn (Canterbury, New Zealand) April 7, 1988
Aspects of Ipso Nitration

Prof. C.A. Nieto de Castro (Lisbon Univ. & Imperial College)
April 18, 1988
Transport Properties of Non-polar Fluids

Graduate Chemists (N.E. Poly & Universities) April 19, 1988
R.S.C. Graduate Symposium *

Prof. D. Birchall (ICI) April 25, 1988
Environmental Chemistry of Aluminium

Dr. R. Richardson (Bristol) April 27, 1988
X-ray Diffraction From Spread Monolayers

Dr. J.A. Robinson (Southampton) April 27, 1988
Aspects of Antibiotic Biosynthesis

Prof. A. Pines (California, USA) April 28, 1988
Some Magnetic Moments *

Dr. W.A. McDonald (ICI Wilton) May 11, 1988
Liquid Crystal Polymers

Dr. J.P. Majoral (Univ. Paul Sabatier) June 8, 1988
Stabilisation by Complexation of Short-lived Phosphorus Species

Prof. G.A. Olah (S. California, USA) June 29, 1988
New Aspects of Hydrocarbon Chemistry