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# Enols Derived from Malonic Acids as Intermediates in Nitrosation and Halogenation

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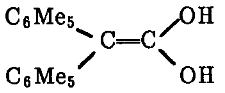
***Abstract:*** *Malonic acid, methylmalonic acid, ethylmalonic acid and phenylmalonic acid react with electrophilic nitrosating agents and also with bromine and iodine via their corresponding enol or enolate forms. In most cases it is possible to make either the enolisation or reaction of the enol rate–limiting by a suitable choice of reactant concentrations and reactivity. The enolisation rate constants agree reasonably well with literature values where they exist. We propose minimum figures of* $1.0 \times 10^{-8}$ *and* $1.6 \times 10^{-8}$ *respectively for* $K_E$ *the enolisation equilibrium constant for malonic acid and methylmalonic acid. The kinetic term second order in [malonic acid] or its derivatives (when enolisation is rate limiting) has been shown to arise from a base catalysed component to the reaction brought about by the malonate ion, which dominates at pH values greater than ca. 3.*

There has been in recent years, something of a resurgence of interest in the chemistry of enols, a recent addition to the Patai series[1] gives an account of many of the newer aspects in this area. One region of interest has been the consideration of the possibility of enol formation from carbonyl–containing compounds other than simple ketones. In particular, attention has been focussed on enols derived from carboxylic acids, esters and more recently amides.[2] Using the technique pioneered by Fuson[3] for the generation of stable enols from ketones, O'Neill and Hegarty[4] have synthesised enols 1 and 2, which are stable in solution for a few hours. There are some reports of kinetic evidence for the involvement of the enol forms of malonic or methylmalonic acids as intermediates in bromination and iodination reactions.[5,6,7,8] Under certain experimental conditions the reaction was found to be zero–order in [halogen], consistent with a rate limiting enolisation process. When the attack of the halogen is rate–limiting the experimental results are consistent with reactions of the enol, enolate ion, enol carboxylate anion or protonated enol forms depending on the pH of the medium. One puzzling feature noted by Bhale et al.[6] was the presence of two kinetic terms in the rate equation for enolisation of malonic acid (MA) as shown in equation 1. No mechanistic explanation has been advanced to account for the term second–order in [MA].



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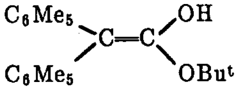

2

$$\text{Rate} = k_o = k[\text{MA}] + k^1[\text{MA}]^2 \tag{1}$$

More recently Hansen and Ruoff[9] have measured the rate constant for enolisation of malonic acid by PMR monitoring the H–atom exchange between the methylene group protons and the solvent.

Another recent development reports the generation of the enol form of mandelic acid by flash photolysis methods.[10] Kinetic measurements of the enolisation and ketonisation rate constants lead to a $pK_E$ value of 15.4. Earlier[11] the photodecomposition of 1,2–naphthoquinonediazide–5–sulphonic acid was studied by nanosecond time – resolved spectroscopy and the transient intermediate assigned as the enol (formed by hydration of the ketene) of the 3–indenecarboxylic acid.

Following our work with nitrosation of enols derived from simple ketones,[12] we were anxious to establish whether reaction pathways existed for nitrosation of carboxylic acids and related systems. We chose to examine the kinetics of nitrosation of malonic and alkyl (and aryl) malonic acids. Reaction of methylmalonic acid with nitrous acid yields the oxime[13] as shown in equation 2; for malonic acid the

$$\text{MeCH(CO}_2\text{H)}_2 + \text{HNO}_2 \longrightarrow \text{HON=C(Me)CO}_2\text{H} + \text{CO}_2 + \text{H}_2\text{O} \tag{2}$$

**initial reaction product is too unstable to be isolated,[14] but the breakdown products are consistent with an initial C–nitrosation. Some of our results have previously been presented in preliminary form.[15]**

## RESULTS AND DISCUSSION

(a) *Nitrosation.* Both malonic acid (MA) and methyl malonic acid (MMA) reacted smoothly with nitrous acid in acid solution. When $[MA]_0$ or $[MMA]_0 >> [HNO_2]_0$ excellent first order behaviour was found. Both reactions were also first order in [MA] or [MMA], as shown by the data in Table 1.

**Table 1**
**Reactions of MA and MMA with $HNO_2$ ($5 \times 10^{-3}$ M) at pH 1.8 (MA) and pH 2.4 (MMA)**

| [MA] or [MMA]/M | $10^4 k_0/s^{-1}$ MA | $10^4 k_0/s^{-1}$ MMA |
|---|---|---|
| 0.20 | 1.25 | 0.70 |
| 0.30 | 1.82 | 0.88 |
| 0.50 | 3.24 | 1.17 |
| 0.75 | 4.90 | 1.68 |

For MA the plot of the first order observed rate constant $k_0$ vs [MA] is linear passing through the origin, whereas for MMA there is a small positive intercept at [MMA] = 0 suggesting a possible small degree of reversibility to the reaction. Both reactions were examined as a function of the pH of the solution over the range 0.8 – 2.2. The results are shown in Tables 2 and 3 respectively.

**Table 2**
**Rate Constants for the Reaction of MA (0.30 M) with $HNO_2$ ($5 \times 10^{-3}$ M) as a Function of pH**

| pH | $10^4 k_0/s^{-1}$ |
|---|---|
| 0.76 | 39.4 |
| 0.89 | 31.5 |
| 0.94 | 19.1 |
| 1.06 | 4.91 |
| 1.24 | 3.32 |
| 1.54 | 2.58 |
| 1.61 | 2.57 |
| 1.88 | 2.48 |
| 1.97 | 2.32 |
| 2.09 | 2.44 |
| 2.15 | 2.47 |

**Table 3**
**Rate Constants for the Reaction of MMA (0.30 M) with $HNO_2$ ($5 \times 10^{-3}$ M) as a Function of pH**

| pH | $10^4 k_0/s^{-1}$ |
|---|---|
| 0.85 | 12.0 |
| 0.93 | 11.6 |
| 1.14 | 8.40 |
| 1.25 | 4.92 |
| 1.64 | 2.78 |
| 1.76 | 2.29 |
| 1.79 | 2.11 |
| 1.93 | 2.04 |
| 2.02 | 1.83 |
| 2.15 | 2.04 |
| 2.29 | 1.84 |

It is quite clear for both substrates that the electrophile ($NO^+$) reacts in the rate limiting step with an intermediate derived from the malonic acid. There is a substantial pH range where $k_0$ is virtually constant (1.54 – 2.15 for MA and 1.76 – 2.29 for MMA) at the higher end of the pH range studied, whereas at lower pH in both cases the reaction is acid catalysed. This suggests that the reactive intermediate at low pH is the enol, whilst at the higher pH values the reactive species is the enolate anion.

Chloride and bromide ion catalysis occurs as expected for a rate–limiting nitrosation, when the reactive reagents are ClNO and BrNO respectively. For the chloride ion catalysed reactions the reaction was first–order in $[HNO_2]$ as for the uncatalysed reaction. For reaction at pH 1.31 the slope of the $k_0$ vs $[Cl^-]$ plot was $1.25 \times 10^{-3}$ $dm^3$ $mol^{-1}$ $s^{-1}$ for the reaction of MA whereas for MMA at pH 1.64 the slope was $9.15 \times 10^{-4}$ $dm^3$ $mol^{-1}$ $s^{-1}$. If the assumption is made that ClNO reacts with both enols at the encounter rate then we obtain minimum values of $K_E$ of $1.0 \times 10^{-8}$ for MA and of $1.6 \times 10^{-8}$ for MMA. There was a change in the kinetic pattern however for the bromide ion catalysed reactions when the first order dependence on $[HNO_2]$ was lost as the $[Br^-]$ increased, as a change towards zero–order behaviour took place. This was more pronounced at both higher $[H^+]$ and $[Br^-]$. The data were analysed graphically in terms of a mixed zero– and first–order reaction, and the results for MMA shown in Table 4.

**Table 4**
**Zero–order Rate Constants for the Reaction of MMA (0.30 M) with $HNO_2$ ($5 \times 10^{-3}$ M) in the Presence of $Br^-$ at Two Acidities**

| $[Br^-]$/M | $10^5$ $k_0$/mol $dm^{-3}$ $s^{-1}$ (a) at $6.5 \times 10^{-2}$ M $[H^+]$ | (b) at 1.33 M $[H^+]$ |
|---|---|---|
| 0.15 | 6.6 | 6.3 |
| 0.20 | 6.5 | 6.4 |
| 0.30 | 6.2 | 8.9 |
| 0.50 | 8.2 | 7.8 |

The results indicate that the $k_0$ values are approximately constant (within the not inconsiderable errors of the graphical analysis) over a range of $[Br^-]$ and of acidity. For MMA (but not for MA) it was possible at higher acidities, in the presence of 0.50 M $Br^-$ to achieve a fully zero–order reaction. These results are in Table 5 and are derived directly from the slopes of the absorbance – time plots. Again within the experimental error the value of $k_0$ is approximately constant over the acidity range.

**Table 5**
**Zero–order Rate Constants for the Reaction of MMA (0.30 M) with $HNO_2$ ($5 \times 10^{-3}$ M) in the Presence of $Br^-$ (0.50 M)**

| $[HClO_4]$/M | $10^3$ $k_0$/mol $dm^{-3}$ $s^{-1}$ |
|---|---|
| 1.33 | 6.4 |
| 1.36 | 5.5 |
| 1.46 | 5.7 |
| 1.69 | 6.4 |
| 1.96 | 6.4 |

The results of the experiments leading to zero–order behaviour clearly support the idea that now, rate–limiting enolisation occurs, which is independent of both $[Br^-]$ and $[H^+]$. Normally enolisation is acid–catalysed, but Leopold and Haim[7] had noted with halogenation experiments, that the enolisation of malonic acid is not acid–catalysed and had proposed a mechanism involving intramolecular acid–catalysis via a six–membered ring transition state. This process involves the transfer of a proton from one of the carboxylic acid groups to the carbonyl oxygen of the other acid group. This either preceeds proton abstraction from the methylene group, or occurs concurrently with it. We find a value for the enolisation rate constant $k_e$ (defined by rate = $k_0 = k_e$ [MMA]) of $2.1 \times 10^{-4}$ $s^{-1}$ from the results in Tables 4 and 5. This value compares well with that reported by Furrow[8] of $1.6 \times 10^{-4}$ $s^{-1}$ obtained from halogenation experiments.

(b) *Halogenation.* Kinetic experiments were carried out in water for both the bromination and iodination of malonic acid (MA), methylmalonic acid (MMA), ethylmalonic acid (EMA), and phenylmalonic acid (PMA). The products of the reactions are well known. The corresponding mono–halo substituted acids dominate except where there is an excess of the halogen when di–substitution also occurs. We have worked throughout with a large deficiency of the halogen and expect only the mono–halo products.

At relatively high $[I_2]$ (~ $6 \times 10^{-4}$ M, limited by the iodine solubility) and with $[MA]_0 >> [I_2]_0$ reaction was zero–order in $[I_2]$ and the zero–order rate constants independent of the acidity as shown in Table 6.

**Table 6**
**Zero–order Rate Constants $k_0$ for the Reaction of Iodine ($6 \times 10^{-4}$ M) with MA (0.10 M)**

| $[HClO_4]$/M | $10^4\ k_0$/mol dm$^{-3}$ s$^{-1}$ |
|---|---|
| 0 | 2.73; 2.54 |
| 0.010 | 2.75 |
| 0.020 | 2.63 |
| 0.025 | 2.79 |
| 0.037 | 2.69 |
| 0.050 | 2.70; 2.49 |
| 0.075 | 2.27 |
| 0.100 | 2.17; 2.54 |
| 0.200 | 2.74 |
| 0.500 | 2.60 |

These results support the earlier work[7] and shows that enolisation is not acid–catalysed. At lower $[I_2]$ there was a change towards first–order kinetic behaviour. True first–order behaviour was not fully realised at $1.0 \times 10^{-4}$ M $I_2$, but was possible by the addition of $I^-$ which converts the iodine substantially to the less reactive $I_3^-$ species. As expected the first–order rate constants obtained under these conditions are also independent of the acidity. Bromination also occurred smoothly with zero–order kinetics at $[Br_2]_0 \sim 2 \times 10^{-3}$ M. It was not possible (with the more reactive halogen) to achieve a change to the first–order rate law, although the effect of the addition of bromide ion was not investigated. All results are consistent with the outline mechanism in Scheme 1.

$$\text{MA} \underset{k_k}{\overset{k_e}{\rightleftharpoons}} \text{ENOL}$$

$$\text{Enol} + I_2\ (\text{or } Br_2) \xrightarrow{k_2} \text{PRODUCT} + I^-\ (\text{or } Br^-)$$

**Scheme 1**

The expected rate equation from such a scheme is given in equation 3 (where $k_k$ is the rate constant for ketonisation of the enol).

$$\text{Rate} = \frac{k_e\ [MA]\ k_2\ [I_2]}{k_k + k_2\ [I_2]} \qquad (3)$$

The two limiting forms resulting in zero– and first–order kinetics (in $I_2$) arise from the inequalities $k_2 [I_2] >> k_k$ or $k_k >> k_2 [I_2]$ respectively.

In the absence of any added mineral acid, and at high $[I_2]$, the zero–order rate constants varied with [MA] according to equation (1) as reported by Bhale et al.[6] It occurred to us that the second order term (which was not interpreted mechanistically) might arise from a base – catalysed component to enolisation, bought about by the malonate ion. The first ionisation of malonic acid occurs with a $pK_a$ of 2.85.[16] The malonate ion catalysed reaction would then be expected to be dominant at pH values > 3. We therefore examined the [MA] dependence at two pH values 1.4 and 3.2 either side of the $pK_a$ value. The results using bromine as the enol scavenger are given in Table 7.

**Table 7**
**Zero–order Rate Constants for the Bromination of MA at pH 1.4 and pH 3.2**

| pH | [MA]/M | $10^4\ k_0$/mol dm$^{-3}$ s$^{-1}$ | $10^3\ k_0$/[MA]/s$^{-1}$ |
|---|---|---|---|
| 1.4 | 0.050 | 2.33 | 4.66 |
| 1.4 | 0.075 | 3.49 | 4.65 |
| 1.4 | 0.100 | 4.55 | 4.55 |
| 1.4 | 0.125 | 5.95 | 4.76 |

| | | | $10^2\ k_o/[MA]^2/dm^3\ mol^{-1}\ s^{-1}$ |
|---|---|---|---|
| 3.2 | 0.050 | 1.49 | 5.96 |
| 3.2 | 0.075 | 3.79 | 6.74 |
| 3.2 | 0.100 | 6.29 | 6.29 |
| 3.2 | 0.125 | 8.52 | 5.45 |

It is clear that at pH 1.4 there is a simple first-order dependence upon [MA], as shown by the virtually constant value of $k_o/[MA]$. Under these conditions (where very little malonate ion exits) enolisation occurs exclusively via the intramolecularly acid-catalysed pathway. However at pH 3.2 where a substantial fraction of the substrate is present as the anion, there is a change to a second-order dependence upon [MA] as shown by the approximately constant value of $k_o/[MA]^2$. Now, the enolisation reaction is entirely via the malonate ion catalysed reaction.

A sample of Me $CD(CO_2D)_2$ was prepared by exchanging MMA with $D_2O$ and used in the iodination experiments at high $[I_2]$. Under these conditions a kinetic isotope effect $k_H/k_D$ of 4.1 was obtained showing that C–H bond breaking occurs in the rate-limiting step of enolisation.

The alkyl (and aryl) substituted malonic acids behaved in a similar fashion to MA itself, showing a zero-order halogen dependence at high [halogen], and concurrent malonate-catalysed and intramolecularly acid-catalysed pathways at appropriate pH values. At reasonably high acidities (which cuts out the malonate-catalysed pathway), we obtained reasonably constant $k_o$ values for each substrate over the range 0.02 – 0.50 M $HClO_4$ for both bromination and iodination. The combined results together with the earlier one for MMA for nitrosation, together with some literature values are gathered together in Table 8.

**Table 8**
**Values of $k_e/s^{-1}$ (Defined by Rate = $k_o = k_e$ [Substrate]) Obtained from a Range of Reactions**

| Substrate | Nitrosation | Iodination | Bromination | Literature |
|---|---|---|---|---|
| MA | – | $2.7 \times 10^{-3}$ | $4.7 \times 10^{-3}$ | $2.0 \times 10^{-3}$ [7]<br>$1.1 \times 10^{-3}$ [9] |
| MMA | $2.1 \times 10^{-4}$ | $1.7 \times 10^{-4}$<br>$1.8 \times 10^{-4}$ | $3.7 \times 10^{-4}$ | $1.6 \times 10^{-4}$ [8] |
| EMA | – | $1.0 \times 10^{-4}$ | $1.3 \times 10^{-4}$ | – |
| PMA | – | $3.0 \times 10^{-3}$ | $5.0 \times 10^{-3}$ | – |

For each acid there is reasonable agreement between the results using a variety of different electrophiles, and with the literature values where available. The agreement is not perfect, resulting from probable errors in obtaining zero-order rate constants (a) from errors arising in measurement of the extinction coefficients of the absorbing species and (b) from errors arising from the presence of a small component of a first-order reaction which is not always easy to detect.

The reduced reactivity of both MMA and EMA compared with MA probably arises from the electron-releasing effect of the alkyl groups which makes proton loss more difficult. The almost nil net effect of the phenyl group probably arises from a combination of electronic and steric effects

## EXPERIMENTAL

All reagents were available at very high purity grades and were used as supplied. Iodine and bromine solutions were prepared in distilled water and standardised by thiosulphate titration. Standard buffer solutions were made up and the pH measurements were accurate to ± 0.02 pH units. Nitrosation reactions were followed kinetically, in water at 25°, by conventional spectrophotometry, noting the decreasing absorbance at 370 nm due to nitrous acid. The halogenation reactions (also in water at 25°) were followed by stopped-flow spectrophotometry noting the disappearance of the absorbance due to the halogen at 459 nm ($I_2$) or 393 nm ($Br_2$). The zero-order rate constants were mostly obtained from the slopes of the absorbance time plots after dividing by the extinction coefficient of the absorbing species at that wavelength. For some of the nitrosation experiments the zero-order rate constants were obtained by a graphical procedure requiring measurement of the slopes of the tangents to the absorbance-time plots (necessarily an inaccurate procedure). The first-order rate constants were obtained from the integrated first-order equation. All rate constants quoted are the mean values of at least five separate measurements, and were reproducible to better then ± 5%.

## CONCLUSIONS

We have shown that nitrosation of malonic and methylmalonic acids takes place *via* the corresponding enol tautomers of the acids. With the more reactive nitrosating system (the bromide ion catalysed reaction) enolisation is rate–limiting, whereas for the less reactive systems (the chloride ion catalysed reaction and reaction in the absence of a nucleophilic catalyst), the reactions of the enols are rate limiting. In addition we have extended the early work reported in the literature on the iodination of malonic acid to include alkyl– and one aryl–substituted malonic acids, and also to the study of the corresponding bromination reactions of all of these substrates. Under our experimental conditions, enolisation is always the rate–limiting process. There is good agreement between our values of the enolisation rate constant $k_e$ and the literature values where comparison is possible; we find also as expected that values of $k_e$ are the same, within experimental error, for the nitrosation, bromination and iodination experiments. The alkyl substituents decrease the rate of enolisation, presumably by a reduction of the acidity of the C–H system, by way of the inductive effect. Our kinetic isotope effect experiments (with MMA) show that the C–H bond breaking occurs in the rate limiting step when enolisation is the slow process. Finally we have shown that the kinetic term second order in [malonic acid] arises from a base catalysed component for enolisation, brought about by the malonate ion. At the higher pH values ($\geqslant$ 3.2) this reaction pathway is the dominant one, whereas at the lower pH values ($\leqslant$ 1.4) the malonate ion catalysed component of the reaction disappears.

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