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26. The Acidity of Malondialdehyde and the Stability of its Complexes with Nickel(II) and Copper(II)

by **M. M. Osman**

Laboratorium für Anorganische Chemie der ETH Zürich and Chemistry Department, Faculty of Science, Alexandria University, Egypt[1])

(17. XI. 71)

Summary. The acidity of malondialdehyde as well as the stability of its 1:1-complexes with Ni^{II} and Cu^{II} have been determined (Table). In comparison with the enolates of aliphatic β-diketones the anion $C_3H_3O_2^-$ has not only a strikingly reduced basicity, but is also a grossly inferior ligand for metal cations.

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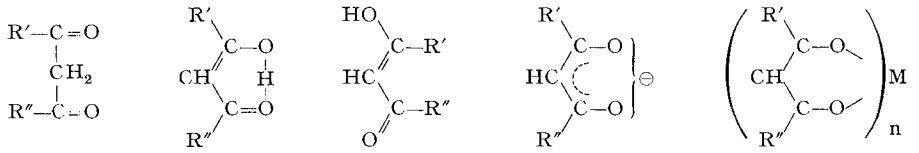
[1]) Present address, Faculty of Education, Chemistry Department, University of Libya, Tripoli, Libya.

The complexes of enolizing β-diketones (I) have received considerable attention in the past. The formation of acetylacetonates (V, R′ = R″ = CH_3) in aqueous as well as in dioxane solution has been studied extensively and a great number of the solid complexes have been described [1]. For some of these even the crystal structure is known. Other examples are trifluoro-thenoylacetone (I, R′ = CF_3, R″ = C_4H_3S), an excellent extracting agent for metals, and hexafluoroacetylacetone (I, R′ = R″ = CF_3) which forms uncharged complexes of interest because of their volatility.



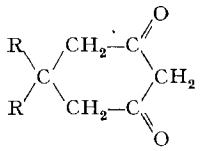
I II III IV V

It is remarkable that malondialdehyde (I, R′ = R″ = H), which is the most simple of the substances of type I, has hardly ever been investigated as a complexing agent. The dialdehyde is unstable (it undergoes self-condensation) and has only been obtained in a more or less pure state since 1941 [2]. However, the sodium salt, $Na[C_3H_3O_2]$, is available. Nothing is known about the stability of the metal complexes. Indeed only the chromium(III)-complex, $Cr(C_3H_3O_2)_3$, has been synthesized [3].

Malondialdehyde is completely enolized in aqueous solution and is as acidic as a carboxylic acid [2], *e.g.* it turns Congo paper violet. This is in striking contrast to the aliphatic β-diketones (I, R′ and R″ = alkyl) which are only 10–20% enolized in water and which are as weakly acidic as phenols.

A recent NMR. investigation [4] has revealed that in non-aqueous solvents the enol of malondialdehyde has the s-*cis*-conformation (II, R′ = R″ = H) in which the acidic proton probably forms a hydrogen bridge between the two oxygens. In aqueous solution, however, the enol seems to have s-*trans*-conformation (III, R′ = R″ = H).

Strongly enolizing and acidic diones of type I are also known in which the substituents R′ and R″ are part of the same ring, for example dihydroresorcinol (VI) and dimedone (VII) [5]. The conclusion may be drawn that the high acidity of VI and VII



VI R = H, pK = 5,25

VII R = CH_3, pK = 5,25

in comparison to I (R′ and R″ = alkyl) must be due to the fact that the loss of conformational entropy resulting from the conversion of the cyclic enols into their anions, is smaller than that resulting from converting the very mobile-molecule I into the rigid, quasi-aromatic enolate IV. When the substituents R′ and R″ in I are hydrogen, however, this loss in conformational entropy during enolisation and deprotonation must also be considerably smaller than when R′ and R″ are bulky alkyls. If this entropy effect is in fact the main cause of the high acidity of malondialdehyde and if the oxygens of its enolate anion have approximately the same nucleophilicity as those in the enolates of acetylacetone and its homologs, the stability constants of the

malondialdehyde complexes should be similar to those of the corresponding acetylacetonates ($\beta_n = [M(C_3H_3O_2)_n]/[M] \cdot [C_3H_3O_2]^n = \sim [M(acac)_n]/[M] \cdot [acac]^n$). The high acidity of malondialdehyde would then be of great advantage, since its complexes would be much more stable towards acids compared to those of acetylacetone. This expectation prompted us to carry out the following quantitative study.

Quantitative investigation. – The titration of the sodium salt of malondialdehyde ($NaC_3H_3O_2 = NaA$) against hydrochloric acid at constant ionic strength and temperature, using a glass electrode, gave the protonation curve of Fig. 1. The degree of protonation $\bar{p}$ is defined by equation (1):

$$\bar{p} = \frac{[HCl] - [H]}{[A]_t} \tag{1}$$

where [HCl] is the concentration of the strong acid added, $[A]_t$ the total concentration of malondialdehyde and [H] the hydrogen ion concentration (not to be confounded with its activity) determined.

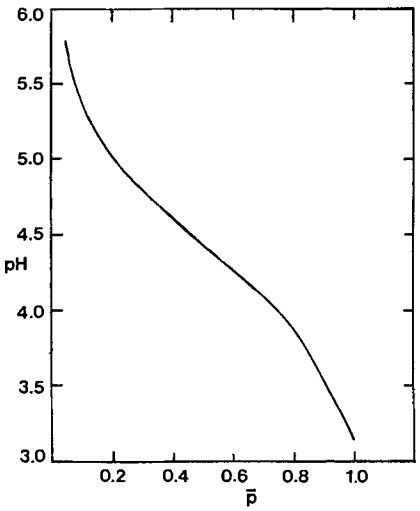


Fig. 1. *Protonation curve of the enolate ion of malondialdehyde* (A^-)
$c = 1.0 \times 10^{-3}$ M; $\mu = 0.1$ (KCl); $t = 25°$

Using equation (2) the acidity constant of malondialdehyde can be calculated from each point on this curve.

$$\log K_{HA} = pK = -\log [H] + \log \frac{\bar{p}}{1 - \bar{p}}. \tag{2}$$

An excellent constancy was obtained, furnishing the following mean value:

$$pK = \log \frac{[HA]}{[H] \cdot [A]} = 4.46 \pm 0{,}01 \qquad \mu = 0.1 \text{ (KCl)}, 25°. \tag{3}$$

This result confirms the conclusion drawn from *Hüttel*'s remark [2] concerning the behaviour of malondialdehyde with Congo red: its acidity is almost that of acetic acid.

In order to determine the complex formation constants, the salt $NaC_3H_3O_2$ was acidified in aqueous solution, in the presence of a 10-fold excess of $NiCl_2$ or $CuCl_2$, respectively: Fig. 2.

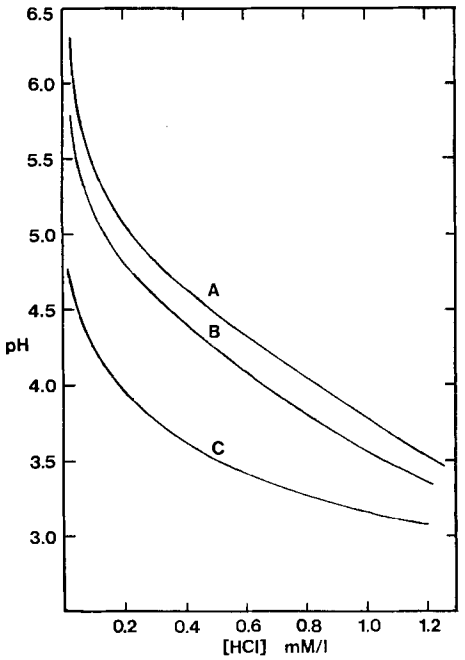


Fig. 2. *Potentiometric curves of cupric- and/or nickel-malondialdehyde systems*
A, free enolate of malondialdehyde (A^-); B, 10:1 molar ratio of Ni^{2+} to A^-; C, 10:1 molar ratio of Cu^{2+} to A^-; $[A]_t = 1.0 \times 10^{-3}$ M; $\mu = 0.1$ (KCl); $t = 25°C$

Again the degree of protonation is calculated from (1) and by means of (2) an apparent acidity constant pK' is obtained; this has the following signification [6]:

$$K'_{HA} = \frac{[HA]}{[H]([A] + [MA])} = K_{HA}(1 + [M] \cdot K_{MA})^{-1} . \quad (4)$$

Due to the large excess of the metal present ($[M]_t \approx [M]$), only the 1:1-complex can be formed and a constant value of pK' ($= \log K'_{HA}$) is obtained using (2) from different points on the neutralisation curve. Taking the mean value of pK' the formation constant of the 1:1-complex, K_{MA}, is then obtained from (4). In order to confirm this result, solutions of $CuCl_2$ and $NaC_3H_3O_2$ in the molar ratio of 1:1 and 1:2 were also titrated. The concentration [M] is no longer constant, but the degree of complex formation n can be calculated by means of equations (5), (6) and (7) ($[M]_t$ and $[A]_t$ are the total concentrations of metal and malondialdehyde, respectively):

$$[HA] = [HCl] - [H]; \tag{5}$$

$$\sum n \cdot [MA_n] = [A]_t - [HA]\,(1 + 10^{pH-pK}); \tag{6}$$

$$\bar{n} = 1/[M]_t \cdot \sum n \cdot [MA_n]. \tag{7}$$

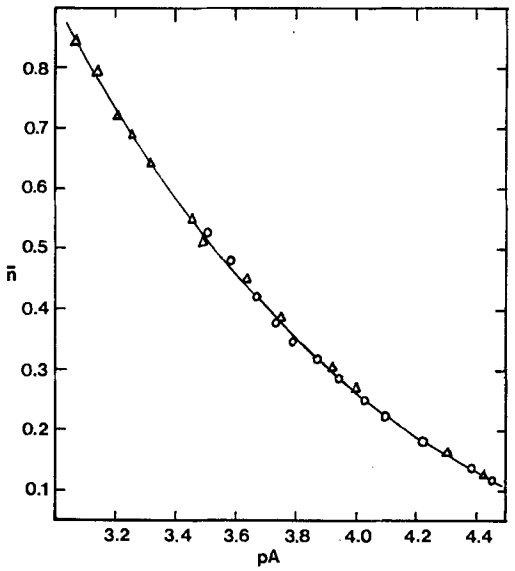


Fig. 3. *Formation curves of the Cu^{2+}-malondialdehyde complex*
–○–○–○–, 1:1 molar ratio of Cu^{2+} to A^-; –△–△–△– 1:2 molar ratio of Cu^{2+} to A^-;
$[M]_t = 1.0 \times 10^{-3}$ M; $\mu = 0.1$ (KCl); $t = 25°$

Fig. 3 illustrates that the same formation curve is obtained from titrations at different metal to malondialdehyde ratio. It was difficult, however, to follow the curve into regions with $\bar{n}$-values above 1 because of the instability of free malondialdehyde. Only for the first constant K_{MA} could a reliable value be obtained.

Discussion. The results are summarized in the Table which also contains literature values for the acidity of acetylacetone and the stability of its metal complexes. The data show that the expectation concerning the high stability of the metal complexes of malondialdehyde has not been substantiated. The enolate $C_3H_3O_2^-$ is not only a very

Stability of the complexes of H^+, Ni^{2+} and Cu^{2+} with the anions of malondialdehyde ($C_3H_3O_2^-$) and acetylacetone ($acac^-$)

Cation	Reaction	HA = Malondialdehyde $\mu = 0.1$ (KCl), 25°	Ref.	HA = Acetylacetone $\mu = 0.1$ ($NaClO_4$) 25°	Ref.
H^+	$H^+ + A^- \rightleftharpoons HA$	4.46 ± 0.01	this paper	8.82	[7]
Ni^{2+}	$Ni^{2+} + A^- \rightleftharpoons NiA^+$	2.07 ± 0.01	this paper	5.72	[7]
Cu^{2+}	$Cu^{2+} + A^- \rightleftharpoons CuA^+$	3.57 ● 0.01	this paper	8.16	[7]

much weaker base than acac$^-$, but is also a much poorer ligand. Although it is generally found that the tendency of a ligand to coordinate to metal cations is reflected in its tendency to add a proton, there is nevertheless reason to believe that the enolate acac$^-$ may have an exceptionally high pK since proton addition should occur mainly at the central carbon (acetylacetone is only weakly enolized); this furnishes the diketone which is less rigid than the enolate in the form of either the free anion acac$^-$ or its metal complexes. This effect undoubtedly exists, but it seems to be of little importance. The oxygens of the enolate acac$^-$ must be much more nucleophilic than those of $C_3H_3O_2^-$ as a result of the different inductive effect of alkyl (R′ and R″ in formulae I, II and IV) in comparison with H. This difference is also manifested in the relative basicities and complex formation abilities of acetate and formate.

Experimental. – 1. *Sodium salt of malondialdehyde:* Prepared by a modification of the method of *Hüttel* [2] as follows: 10 g of malondialdehyde-ethyl-trimethyl-diacetal (*Kay-Fries Chemicals Co.*, New York) was shaken for $2^1/_2$ h at about 10–15° with 100 ml of 3% aqueous sulfuric acid. The resulting solution was brought to a pH between 8 and 9 with 1N sodium hydroxide and evaporated to dryness in the cold, under reduced pressure. The sodium salt of the dialdehyde was extracted from the residue with absolute alcohol, the solvent was removed and the salt purified by dissolution in a minimum of water followed by precipitation with acetone. The product was dried over phosphorous pentoxide *in vacuo*.

$C_3H_3NaO_2$ Calc. C 38.31 H 3.22 Na 24.45% Found C 38.18 H 3.37 Na 24.41%

2. *Preparation of solutions:* The aqueous solutions of the sodium salt of malondialdehyde were freshly prepared for each series of measurements. Stock solutions of cupric and nickel chlorides were standardized complexometrically. Hydrochloric acid was standardized against carbonate-free sodium hydroxide.

3. *Potentiometric titrations* of the sodium salt of malondialdehyde against hydrochloric acid were carried out at 25°C in the absence and in the presence of cupric or nickel ions. The ionic strength of the media was kept constant at 0.1 by using potassium chloride. Purified nitrogen was passed through the solution throughout the course of titration. A polymetron precision pH meter (Type 111) fitted with glass and thermostated calomel extension electrodes was used to determine the hydrogen ion concentration. Before each set of measurements, the electrode system was calibrated by direct titration of acetic and/or hydrochloric acid solutions of known concentrations.

The present work was initiated during a period spent by the author at the Department for Inorganic Chemistry of the Swiss Federal Institute of Technology (ETH) in Zürich. I wish to thank Professor *G. Schwarzenbach* for his hospitality during this stay, for suggesting the problem, for his continuous interest and for his great help in preparing this manuscript. – Thanks are also due to the Kay-Fries Chemicals Company for a gift of malondialdehyde diacetal.

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