# The Acidity and General Base-Catalyzed Hydrolysis of Meldrum's Acid and Its Methyl Derivatives

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The hydrolysis reactions of 2,2-dimethyl-1,3-dioxane-4,6-dione (Meldrum's acid; *1*) and its 5-methyl (*2*) and 5,5-dimethyl derivatives (*3*) were found to be subject to general base catalysis. The Brønsted equation with slope $\beta = 0.40$ is satisfactorily obeyed. *1* and *2* were inert in alkaline solution owing to their pseudo acid character. The pK values of these pseudo acids were determined by a spectrophotometric method.

The neutral and acid-catalyzed hydrolysis reactions of 2,2-dimethyl-1,3-dioxane-4,6-dione (*1*) and its methyl derivatives (*2* and *3*) have been investigated previously.[1]
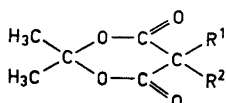
1	$R^1 = R^2 = H$
2	$R^1 = CH_3;\ R^2 = H$
3	$R^1 = R^2 = CH_3$

3 decomposes almost instantaneously in alkaline solution but the other two compounds do not.[1] A study of the hydrolysis in buffer solutions may reveal whether *1* and *2* are enolized or they are in equilibrium with enolate anion (eqn. 1) since the latter ion is not hydrolyzed by base because its carbonyl carbon is not nucleophilic enough.

R = H or CH₃
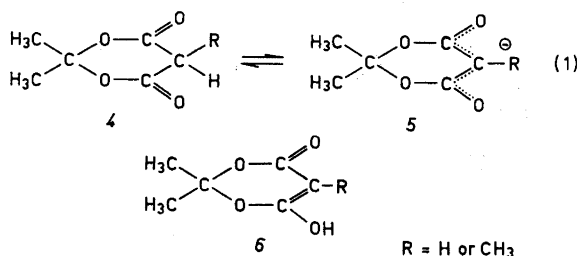
Several authors have investigated the above equilibria (eqn. 1) and found that the equilibria are pH-dependent.[1-4] The enolate anion has an absorption maximum around 260—270 nm.[2] The proportion of the enol form (6) was showed to be negligible but the enolate anion (5) predominates in basic conditions and the keto form (4) in acidic media.[4] We have used this effect to determine the pK values of 1 and 2 by spectrophotometry and investigated the hydrolysis of I and III in several buffer solutions.

EXPERIMENTAL

Meldrum's acid and its methyl derivatives (1—3) were prepared earlier.[1] Their NMR spectra were recorded on a 60 Mcs Perkin-Elmer R 10 NMR spectroscope at 33.5°C. The solvent was $(CD_3)_2CO$ and TMS was used as internal standard. 1 and 3 give an average

Table 1. Characteristic NMR lines for diethyl malonate, diethyl methylmalonate, and for the cyclic isopropyliden malonates 1—3. The solvent is $(CD_3)_2CO$.

Compound	Chemical shifts, ppm					
	Ester CH_2	Acid H	Acid Me	2-Me	5-H	5-Me
$CH_2(COOEt)_2$	5.82^a	6.63^b	—	—	—	—
$MeCH(COOEt)_2$	5.84^a	6.53^c	8.68^d	—	—	—
1	—	—	—	8.24^e	6.16^e	—
2	—	—	—	8.10^i	5.79^f	8.55^g
				8.27^i		
3	—	—	—	8.26^h	—	8.42^h

^{a} Quartets. ^{b} Average singlet. ^{c} Quartet; $J = 7.0$ cps. ^{d} Doublet; $J = 7.0$ cps. ^{e} Average singlets. ^{f} Quartet; $J = 6.95$ cps. ^{g} Doublet; $J = 6.95$ cps. ^{h} Average singlets. ^{i} The different shifts for 2-methyl groups.

Table 2. Hydrolysis of 2,2,5,5-tetramethyl-1,3-dioxane-4,6-dione (3) in formic acid-formate (5:1) buffer at 45°C. $[HCOO^-] = 0.05$ M.

t, min	0	30	70	120	180	240
$v_i - v_t$, ml	8.75	8.30	7.50	6.65	5.83	5.05
$10^5 k_{obs}$, s^{-1}	—	3.61	3.67	3.81	3.76	3.82

t, min	295	370	450	530	620	740
$v_i - v_t$, ml	4.65	4.05	3.37	2.88	2.35	1.75
$10^5 k_{obs}$, s^{-1}	3.57	3.47	3.53	3.49	3.53	3.63

t, min	890	i				
$v_i - v_t$, ml	1.20	0				
$10^5 k_{obs}$, s^{-1}	3.72	—				

Mean $k_{obs} = (3.63 \pm 0.04) \times 10^{-5}$ s^{-1}

spectrum at this temperature whereas the 5-proton of *2* gives a typical quartet with $J = 6.95$ cps. The chemical shifts compared with those of some acyclic malonates are presented in Table 1.

Kinetic experiments. Hydrolysis reactions in the buffer solutions were followed by titrimetric method (formate buffers) or spectrophotometric method (phosphate and carbonate buffers).[1] The kinetic measurements were carried out at 45°C varying the buffer concentration to determine the catalytic coefficients of the formate and hydrogen phosphate ions. Only approximate value was obtained for the catalytic coefficient of the divalent carbonate ion since the formed malonic acid liberated carbon dioxide from the solution. A typical series of data for the reaction of *3* in formate buffer is shown in Table 2. The experimental data are summarized in Table 3.

Table 3. Rate coefficients of the hydrolysis of 2,2-dimethyl-1,3-dioxane-4,6-dione (*1*) and 2,2,5,5-tetramethyl-1,3-dioxane-4,6-dione (*3*) in different buffer solutions at 45°C. A, HCOOH and HCOO⁻ in a molar ratio of 5 to 1. B, $H_2PO_4^-$ and HPO_4^{2-} in a molar ratio of 1 to 4. The ionic strengths of the buffer solutions were adjusted with sodium chloride. [B] denotes the concentration of the more basic component of the buffer system.

Compound	Buffer system	Ionic strength	[B] M	$10^5 k_{obs}$, s^{-1}
1	A	1.72	0.02	1.87 ± 0.03^a
1	A	1.72	0.05	2.10 ± 0.01
1	A	1.72	0.10	2.53 ± 0.02
3	A	1.72	0.02	3.18 ± 0.05
3	A	1.72	0.05	3.63 ± 0.04
3	A	1.72	0.10	4.23 ± 0.07
3	B	2.47	0.10	63.6 ± 0.5
3	B	2.47	0.20	85.3 ± 0.5
3	B	2.47	0.40	134 ± 1

a Standard error of the mean.

pK measurements. The pK values of *1* and *2* were determined spectrophotometrically[5] by measuring the absorption of the enolate anion (*5*) at $250-270$ nm (*1*; λ_{max} 260 nm) or at $264-284$ nm (*2*; λ_{max} 274 nm) in 0.08 M NaOH, 0.08 M HCl, and 0.008 M NaOAc—HOAc (1:1) buffer solutions (Fig. 1). The substrate concentration was about 5×10^{-5} M.

EQUATIONS AND CALCULATIONS

The values of the catalytic coefficients of the bases were obtained from the least squares plots of the observed rate coefficients *versus* base concentration since

$$k_{obs} = k_t + k_B[B] \tag{2}$$

where

$$k_t = k_0 + k_a[H^+] + k_{OH}[OH^-] \tag{3}$$

In formate buffers, both $k_a[H^+]$ and $k_{OH}[OH^-]$ are so small that k_t is equal to k_0 at the ionic strength in question. In phosphate buffer ($[HPO_4^{2-}]/[H_2PO_4^-] = 4$) pH is about 7.4 at 45°C. The hydroxide ion concentration in the buffer is approximately 10^{-6} M and because $k_{OH} \gg k_0$,
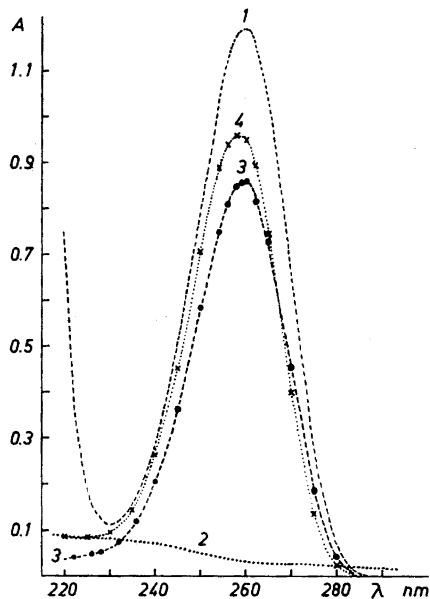
Fig. 1. The UV spectra of 2,2-dimethyl-1,3-dioxane-4,6-dione. 1: in sodium hydroxide solution, $c = 5.4 \times 10^{-5}$ M; 2: in hydrogen chloride solution, $c = 5.4 \times 10^{-5}$ M; 3: in water, $c = 2.2 \times 10^{-4}$ M; 4: in methanol.
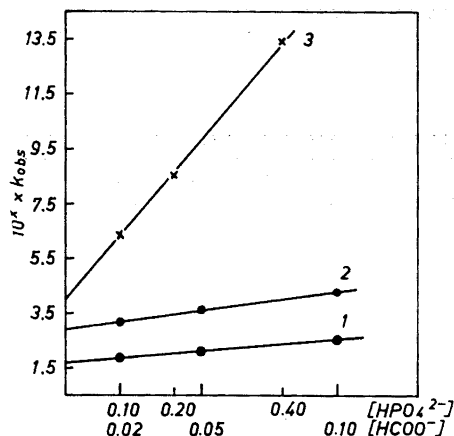
Fig. 2. The observed rate coefficients of *1* and *3 versus* base concentration. 1: 2,2-dimethyl-1,3-dioxane-4,6-dione (*1*) $x = 5$; 2: 2,2,5,5-tetramethyl-1,3-dioxane-4,6-dione (*3*), $x = 5$; 3: 2,2,5,5-tetramethyl-1,3-dioxane-4,6-dione (*3*), $x = 4$; 1 and 2 in buffer A and 3 in buffer B (Table 3).

$$k_t = k_0 + k_{OH}[OH^-] \qquad (4)$$

in this case. The plots of k_{obs} *versus* [B] are presented in Fig. 2 and the values of k_B in Table 4.

Table 4. Catalytic coefficients k_B of different bases in the hydrolysis of 2,2-dimethyl-(*1*) and 2,2,5,5-tetramethyl-1,3-dioxane-4,6-dione (*3*) in water solution at 45°C.

Compound	Catalyst	$10^3 k_B$, $M^{-1}s^{-1}$
1	H_2O	0.000418 [a]
1	$HCOO^-$	0.0829
3	H_2O	0.000611 [a]
3	$HCOO^-$	0.130
3	HPO_4^{2-}	2.37
3	CO_3^{2-}	50 — 100

[a] $k_0/[H_2O]$; k_0 taken from Ref. 1.

The pK values of *1* and *2* were computed from eqn. (5)

$$pK° = (pH)_0 + \log \delta \tag{5}$$

where

$$(pH)_0 = (pH)_{obs} + \frac{0.509 \sqrt{\bar{I}}}{1 + \sqrt{\bar{I}}} \tag{6}$$

and

$$\delta = \frac{D - D_{A^-}}{D_{HA} - D} \tag{7}$$

In the latter equation D_{HA} is the absorption of the keto form in acidic solution, D_{A^-} the absorption of the enolate anion in alkaline solution and D a linear combination of the absorptions of both forms in buffer solution. The results are presented in Tables 4 and 5.

Table 5. The acid strength of 2,2-dimethyl-1,3-dioxane-4,6-dione (Meldrum's acid). $\lambda_{max} = 260$ nm. Buffer: $(pH)_0 = 4.63 + 0.04 = 4.67$.

λ	0.08 M HCl	0.008 M buffer NaOAc—HOAc, 1:1	0.08 M NaOH	δ	$\log \delta$	$pK_a°$
250	-0.043^a	0.184^b	0.625^c	1.943	0.29	4.96
1	41	0.202	0.678	1.959	0.29	4.97
2	39	0.220	0.733	1.981	0.30	4.97
3	37	0.237	0.782	1.989	0.30	4.97
4	36	0.252	0.828	2.000	0.30	4.98
5	35	0.269	0.873	1.987	0.30	4.97
6	35	0.280	0.904	1.981	0.30	4.97
7	35	0.290	0.937	1.991	0.30	4.97
8	35	0.298	0.957	1.979	0.30	4.97
9	35	0.300	0.964	1.982	0.30	4.97
260	-0.035	0.304	0.964	1.947	0.29	4.96
1	35	0.298	0.958	1.982	0.30	4.97
2	35	0.292	0.948	2.006	0.30	4.98
3	35	0.284	0.917	1.984	0.30	4.97
4	35	0.272	0.880	1.980	0.30	4.97
5	35	0.257	0.828	1.956	0.29	4.97
6	35	0.239	0.773	1.949	0.29	4.96
7	35	0.219	0.720	1.972	0.30	4.97
8	36	0.199	0.651	1.923	0.28	4.96
9	36	0.180	0.581	1.857	0.27	4.94
270	-0.037	0.152	0.507	1.888	0.28	4.95

$^a D_{HA}.$ $^b D.$ $^c D_{A^-}.$

Mean 4.97
$K_a° = 1.07 \times 10^{-5}$

Table 6. The acid strength of 2,2,5-trimethyl-1,3-dioxane-4,6-dione. $\lambda_{max} = 274$ nm. Buffer: $(pH)_0 = 4.63 + 0.04 = 4.67$.

λ	0.08 M HCl	0.008 M buffer NaOAc−HOAc, 1:1	0.08 M NaOH	δ	log δ	pK_a^0
264	− 0.022 [a]	0.252 [b]	0.607 [c]	1.296	0.11	4.79
5	23	0.270	0.648	1.290	0.11	4.79
6	24	0.287	0.686	1.283	0.11	4.78
7	24	0.304	0.721	1.271	0.10	4.78
8	24	0.318	0.755	1.278	0.11	4.78
9	22	0.330	0.783	1.287	0.11	4.78
270	− 0.022	0.343	0.804	1.263	0.10	4.78
1	22	0.350	0.827	1.282	0.11	4.78
2	22	0.355	0.841	1.289	0.11	4.78
3	21	0.362	0.846	1.260	0.10	4.78
4	21	0.363	0.848	1.263	0.10	4.78
5	20	0.361	0.842	1.262	0.10	4.78
6	20	0.356	0.834	1.271	0.10	4.78
7	20	0.350	0.814	1.254	0.10	4.77
8	20	0.342	0.789	1.235	0.09	4.77
9	19	0.329	0.760	1.239	0.09	4.77
280	− 0.018	0.315	0.723	1.225	0.09	4.76
1	19	0.296	0.679	1.219	0.09	4.76
2	19	0.277	0.631	1.196	0.08	4.75
3	17	0.256	0.585	1.205	0.08	4.76
4	− 0.017	0.233	0.528	1.180	0.07	4.75

[a] D_{HA}. [b] D. [c] D_{A^-}.

Mean   4.77
$K_a^0 = 1.70 \times 10^{-5}$

RESULTS AND DISCUSSION

General base catalysis. Brønsted equation gives the relationship between the catalytic rate coefficient k_B of a base B and its base strength K_B.[6] Fig. 3 shows that this equation is obeyed in the general base catalyzed hydrolysis of *1* and *3*. The similarity of *1* and *2* suggest that also the general base catalyzed hydrolysis of *2* is consistent with the Brønsted equation. Also the points for the neutral hydrolysis [1] (k_0 divided by the molar water concentration) falls on the same line with the points for other bases. The slopes $\beta = 0.40$ for *1* and *3* are in agreement with the value of the slopes for ethyl dichloroacetate [7] (0.47) and chloromethyl chloroacetate [8] (0.42).
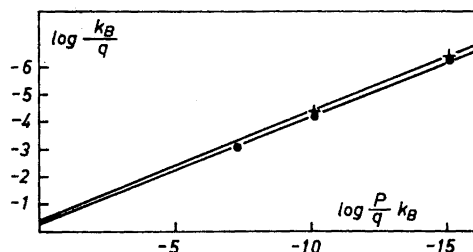

Fig. 3. The Brønsted plots of *1* and *3*. *1*: +; *3*: ●.

The value, $370\ M^{-1}s^{-1}$, is obtained for k_{OH} of 2,2,5,5-tetramethyl-1,3-dioxane-4,6-dione (3) from the observed rate coefficients in buffer B (Table 3) using the values $0.3 \times 10^{-4}\ s^{-1}$ and $10^{-6}\ M$ for k_0 (Ref. 1) and hydroxide ion concentration (see experimental section), respectively. This value confirms the observation that the rate of alkaline hydrolysis of 3 is too high even at 5°C to be measured with the conventional methods. Moreover, the fact that the point for the alkaline hydrolysis of 3 lies clearly above the Brønsted line (Fig. 3) is in agreement with previous data on general base catalysis of carboxylic esters.[6]

The observed general base catalysis and the magnitude of Brønsted β values suggest that 1, 2, and 3 are typical esters in agreement with the results of a study of their acid-catalyzed and neutral hydrolysis.[1]

Keto-enol-enolate equilibria. Several authors have studied the equilibria shown in eqn. 1. The most reliable results were obtained by Eigen *et al.*,[4] who investigated these equilibria by relaxation measurements. They reported the value, $[6]/[4]=0.0045$, for the equilibrium constant betwen the enol and keto forms of 1. In the case of 2 ($R = CH_3$), the situation is obviously similar because of 1 and 2 are almost equally strong acids.

The fact that 2,2-dimethyl- (1) and 2,2,5-trimethyl-1,3-dioxane-4,6-dione (2) are not hydrolyzed in alkaline solution is easily understood. It was found that the enolate anion (5) predominates in alkaline solution and its mesomeric nature decreases the nucleophilicity of the carbonyl carbons below the level which is necessary for a successful attack of the hydroxide ion.

Table 7. The pK values of 2,2-dimethyl- (1) and 2,2,5-trimethyl-1,3-dioxane-4,6-dione (2) at 25°C obtained in this work and those reported by other authors.

Compound	Ionic strength	pK_a	$pK_a{}^0$	Ref.
1	0.008	4.93	4.97	This work
1	0.01	4.83	4.88	1
1	0.1	4.83	4.95	4
1	—	4.0	—	3
1	—	5.2	—	2
2	0.008	4.73	4.77	This work
2	0.01	4.70	4.75	1

*p*K *values.* The pK values of 1 in water[1] and in methanol-water (60:40)[3] have been measured by a potentiometric method but the pK of 2 seems to have been determined only by the present authors.[1] The values obtained in this work and those reported by other investigators are collected in Table 6. Except for the value measured by Adametz *et al.*[3] in methanol-water the values for 1 are generally in good agreement. Swoboda *et al.*[3] have established the pseudo-activity of 1 by observing that the following exchange reaction occurs only in alkaline solution:

(8)
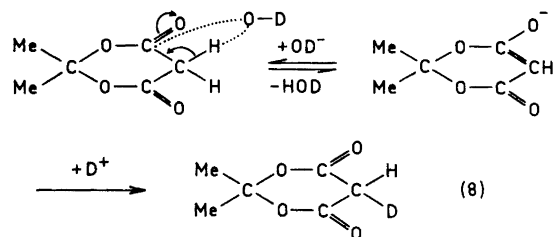
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