

A Study of the Rates of Hydrolysis of Certain Enaminones

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The rates of hydrolysis of fourteen enaminones at 37° over the pH range 2—11, have been determined. In only five cases was a simple acid catalysed mechanism found to operate and for these, second-order rate constants are presented. In the other examples studied, the plots of first-order rate constant vs. $[H^+]$ showed either a maximum or minimum value. Mechanistic interpretations for these observations are made.

ENAMINONE derivatives of ammonia, and primary and secondary amines are, in general, easy to prepare in good yield.¹ Hydrolysis of the derivatives to give back the base and the parent 1,2-dione also appeared to be straightforward, although we had noticed that the conditions required for hydrolysis to occur varied considerably over the range of enaminones we were handling. This suggested that a suitable 1,3-dione may serve as a protective group for a primary or secondary amine during a synthetic route. Alternatively, if the base concerned has physiological action, the enaminone derivative may act as a transport form which would cross the physio-

logical barriers so that the active compound could be released by hydrolysis close to its site of action. (We assume, for the moment, that no enzymatic hydrolysis would occur.)

To enable the choice of suitable 1,3-diones to be made for these purposes, the rates of hydrolysis of a range of compounds at 37° (body temperature) from pH 2 to 11 have been determined. Enaminones all absorb strongly in the u.v. and it is convenient to follow the reaction by means of the change in the spectrum.

EXPERIMENTAL

A list of the compounds studied is presented in Table 1, together with their u.v. data. Compounds (1)—(12) were

¹ J. V. Greenhill, *J. Chem. Soc. (B)*, 1969, 299.

prepared as described in the literature and carefully purified by distillation or recrystallisation.

2-Bromo-3-piperidinocyclohex-2-enone (13) Hydrobromide.—Bromine (4.5 g) was added dropwise to 3-piperidinocyclohex-2-enone (5 g) in dry chloroform (20 ml) and refluxed for 1.5 h. Evaporation of the solvent gave the *enaminone hydrobromide* (7.6 g, 80%), m.p. 168° (from ethanol-ether) (Found: C, 39.2; H, 4.9; N, 4.2. $C_{11}H_{17}Br_2NO$ requires C, 38.9; H, 5.0; N, 4.1%).

2-Nitro-3-piperidinocyclohex-2-enone (14).—3-Piperidinocyclohex-2-enone (2 g) was dissolved in concentrated sulphuric acid (7 ml) and the solution cooled in an ice-bath. Concentrated nitric acid (2 ml) was added dropwise while the temperature was maintained below 5°. The resulting solution was shaken with chloroform (3 × 50 ml), the combined extracts washed with water (10 ml), dried ($MgSO_4$), filtered, and the volume reduced to *ca.* 20 ml. Addition of light petroleum gave the required *enaminone* (1.8 g, 70%), m.p. 125° [from ethanol-light petroleum (b.p. 40–60°)] (Found: C, 58.8; H, 7.0; N, 12.4. $C_{11}H_{16}N_2O_3$ requires C, 58.9; H, 7.1; N, 12.5%).

Determination of Rates of Hydrolysis.—The buffer solution was prepared according to the method of Teorell and Stenhagen.² Citric acid (6.403 g), $N-H_3PO_4$ (3.26 g), boric acid (3.45 g), and $N-NaOH$ (343 ml) were dissolved in water and diluted to 1 l. A 20 ml portion of this solution and between 73.3 and 14.5 ml of 0.1N-HCl were diluted to 100 ml (to give the pH range 2–11). A *ca.* $2 \times 10^{-3}M$ solution of the enaminone was prepared in water, or, in the case of the faster reactions [compounds (4)–(6), (8), and (9)] in 25% alcohol; 1 ml was accurately transferred to *ca.* 95 ml of the appropriate buffer pre-warmed to 37°. This was taken as zero time. The solution was made up to 100 ml with a further quantity of the same buffer and maintained in a thermostatically controlled water-bath at $37 \pm 0.1^\circ$ throughout the experiment. A sample of the solution was transferred to a 1 cm silica cell and the u.v. spectrum determined using a Unicam SP 800 spectrometer having a thermostatically controlled cell carrier. The spectrum was recorded immediately after preparation of the solution and at suitable intervals to give at least six more readings during the course of the hydrolysis. (The use of 25% alcohol in the preparation of some of the master solutions produced a considerable reduction in the extent of hydrolysis before the first reading could be taken. When the final solution was prepared, the alcohol concentration was reduced to 0.25% and this was assumed to have no significant effect on the rate of hydrolysis determined.) A Pye Dynacap pH meter with glass and calomel electrodes was used to check the pH of the solution at the beginning and end of each run. In no case did the pH change by more than 0.1 unit. Hydrolysis rates were determined at 1 pH unit intervals except where a maximum occurred in the plot for first-order rate constants *vs.* $[H^+]$ when 0.1 pH unit intervals were used.

For each solution the optical density at λ_{max} was plotted against time and extrapolated to give the optical density at zero time and hence the molar extinction coefficient.

The buffer used is a dilute one and any catalysis by the components has been ignored. This was justified because the hydrolysis of compounds (1), (3), (4), and (13) in unbuffered aqueous solution and of compound (4) in dilute HCl (pH 4.15) and dilute NaOH (pH 10.43) was followed. In each case the initial pH was measured and the initial rate of hydrolysis was determined from a plot of optical density *vs.* time. This was compared with the hydrolysis

rate determined at the same pH in buffered solution and in all cases was well within the limits of experimental error.

Pure samples of each of the diones produced on hydrolysis of the enaminones were prepared and subjected to the same conditions of pH and temperature. The u.v. spectrum of each dione was recorded immediately after preparation of the solution and at suitable intervals thereafter. Only 2-methylcyclohexa-1,3-dione did not absorb significantly at the λ_{max} of the enaminone so for compound (12) the change in optical density was proportional to the degree of hydrolysis.

In all other cases, the dione produced by hydrolysis showed significant absorption at the λ_{max} of the enaminone. In some cases the dione itself hydrolysed. Reverse aldol hydrolysis of 1,3-diones is well known and the products, as confirmed by our experiments, show no significant absorption in the u.v. At any particular time (*t*) during a run the solution contained two absorbing components and it was therefore necessary to solve the simultaneous equations (1) and (2) where D_E and D_K represent the optical density at the enaminone λ_{max} and diketone λ_{max} respectively,

$$D_E = C_E \epsilon_E + C_K \epsilon_{K'} \quad (1)$$

$$D_K = C_E \epsilon_{E'} + C_K \epsilon_K \quad (2)$$

C_E and C_K the molar concentration of enaminone and dione at time *t*, and ϵ_E , $\epsilon_{E'}$, ϵ_K , and $\epsilon_{K'}$ are, respectively, the molar extinction coefficient of enaminone at its λ_{max} , of enaminone at the λ_{max} of the dione, of the dione at its λ_{max} , and of the dione at the λ_{max} of the enaminone. ϵ_K and $\epsilon_{K'}$ were obtained from the spectrum of pure dione at the appropriate pH.

In those cases where no significant hydrolysis of the dione occurred during the run, one molecule of enaminone hydrolysed to give one molecule of dione and equation (1) simplifies to (3) where *d* and *d'* represent the optical density of the

$$x = (D_E - d')/(d - d') \quad (3)$$

solution before hydrolysis begins and at the completion of hydrolysis respectively and *x* is the proportion of enaminone remaining. Since *d* – *d'* is a constant for any particular solution it follows that the first-order rate constant could be determined from a plot of $\log_{10} D_E - d'$ *vs.* time.

For compounds (1)–(8) no significant hydrolysis of the dione occurred at pH 7 and below so this method was applicable. Above pH 7 the dione underwent hydrolysis at a significant rate. For each spectrum, therefore it was necessary to solve the simultaneous equations for C_E . The first-order rate constant was then given from a plot of $\log_{10} C_E$ *vs.* time. For compound (9) the dione produced, ethyl acetoacetate, showed absorbance of <1% of that of the enaminone up to pH 8 and was ignored. Above pH 8 the dione hydrolysis was found to be much faster than that of the enaminone so C_E was taken as being proportional to the optical density. Cyclohexa-1,3-dione and 2-bromocyclohexa-1,3-dione showed no hydrolysis throughout the pH range so equation (3) was employed for all results. 2-Nitrocyclohexa-1,3-dione showed acid catalysed hydrolysis so equations (1) and (2) were solved for every result on compound (14).

RESULTS AND DISCUSSION

U.v. data for the compounds under investigation are included in Table 1. The figures are as expected from

² T. Teorell and E. Stenhagen, *Biochem. Z.*, 1938, **299**, 416.

previous work on the u.v. spectra of enaminones;^{1,3} only those for compound (14) call for comment. This compound carries the strongly electron-withdrawing nitro-group in the 2-position and fails to give the normal hypsochromic shift in 0.1N-acid. Enaminones are generally weak bases¹ and it is apparent in the case of compound (14) that it is too weakly basic to be protonated under these conditions.

(13) and (14) the plot shows a minimum value as illustrated in Figure 2. The remaining enaminones [(2), (3), and (6)] showed a non-linear plot which suggested that they also have a maximum rate of hydrolysis below pH 5 but the reaction was too rapid to measure accurately under highly acid conditions.

The hydrolysis of oximes, semicarbazones, and amine derivatives of carbonyl compounds has been carefully

TABLE I
Enaminones and u.v. data

No.	R ¹	R ²	R ³	R ⁴	0.1N-HCl		H ₂ O		0.1N-NaOH		Ref.
					λ _{max.} /nm	ε/l mol ⁻¹ cm ⁻¹	λ _{max.} /nm	ε/l mol ⁻¹ cm ⁻¹	λ _{max.} /nm	ε/l mol ⁻¹ cm ⁻¹	
(1)	H	H	H	Me	287		300	16,800	300	16,800	a
(2)	H	Me	H	Me	288		309.5	17,500	309.5	18,550	a
(3)	H	Et	H	Me	288		310	18,700	301.5	18,700	b
(4)	[CH ₂] ₄	H	H	Me	291	1440	313.5	35,200	313.5	35,200	5
(5)	Et	Et	H	Me	291	1200	315	27,200	315	27,200	b
(6)	Me	Me	H	Me			312.5	29,800	312.5	29,800	c
(7)	H	H	H	Ph	322	9550	330	19,600	330	19,600	a
(8)	H	H	Me	Me			317.5	14,300	317.5	14,300	b
(9)	H	H	H	OEt			275.5	16,500	275.5	16,500	d

R ¹		R ²		λ _{max.} /nm		ε/l mol ⁻¹ cm ⁻¹		λ _{max.} /nm		ε/l mol ⁻¹ cm ⁻¹		Ref.
(10)	Piperidino	H	H	287	23,600	304.5	35,000	304.5	35,000		c	
(11)	2-Phenylethylamino	H	H	282.5	25,800	293	33,600	293	33,600		1	
(12)	Piperidino	Me	Me	308		329.5	28,000	329.5	28,000		f	
(13)	Piperidino	Br	Br	307	23,000	324.1	25,900	324.1	25,900			
(14)	Piperidino	NO ₂	NO ₂	283.5	12,600	283.5	12,600	283.5	13,700			

^a H. H. Holtzclaw, J. P. Coleman, and R. M. Alire, *J. Amer. Chem. Soc.*, 1958, **80**, 1100. ^b A. Combes and C. Combes, *Bull. Soc. chim. France*, 1892, 7778. ^c K. W. R. Kohlrath and A. Pongratz, *Monatsh.*, 1937, **70**, 226. ^d S. A. Glickman and A. C. Cope, *J. Amer. Chem. Soc.*, 1945, **67**, 1017. ^e J. V. Greenhill, *J. Chem. Soc. (C)*, 1970, 1002. ^f D. Pitea and F. Gavini, *J.C.S. Perkin II*, 1972, 291.

TABLE 2
Rate constants (±5%) for enaminone hydrolysis

Compound	10 ⁷ k/s ⁻¹										pH of rate maximum	
	pH											
(1)				21,600	2270	350	132	64.0	36.1	23.8	217	
(2)				8880	1310	312	154	13.6	13.4			
(3)				5220	875	247	126	108	105			
(4)			4860	7160	8700	8090	7560	7262	7070	6960		6.25
(5)			2070	3440	5910	5980	5510	5300	5190	5100		6.06
(6)				40,300	20,800	13,700	11,200	10,300	10,000	10,000		
(7)			32,000	3830	375	44.4	9.40	3.50	2.25	3.90	38.5	
(8)					54,000	8102	1230	510	435	428	7720	
(9)						15,900	2400	498	359	333	16,750	
(10)	477	444	154	17.2	2.11							2.55
(11)	169	323	92.5	16.5								2.93
(12)				17,300	2360	590	382	260	108	71.0	1992	
(13)		47.3	23.1	14.6	10.6	8.80	9.52	12.3	18.1	31.3		
(14)	40.0	20.6	17.2	16.6	20.0	36.0	188	20,700				

The first-order rate constants are given in Table 2. Only for compounds (1), (7)–(9), and (12) did the plot of first-order rate constant vs. [H⁺] give a straight line, from the slope of which a second-order rate constant could be determined. The same plots for compounds (4), (5), (10), and (11) show a maximum; this is illustrated for compound (4) in Figure 1. For compounds

studied.⁴ The general observation in these cases is of a maximum rate of hydrolysis somewhere in the pH range 2–5. The mechanisms which have been shown to hold for these reactions may be applied to the present examples, modified where necessary, for the effect of the carbonyl group. It is clear that all the enaminones studied can be hydrolysed under acid catalysis and it has been demonstrated that enaminones are protonated on oxygen.^{3,5} The mechanism in Scheme 1 accounts satisfactorily for the observed acid catalysed hydrolysis.

³ J. V. Greenhill, *J. Chem. Soc. (C)*, 1971, 2699.

⁴ W. P. Jencks, *Catalysis in Chemistry and Enzymology*, McGraw-Hill, New York, 1969, p. 490.

Thus the normal *O*-protonation of an enaminone (15) gives the cationic imine (16). Attack by water (17) and

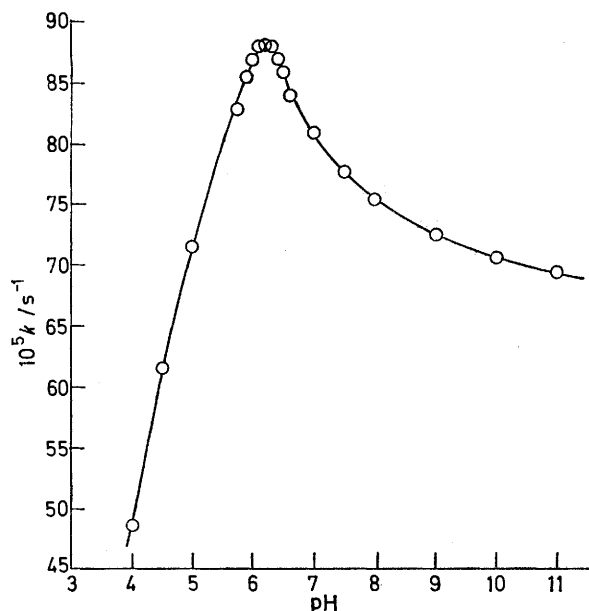


FIGURE 1 First-order rate constants vs. pH for compound (4)

proton transfer (18) would then occur as in the accepted mechanism for oxime hydrolysis.⁶ However, the difference between the intermediate (18) and the comparable oxime hydrolysis intermediate is that (18) also contains an enol group. Thus (18) may be converted

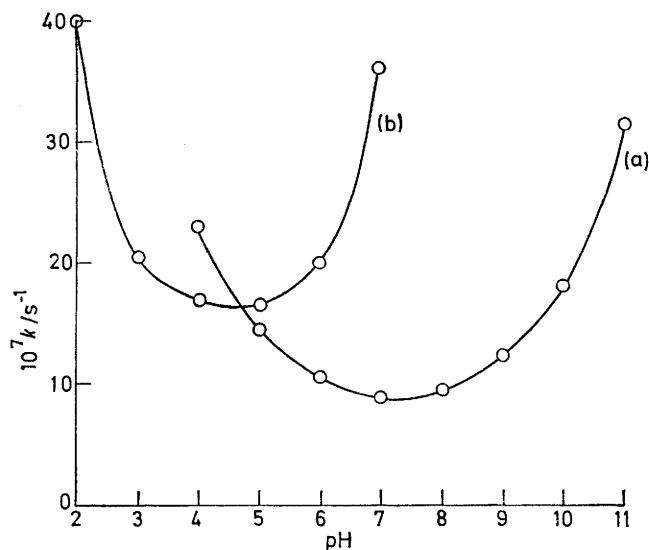


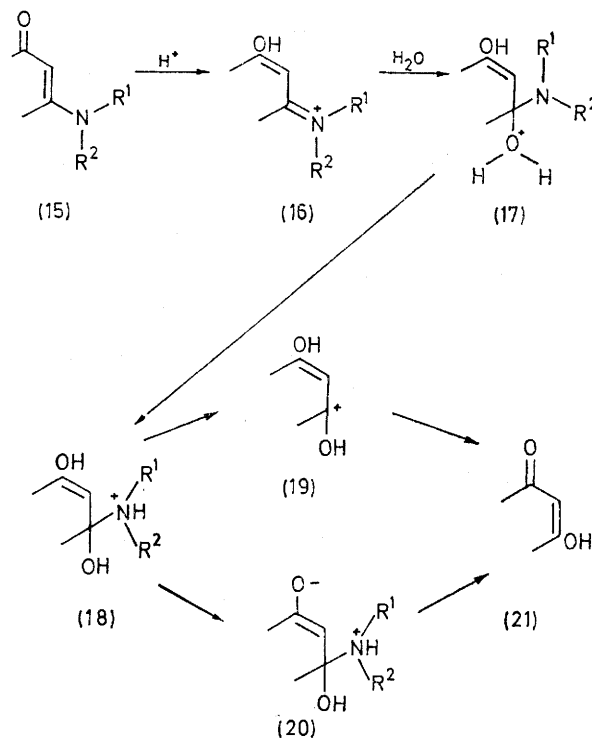
FIGURE 2 First-order rate constants vs. pH for (a) compound (13) and (b) compound (14)

into the product (21) *via* intermediate (19) or *via* intermediate (20).

⁵ N. J. Leonard and J. A. Adamcik, *J. Amer. Chem. Soc.*, 1959, **81**, 595.

⁶ W. P. Jencks, *J. Amer. Chem. Soc.*, 1959, **81**, 475.

Of the open chain enaminones studied those where $R^1 = R^2 = H$ [(1) and (7)–(9)] are the only ones for which a second-order rate constant could be determined. These would form the strongest conjugate acids (18) and may go *via* (19) to the dione (21). Nevertheless, the overall rate of reaction depends only on [Enaminone] and $[H^+]$ and presumably the attack of water [(16) \rightarrow (17)] is rate determining. The open chain compounds (4) and (5) for which a pH-dependent maximum rate of



hydrolysis was discovered are both tertiary amines, would form weaker conjugate acids, and may follow the route (18) \rightarrow (20) to the dione (21). The overall route is then comparable with the route of hydrolysis of oximes. Above the maximum, step (16) \rightarrow (17) is rate determining but below the maximum the rate of betaine formation [(18) \rightarrow (20)] is rate determining.

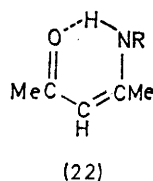
In spite of the variation in the shapes of second-order plots observed, inspection of Table 2 for pH 7 allows various general conclusions to be made about the effect of different substituent groups on the stability of enaminones in neutral solution. Of the derivatives of acetylacetone, the primary (1) and secondary (2) and (3) enaminones are considerably more stable than the tertiary compounds (4)–(6). This is probably due to the hydrogen bonded structure (22) which cannot form when the nitrogen is dialkylated. It has been clearly demonstrated by n.m.r.,⁷ i.r.,⁸ and u.v.⁹ methods that primary and secondary enaminones exist in form (22).

⁷ G. O. Dudek and R. H. Holm, *J. Amer. Chem. Soc.*, 1961, **83**, 2099; 1962, **84**, 2691.

⁸ J. Dabrowski, *Spectrochim. Acta*, 1963, **19**, 475.

⁹ D. L. Ostercamp, *J. Org. Chem.*, 1970, **35**, 1632.

Compound (8) is derived from 3-methylacetylacetone and the second-order hydrolysis constant is high because the inductive effect of the extra methyl group is base strengthening and rate-determining protonation is faster.

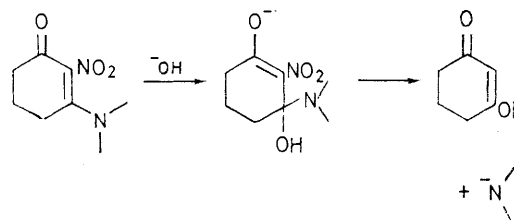


The phenyl group in compound (7) is base weakening and leads to a reduction in the second-order rate constant. Compound (9) is derived from a keto-ester rather than a diketone and is probably protonated on carbon ¹⁰ as is a simple enamine, but over the range studied (pH 7–11) it showed very rapid second-order hydrolysis.

The five compounds (10)–(14) derived from cyclohexane-1,3-dione show considerably lower rates of hydrolysis than any of the open chain structures. This is probably due to the rigid geometry and inherent stability of the cyclohexenone system. Compounds (10) and (11) carry a proton on C-2, are hydrolysed at a measurable rate only under acidic conditions, and show a maximum rate of hydrolysis at pH 2.55 and 2.93 respectively. This indicates that in these ring compounds the balance is in favour of the route (18) → (20) → (21) in spite of the nitrogen being tertiary. Molecular models of compounds (12)–(14) show that the group substituted on C-2 introduces strain into the molecule. The result is that the plane of the piperidine ring is twisted out of the plane of the cyclohexenone ring and maximum overlap of the nitrogen lone pair with the π system is no longer allowed. The extinction coefficients (Table I) show that the methyl group and the bromine atom have comparatively little effect but the bulkier nitro-group causes a considerable twist. Hydrolysis is accompanied by relief of strain and all three compounds are hydrolysed faster than the unsubstituted enaminones

(10) and (11). The methyl group of compound (12) is base strengthening but its steric interaction with the protonated nitrogen in the intermediate of type (18) appears to cause the hydrolysis to follow the pathway *via* (19) since the reaction has second-order kinetics.

Compounds (13) and (14) clearly show an acid catalysed hydrolysis at low pH values but this is slow compared with compound (10) because the 2-bromo-substituent (13) and 2-nitro-substituent (14) are base weakening by their inductive effects and slow the rate-determining step. However, with increase in pH, these two compounds clearly show a change to a base catalysed mechanism. The electron-withdrawing substituents must allow attack by hydroxide ion to give hydrolysis by a mechanism analogous to the well known



SCHEME 2

route of hydrolysis of amides (Scheme 2). It is interesting that compound (7) which contains the electron-withdrawing phenyl ring showed slight deviation from second-order behaviour above pH 10 suggesting that the base catalysed mechanism is contributing in highly alkaline solution.

These results demonstrate that enaminones derived from readily available 1,3-diones have a wide range of hydrolysis rates. We are already making use of the information provided by this work both in the design of synthetic routes where *N*-protection is needed and also in the preparation of physiologically active compounds.

[3/1306 Received, 21st June, 1973]

¹⁰ J. C. Powers, *J. Org. Chem.*, 1965, **30**, 2534.