

Kinetics of degradation of 2-hydroxyiminomethyl-1-methylpyridinium methanesulphonate

MOUNG CHOUNG FAN, J. GRAHAM NAIRN AND GEORGE C. WALKER

The decomposition of 2-hydroxyiminomethyl-1-methylpyridinium methanesulphonate (P_2S) was studied at different temperatures and pH values. The initial rate of decomposition was found to be first order with respect to P_2S concentration. The pH for maximum stability appears to be about 5.

THE methanesulphonate of 2-hydroxyiminomethyl-*N*-methylpyridinium, P_2S , is one of the salts effective in reactivating cholinesterases which have been poisoned by anticholinesterase compounds, notably the organic phosphates (Ladell, 1958). P_2S has been reported to be unstable to heat, changing from pale yellow to orange-brown in aqueous solution, and producing cyanide as one of the end products in alkali medium. The rate of this change has also been found to depend on the temperature and pH of the solution (Creasy & Green, 1959; Kondritzer, Ellin & Edberg, 1961). More detailed information about these dependencies would be of interest. We have therefore examined the rate of degradation of P_2S in relation to temperature and pH. The results of studies on pralidoxime iodide (2-PAM, pyridine-2-aldoxime methiodide) were reported while this study was in progress (Ellin, Carlese & Kondritzer, 1962).

TABLE 1. BUFFERS FOR P_2S SOLUTIONS

pH	Composition	Dilution
1	0.1N hydrochloric acid	None
2	50.0 ml 0.2M potassium chloride and 7.8 ml 0.2M hydrochloric acid	to 200 ml
3	6 ml glacial acetic acid	to 1000 ml
4	1.8 ml 0.2M sodium acetate and 8.2 ml 0.2M acetic acid	None
5	7.0 ml 0.2M sodium acetate and 3.0 ml 0.2M acetic acid	None
6	12.3 ml 0.2M disodium phosphate and 87.7 ml 0.2M monosodium phosphate	to 200 ml
7	61.0 ml 0.2M disodium phosphate and 39.0 ml 0.2M monosodium phosphate	to 200 ml
9	50.0 ml 0.025M borax and 4.6 ml 0.1M hydrochloric acid	to 100 ml
11	50.0 ml 0.05M disodium phosphate and 4.1 ml 0.01M sodium hydroxide	to 100 ml
13	0.1N sodium hydroxide	None

Methods

The pH of the test solutions was maintained by using buffer solutions or excess of acid or alkali. The buffers are listed in Table 1 and were found to be "transparent" throughout the ultra-violet range of the

From the Faculty of Pharmacy, University of Toronto, Canada.

spectrophotometer (Beckman DK 2) and did not interfere with the absorption of the P_2S solutions. The spectra of freshly made solutions of P_2S (Aldrich Chemical Company, recrystallised from ethanol, m.p. 156.5–157.5°) show absorption peaks of 292 $m\mu$ in acid medium and 336 $m\mu$ in alkaline medium (Creasy & Green, 1959). P_2S was found to follow Beer's Law, but in view of the absorption of *N*-methyl- α -pyridone, a decomposition product, at 293 $m\mu$ in 0.1N HCl and 0.1N NaOH, all assays were made by adding 1.0 ml of 1N NaOH to a 5 ml sample where necessary and the absorption measured at 336 $m\mu$ (Creasy & Green 1959).

Solutions of P_2S in various media, at a concentration of about 23 $\mu\text{g/ml}$ were introduced into colourless 10 ml ampoules which were immersed in thermostatically-controlled baths at 40°, 50° and 60°. At appropriate intervals, depending upon the rate of degradation, two ampoules of each medium from each bath were removed and immediately assayed for P_2S and cyanide.

The cyanide content was estimated according to Aldridge's method (Aldridge, 1945) whereby the cyanide is converted into cyanogen bromide

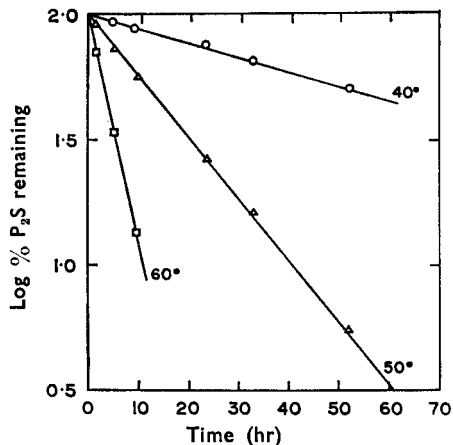


FIG. 1. Typical first-order rate plots for the decomposition of P_2S at pH 10.9 at different temperatures.

and then allowed to react with benzidine and pyridine. The magenta-coloured complex of cyanide was found to absorb in the visible range with a peak at 526 $m\mu$. As this complex is formed only in neutral or acid medium, 2 ml samples were made acid by adding 0.2 ml of 50% sulphuric acid where necessary and the concentration of cyanide estimated spectrophotometrically.

Results

P_2S DEGRADATION

The observed rate of degradation of P_2S follows the classical first order equation $\ln c = kt + \text{constant}$, where k is the first order rate constant at a constant pH. First order plots for the decomposition of P_2S at pH 10.9 are shown in Fig. 1. Using the Arrhenius equation $k =$

KINETICS OF DEGRADATION OF P₂S

$Ae^{-E/RT}$ the temperature dependence of the rate constant is shown in Fig. 2. The pH dependence of the rate constant is shown in Fig. 3 which shows a pattern similar to that for pralidoxime iodide (Ellin & others, 1962) and it is probable that P₂S and pralidoxime iodide degrade in the same manner.

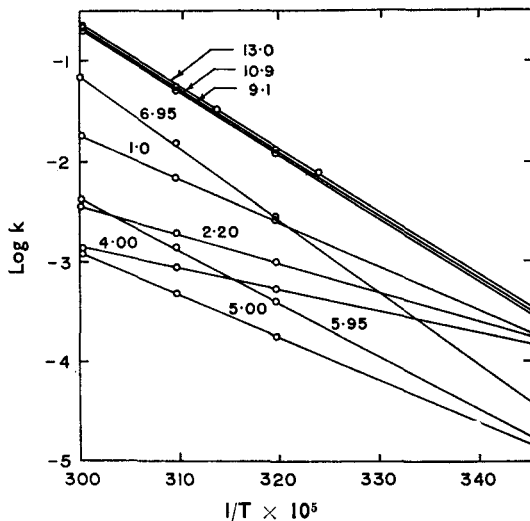


FIG. 2. Temperature dependency of the rate constant for the decomposition of P₂S at different pH values.

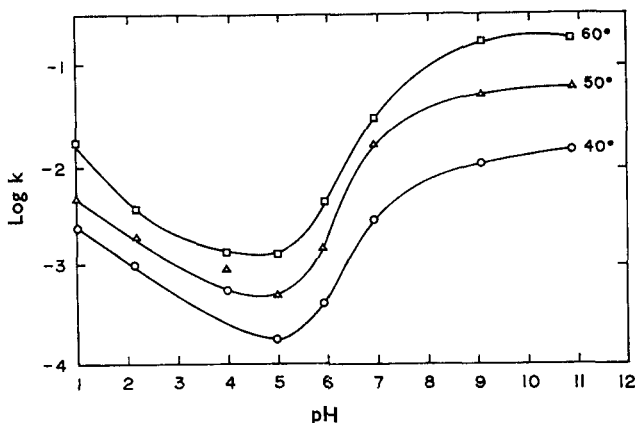


FIG. 3. pH profile of the logarithm of the first-order rate constants for the decomposition of P₂S.

First order rate constants for the degradation of P₂S at lower temperatures may be obtained from Fig. 2. The predicted half-lives of P₂S at various pH values and temperatures are shown in Table 2. It should be borne in mind, however, that the constants were obtained from the initial overall first order reactions only. Fig. 3 and Table 2 suggest

that the maximum stability of P₂S occurs at about pH 5 in aqueous solutions.

TABLE 2. PREDICTED HALF-LIFE (DAYS) OF P₂S IN AQUEOUS SOLUTIONS AT VARIOUS TEMPERATURES AND PH VALUES

Temp. °C	pH								
	1.0	2.20	4.00	5.00	5.95	6.95	9.10	10.90	13.0
60	1.65	7.776	20.06	24.10	4.18	1.03	0.14	0.15	0.13
50	4.04	14.04	32.74	59.71	20.22	1.82	0.59	0.51	0.49
40	11.4	28.59	51.44	160.4	69.66	10.02	3.30	2.17	2.09
30	31.7	56.30	69.23	432.0	251.3	57.61	10.48	10.10	9.56
20	97.83	123.1	155.1	1320.0	977.3	371.9	53.76	51.35	49.03
10	339.2	272.6	288.7	4271.0	4174.0	2821.0	313.0	302.4	288.4

CYANIDE FORMATION

The amount of cyanide ion found in the solutions at various temperatures and pH is shown in Table 3. Below pH 4, no cyanide was found even after prolonged periods of heating. Curves plotted from the various cyanide determinations did not appear to follow any general

TABLE 3. CYANIDE ION FORMED IN AQUEOUS SOLUTIONS OF P₂S AT VARIOUS TEMPERATURES AND PH VALUES

pH	µg/ml CN ⁻		
	40°	50°	60°
4	0 (210)*	0 (209)*	0 (80)*
5	0 (229)	0.013 (120)	0.035 (60)
5.95	0.01 (70)	0.043 (70)	0.35 (60)
6.95	0.29 (70)	0.65 (50)	1.31 (50)
9.10	0.83 (40)	1.44 (50)	

* Figures in brackets represent the number of hr.

pattern, although the amount of cyanide formed was higher when more P₂S was degraded. Assuming that P₂S degrades in a similar manner to pralidoxime iodide, then one mole of cyanide should be formed from one mole of P₂S (Ellin, 1958). However, the relation between cyanide formed and P₂S degraded is not constant. This would suggest that part of the degraded P₂S remained as intermediates and further studies of these intermediates and their rate constants would be necessary before a logical prediction of the amount of cyanide formed is possible.

Acknowledgements. The research for this paper was supported (in part) by the Defence Research Board of Canada, Grant number 9370-06.

References

Aldridge, W. N. (1945). *Analyst*, **70**, 474-475.
 Askew, B. M. (1956). *Brit. J. Pharmacol.*, **11**, 417-423.
 Creasey, N. H. & Green, A. L. (1959). *J. Pharm. Pharmacol.*, **11**, 485-490.
 Davies, D. R., Green, A. L. & Willey, G. L. (1959). *Brit. J. Pharmacol.*, **14**, 5-8.
 Ellin, R. I. (1958). *J. Amer. chem. Soc.*, **80**, 6588-6590.
 Ellin, R. I., Carlese, J. S. & Kondritzer, A. A. (1962). *J. pharm. Sci.*, **51**, 141-148.
 Kondritzer, A. A., Ellin, R. I. & Edberg, L. J. (1961). *Ibid.*, **50**, 109-112.
 Ladell, W. S. S. (1958). *Brit. med. J.*, **2**, 141-142.