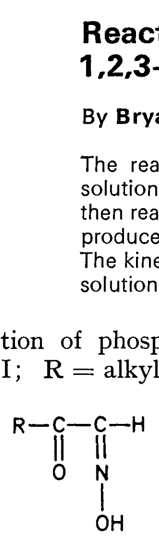
Reaction of Isopropyl Methylphosphonofluoridate with 1-Phenylbutane-1,2,3-trione 2-Oxime

By **Bryan W. Ford** and **Peter Watts,*** Chemical Defence Establishment, Porton Down, Salisbury, Wiltshire

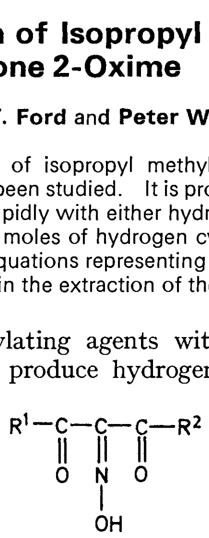
The reaction of isopropyl methylphosphonofluoridate with 1-phenylbutane-1,2,3-trione 2-oxime in aqueous solution has been studied. It is proposed that the initial product of the reaction is the phosphonylated oxime which then reacts rapidly with either hydroxide ion to produce one mole of hydrogen cyanide or with the oxime anion to produce two moles of hydrogen cyanide. The immediate precursor of the hydrogen cyanide is benzoyl cyanide. The kinetic equations representing these reactions are complex and an analogue computer was necessary for their solution and in the extraction of the various rate constants from the experimental data.

THE reaction of phosphorylating agents with oximes such as (I; R = alkyl) to produce hydrogen cyanide



$R{-}C({=}O){-}C({=}N{-}OH){-}H$

(I)



$R^1{-}C({=}O){-}C({=}N{-}OH){-}C({=}O){-}R^2$

(II)

was first investigated by Green and Saville [1] and a mechanism involving the breakdown of a phosphoryl oxime was suggested. The reaction with oximes such as (II) was also described but, as no simple stoicheiometry was observed, it was not considered further. This paper reports the results of an investigation of 1-phenylbutane-1,2,3-trione 2-oxime (OX) (II; R^1 = Ph, R^2 = Me) with isopropyl methylphosphonofluoridate (PF).

EXPERIMENTAL

Materials.—1-*Phenylbutane*-1,2,3-*trione* 2-*oxime*. Sodium nitrite (23·4 g, 0·34 mol) in water (60 ml) was added dropwise over 15 min to a stirred, cooled (0—5°) solution of benzoylacetone (50 g, 0·31 mol) in aqueous sulphuric acid (7%; 350 ml) containing sufficient dioxan to give a clear solution. After stirring for 1 h at 0—5° and 1 h at room temperature, the solution was extracted with ether (2 × 500 ml), the extracts bulked, and dried ($MgSO_4$); after filtration the ether was removed using a rotary evaporator. The residue was washed with boiling light petroleum (b.p. 40—60°), dried, and then recrystallised from benzene. Further recrystallisation from water gave *needles* (28·8 g, 49%), m.p. 126—128°, τ (Me_2SO) 7·51 (3H, s) and 2·15—2·6 (5H, Ph), $\nu_{max.}$ 3420s and 1700s,sh cm^{-1} ($C_{10}H_9NO_3$ requires C, 62·8; H, 4·75; N, 7·3. Found: C, 62·7; H, 4·8; N, 7·4%). The compound was >99% pure as determined by potentiometric titration (*vide infra*). The configuration of OX as prepared above is unknown. Isomerisation was attempted (heating in chloroform or dimethyl sulphoxide solution) so that a configuration could be assigned by a comparison of n.m.r. spectra, but failed.

Acetyl derivative of OX. Acetyl chloride (1·8 g, 0·022 mol) was added dropwise (over 10 min) with stirring to OX (3·8 g, 0·020 mol) in ether (50 ml) containing triethylamine (2·2 g, 0·022 mol). After stirring for 1 h the precipitate was filtered off and washed with ether (25 ml). The filtrate and washings were combined, dried (Na_2SO_4), and the ether removed using a rotary evaporator. The i.r. and n.m.r. spectra of the residue were consistent with the proposed product. All attempts at further purification failed as the compound decomposed.

Benzoyl derivative of OX. Benzoyl chloride (4·0 g, 0·029 mol) in ether (25 ml) was added dropwise (over 15 min) to a stirred solution of OX (3·8 g, 0·020 mol) in ether (25 ml) containing triethylamine (2·2 g, 0·022 mol). After stirring for 1 h the precipitate of triethylamine hydrochloride and benzoylOX was filtered off. This precipitate was washed rapidly with water to remove the hydrochloride. Little hydrolysis of benzoylOX occurred owing to its extreme insolubility. *BenzoylOX* was dried *in vacuo* at room temperature to give crystals (2·75 g, 47%), m.p. 123—125° ($C_{17}H_{13}O_4N$ requires C, 69·15; H, 4·4; N, 4·7. Found: C, 69·2; H, 4·4; N, 4·5%). τ ($CHCl_3$) 7·31 (3H, s) and 2·1—2·8 (10H, 2 × Ph), $\nu_{max.}$ 1680s, 1710s, and 1770s cm^{-1}.

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[1] A. L. Green and B. Saville, *J. Chem. Soc.*, 1956, 3887; B. Saville, *Analyst*, 1957, **82**, 209.

Isopropyl methylphosphonylOX. OX (3·8 g, 0·020 mol) and triethylamine (2·2 g, 0·022 mol) were dissolved in ether (50 ml) and the solution was added dropwise over 20 min to a stirred solution of PF (2·0 g, 0·014 mol) in ether (50 ml). After stirring for 1 h no visible reaction had occurred. After storing overnight a trace amount of a yellow oil separated. Further storing led to decomposition.

Isopropyl methylphosphonofluoridate. This was prepared by published procedures [2] and was >98% pure as assayed by fluoride ion or acid produced on hydrolysis.

Apparatus.—A Radiometer pH stat (TTT1, SBR2) fitted with either a Pye–Ingold combined glass and reference miniature electrode type 401-M5 or a Radiometer type G202B glass electrode was used for pH measurement, potentiometric titration, and for measurement of rates of acid production. Fluoride ion was determined using an Orion specific fluoride ion electrode, type 94-09A.

It was found that acid production could not be monitored with accuracy over several hours using a normal Radiometer cell assembly owing to some carbon dioxide absorption occurring but more importantly to loss of hydrogen cyanide from the solution. These problems were overcome by using as a cell a conical flask (100 ml) fitted with a rubber bung through which passed the inlet tube from the pH stat and the dual electrode. The reaction solution volume was 100 ml to reduce air space. When monitoring fluoride ion production an open cell (50 ml) was used, the pH being kept constant using the pH stat but no account was taken of the acid production.

U.v. measurements were made using 10 mm silica cells and a Unicam SP 700A spectrophotometer. N.m.r. spectra were measured with a JEOL JNM-4H-100 spectrometer at 100 MHz using tetramethylsilane as internal standard. I.r. spectra were measured with a Perkin-Elmer Infracord using KBr discs.

Preparation of Solutions.—PF was made up in AnalaR propan-2-ol (usually 1·0M) and OX in 50% aqueous ethanol. Very reactive compounds such as acetylOX, benzoyl cyanide, and acetyl cyanide were made up in dry, purified dioxan. These solutions were prepared daily. All other solutions were made up in glass distilled water.

Determination of $\mathrm{p}K_\mathrm{a}$ *Values.*—Potentiometric titrations were conducted on the Radiometer apparatus previously described. Calculations of $\mathrm{p}K_\mathrm{a}$ values from the potentiometric curves were made according to Albert and Serjeant: [3] ($I = 0{\cdot}1$ with KNO_3 at 25·0°) OX in 5% aqueous ethanol, $\mathrm{p}K_\mathrm{a}$ $7{\cdot}14 \pm 0{\cdot}02$; OX in 20% aqueous ethanol, $\mathrm{p}K_\mathrm{a}$ $7{\cdot}63 \pm 0{\cdot}02$; HCN in 5% aqueous ethanol, $\mathrm{p}K_\mathrm{a}$ $9{\cdot}06 \pm 0{\cdot}04$; and HCN in 20% aqueous ethanol, $\mathrm{p}K_\mathrm{a}$ $9{\cdot}13 \pm 0{\cdot}03$.

Kinetic Methods.—All kinetic runs were conducted at I 0·1 (with KNO_3) at 25·0°. The solvent was 5% aqueous ethanol except where otherwise stated. The usual initial concentrations when acid production was to be monitored were 10^{-3}M-PF and 5×10^{-3}M-OX, and the initial concentrations when fluoride ion production was to be monitored were usually 10^{-4}M-PF and 10^{-3}M-OX. Fluoride ion and acid production were not measured simultaneously as the acid production required an initial PF concentration of *ca.* 10^{-3}M and at this level the isopropyl hydrogen methylphosphonate produced interfered with the fluoride ion electrode. The reactions were initiated by addition of PF solution.

Estimation of OX and HCN *Concentrations at the Completion of a Kinetic Run.*—The pH of the reaction solution was adjusted to pH 6·6—6·8 with 1·0M-nitric acid and a potentiometric titration curve recorded up to pH 9·9. The OX concentration was calculated from the titre between pH 7·0 and 7·6. Owing to the relative concentrations of OX and HCN the correction required for HCN ionisation in this pH region was small enough to be ignored. The HCN concentration was calculated from the titre between pH 9·0 and 9·6 with a correction for OX concentration. The production of cyanide ion was confirmed by the electrometric technique of Baker and Morrison.[4]

Identification and Estimation of Ethyl Benzoate.—Reactions were conducted in 5 and 20% aqueous ethanol and the acid production was monitored. After assaying the OX concentration by potentiometric titration, the solution was divided into two equal portions. To one, a known amount of ethyl benzoate was added and then to both, solid sodium carbonate was added. The aqueous solutions were now extracted with heptane (4 × 25 ml) and the ethyl benzoate assayed from its absorption at 227 nm. Positive identification of ethyl benzoate was made by measuring the i.r. and n.m.r. spectra.

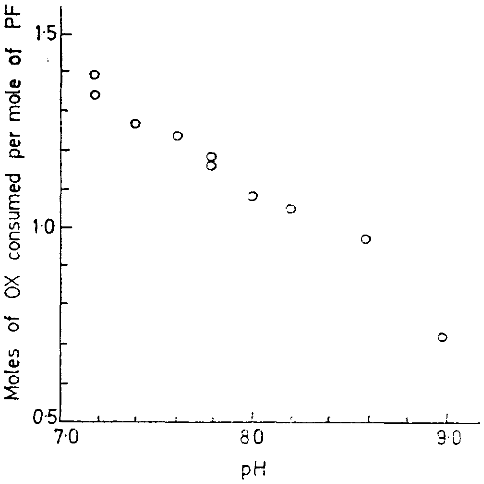

FIGURE 1 Moles of OX consumed per mole of PF as a function of pH

Analysis of Kinetic Results.—First-order rate coefficients (where appropriate) were obtained from the data using a least-squares curve-fitting program. Other rate coefficients were obtained by manually matching the output of a Solartron HS7-1 analogue computer, programmed to solve the differential equations appropriate to the kinetic model, with the experimental data on a Bryans 26000 A3 XY recorder. Details of the program are given in the Appendix.

RESULTS AND DISCUSSION

Stoicheiometry of the PF–OX Reaction.—As expected from the work of Green and Saville [1] no obvious simple stoicheiometry for the reaction between PF and OX was observed. It was found that the molar ratio of oxime consumed to PF initially present varied according to the pH and could be greater than 1. This is shown in Figure 1. The results of the potentiometric titrations

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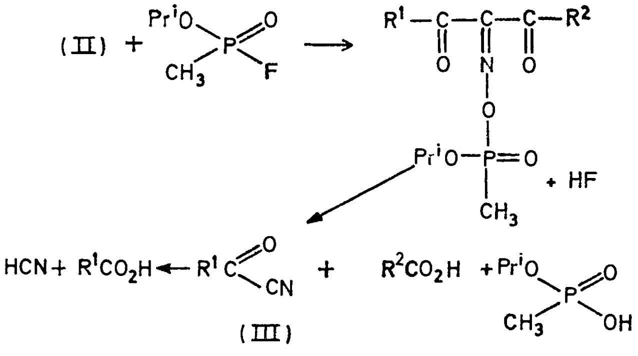
[2] P. J. R. Bryant, A. H. Ford-Moore, B. J. Perry, A. W. H. Wardrop, and T. F. Watkins, *J. Chem. Soc.*, 1960, 1553.

[3] A. Albert and E. P. Serjeant, 'Ionisation Constants of Acids and Bases,' Methuen, London, 1962.

[4] B. B. Baker and J. D. Morrison, *Analyt. Chem.*, 1955, **27**, 1306.

following the kinetic experiments showed that one mole of hydrogen cyanide was produced for each mole of OX consumed. From the structure of the oxime it can be expected that for each mole of oxime that breaks down to give a mole of hydrogen cyanide, one mole each of acetic and benzoic acids should be produced according to Scheme 1. The results of the kinetic experiments in which acid production was monitored, followed by potentiometric titration to determine the OX consumed and the hydrogen cyanide produced, showed that 0·20 (±0·05) mole of acid per mole of OX consumed could not be accounted for. As the reaction medium contained 5% ethanol it was thought that the missing acid could be present as an ethyl ester. If this were so, increasing the ethanol to 20% should increase the amount of ester produced and cause a corresponding decrease in the available acid. In 20% ethanol the acid deficiency increased to 0·85 mole of OX consumed. Ethyl benzoate was searched for as described in the Experimental section and was found in the correct molar quantities.



$R^1 = Ph$, $R^2 = Me$ or $R^1 = Me$, $R^2 = Ph$

SCHEME 1

In conjunction with the search for the ' missing ' acid and the postulated ester the fates of the two acyl cyanides (III; R^1 = Me or Ph) which could have been the immediate precursors of the ester, were examined in aqueous ethanol. Acetyl cyanide (5×10^{-4}M) and aqueous ethanol (both 5 and 20%) reacted immediately to yield the correct amount of acid indicating no production of ethyl acetate. Benzoyl cyanide (5×10^{-4}M) and aqueous ethanol (both 5 and 20%) also reacted immediately to produce both acid and ethyl benzoate in the amounts expected if benzoyl cyanide was the immediate precursor of the ethyl benzoate produced in the PF–OX reaction.

There are two mechanisms whereby more than one mole of OX per mole of PF may be consumed. Both mechanisms result in the production of an acylOX which then breaks down in a similar fashion to the phosphorylOX initially produced in the PF–OX reaction. One mechanism is that in which the benzoyl cyanide produced in the breakdown of the phosphorylOX reacts with OX to yield benzoylOX. The other mechanism is for OX to attack the phosphorylOX to produce acetylOX.

Benzoyl cyanide (5×10^{-4}M) was allowed to hydrolyse at pH 8·2 in the pH stat in the presence and absence of OX (5×10^{-3}M). In both cases the reaction was too fast to follow and the same quantity of acid was produced indicating that there was no reaction with OX. It therefore follows that phosphorylOX must react with OX to produce acetylOX. It was a further possibility that the acetylOX formed would in turn react with OX to regenerate acetylOX in a chain process in which HCN would also be liberated; this was investigated in two ways.

AcetylOX (5×10^{-4}M) was hydrolysed in the presence and absence of OX (5×10^{-3}M) and the same amount of acid was found to be produced in each case. AcetylOX was produced *in situ* from *p*-nitrophenyl acetate (10^{-3}M) and OX (5×10^{-3}M) in the pH stat at pH 7·6. The reaction was too fast to monitor continuously but at completion of the reaction 2·80 moles of acid had been produced and potentiometric titration showed only one mole of OX consumed. Thus not only does acetylOX not react with OX as does isopropyl methylphosphonylOX but it also breaks down considerably more rapidly.

Rate of Hydrolysis of PF.—The rate of alkaline hydrolysis of PF was measured by following either fluoride ion production or acid production. The results were the same within experimental error and a second-order rate constant for the hydroxide ion catalysed hydrolysis of 37·5 l mol^{-1} s^{-1} with an accuracy of ±5% was obtained.

Rate of Reaction of PF and OX.—The rate of phosphorylation of OX by PF can be measured unambiguously by monitoring fluoride ion production. As was expected the first-order rate coefficient is linearly dependent upon oximate ion concentration and the second-order rate constant has a value of 1·2 l mol^{-1} s^{-1} with an accuracy of ±10%. The interpretation of the rate of acid production was dependent upon the use of an analogue computer as the analytical solution of the kinetic equations derived from even the simplest reaction schemes is very difficult. The technique used to interpret the rate of acid production involved the simulation of the various reaction schemes on the analogue computer and the matching of the computer produced curves with the experimental data. The excellent agreement between the observed and computed data is shown by Table 1. Because of the nature of analogue techniques it is not possible to produce statistical limits on the values of the parameters obtained.

Development of the Kinetic Scheme.—As the rates of fluoride ion and of acid production in the reaction of PF and OX do not obey the same rate law the kinetic scheme should include steps for the formation and for the breakdown of phosphorylOX. Three processes for the breakdown of phosphorylOX must be considered; reaction with water or hydroxide ion to yield cyanide ion *via* benzoyl cyanide, reaction with more OX to yield

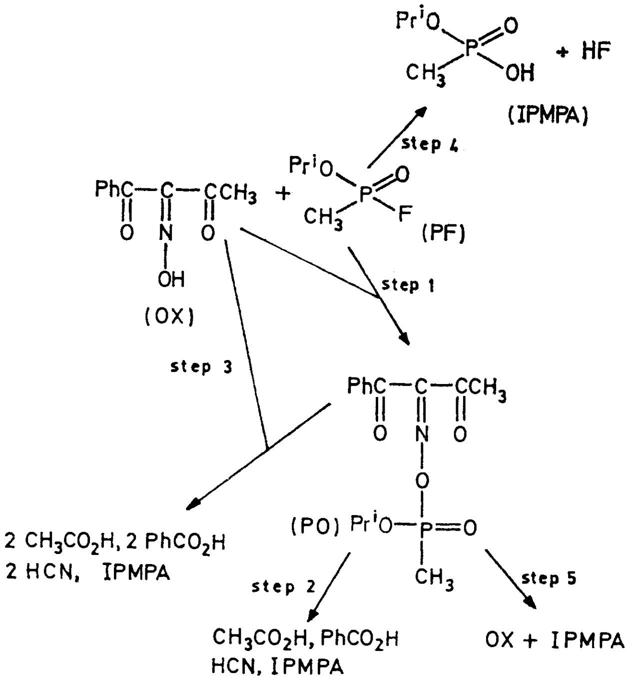
TABLE 1

Comparison of observed and computed data for the reaction of OX (5×10^{-3}M) and PF (10^{-3}M) at pH 8·4

t/min	Moles of acid produced per mole of PF: Observed	Moles of acid produced per mole of PF: Computed
0·5	0·459	0·485
1	0·904	0·918
1·5	1·248	1·248
2	1·535	1·540
2·5	1·765	1·765
3	1·950	1·941
4	2·240	2·240
5	2·435	2·440
7	2·687	2·691
9	2·824	2·824
17	2·965	2·965

cyanide ion *via* both benzoyl cyanide and acetylOX, and reaction with hydroxide ion to yield OX and phosphorus acid. Hydroxide ion catalysed hydrolysis of PF must also be included. These reactions are shown in Scheme 2.

As the rate constants for steps 1 and 4 are known, three parameters have to be determined from the acid production runs. For each pathway at any particular pH it is possible to calculate the amount of acid produced not forgetting to take into consideration that only 0·80 mole of each putative mole of benzoic acid produced is available as free acid owing to the formation of ethyl benzoate.



SCHEME 2

Analogue computer simulation rapidly showed that it was unnecessary to include step 5 in order to attain agreement between the simulated and observed rates of acid production. It was apparent that as expected the active nucleophiles in steps 2 and 3 are hydroxide ion and hydroxyiminate ion respectively. In order to demonstrate the precision with which rate parameters may be extracted using this technique it was arbitrarily decided to allow all the error to appear in the rate coefficient for step 2. The rate coefficients for step 2 as a function of pH are shown in Figure 2 and it is seen that excellent linearity occurs. The differential equations and unscaled flow diagram are given in the Appendix. The rate constants for the four reactions are given in Table 2.

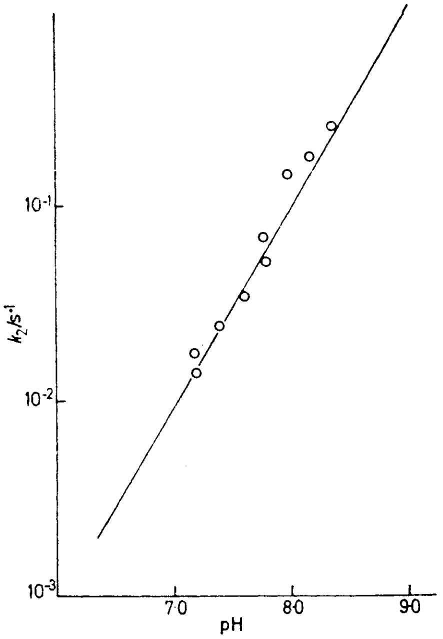


FIGURE 2 Rate of breakdown of phosphonylated oxime by path 2 as a function of pH

TABLE 2

Rate constants for the PF–OX reaction at $I = 0{\cdot}1$, 25·0° in 5% EtOH–H_2O

Step	Reactants	k/l mol^{-1} s^{-1}
1	PF + OX anion	1·2
2	Phosphoryl OX + hydroxide ion	$9{\cdot}0 \times 10^4$
3	Phosphoryl OX + OX anion	3·3
4	PF + hydroxide ion	38

It is appreciated that with such a complex reaction scheme as proposed here, one can claim no more than that the developed kinetic scheme is consistent with the data. However, attempts to postulate other reaction schemes which are consistent with the data but which are not more complex have been unsuccessful.

Mechanisms of the Reactions of PF and OX.—Comparison of the rate constant for the reaction of OX anion and PF with the rate constants obtained by Green and Saville [1] shows that OX acts as a typical oxime and hence no further discussion of this reaction is needed.

The direction of breakdown of phosphorylOX is that expected from a consideration of the relative electron densities of the two carbonyl groups and is the same as that observed in the hydrolysis of benzoic acetic anhydride.[5] The production of ethyl benzoate has pointed to, but not proved, the initial formation of

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[5] P. S. Bailey and Y.-G. Chang, *J. Org. Chem.*, 1962, **27**, 1192.

benzoyl cyanide in contrast to the conclusions of Green and Saville regarding their comparable reactions.[1] If nucleophilic attack upon a carbonyl group was the rate-limiting step it would be expected that a ratio of second-order rate constants for the hydroxide and OX anion reactions of <50 would be observed as is the case with displacement of fluoride ion from PF. A ratio of *ca.* 1 for hydroxide ion and an oxime with pK_a close to that of OX is found for reaction with *p*-nitrophenyl acetate.[6] The observed ratio of second-order rate constants for the hydroxide and OX anion reactions with phosphorylOX is *ca.* 3×10^4, but this unfortunately does not help with the elucidation of the reaction mechanism as the same arguments of steric hindrance and/or desolvation of the transition state or initial adduct can be used for mechanisms involving either rate-limiting nucleophilic attack or a pre-equilibrium nucleophilic addition followed by a rate-limiting disproportionation.

Although an absolute measure of the relative leaving group tendencies of the acetyl and phosphoryl groups cannot be made with the present data, the superiority of the acetyl group is shown in two ways. The rate of breakdown of acetylOX is too rapid to be measured in contrast to phosphorylOX. The lack of participation of OX in the breakdown of acetylOX is probably due to the neutral or water catalysed hydrolysis contributing to the overall rate to such an extent that the OX reaction is negligible. This is to be expected if acetyl is superior to phosphoryl in leaving group ability. The relative poorness of the phosphoryl group is probably caused by delocalisation of charge on the phosphorus owing to $d_\pi - p_\pi$ bonding but more work involving a variety of phosphorus compounds is necessary in order to understand the mechanism in detail.

APPENDIX

The differential equations appropriate to Scheme 2 are as follows:

$$d[OX]/dt = -k_1 f_{OX}[\overline{OX}][PF] - k_3 f_{OX}[\overline{OX}][PO] + k_5[PO]$$

$$d[PF]/dt = -k_1 f_{OX}[\overline{OX}][PF] - k_4[PF]$$

$$d[PO]/dt = k_1 f_{OX}[\overline{OX}][PF] - k_2[PO] - k_3 f_{OX}[\overline{OX}][PO] - k_5[PO]$$

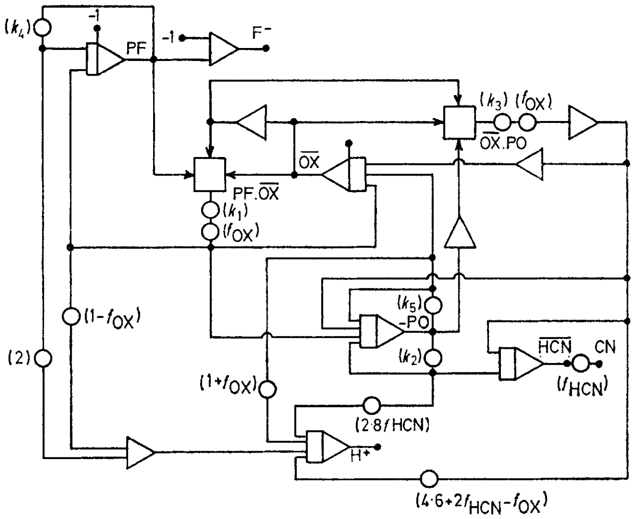

FIGURE 3 Unscaled flow diagram for the PF–OX system

$$d[HCN]/dt = k_2[PO] + 2k_3 f_{OX}[\overline{OX}][PO]$$

$$d[H^+]/dt = k_1 f_{OX}[\overline{OX}][PF](1 - f_{OX}) + k_2[PO](2{\cdot}8 + f_{HCN}) + k_3 f_{OX}[\overline{OX}][PO](4{\cdot}6 + 2f_{HCN} - f_{OX}) + 2k_4[PF] + k_5[PO](1 + f_{OX})$$

$[\overline{X}]$ Indicates the total concentration of the compound, f_X indicates the fraction of X ionised at that pH.

[3/1247 *Received*, 14*th June*, 1973]

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[6] W. P. Jencks and J. Carriuolo, *J. Amer. Chem. Soc.*, 1960, **82**, 1778.