Subsequent purification procedures as outlined above yielded white platelets of dianilinium phosphate (m.p. 182–183° dec.).

Anal. Calcd. for $C_{12}H_{17}O_4N_2P$: P, 10.9; neut. equiv., 142.12. Found: P, 10.8; neut. equiv., 141.1.

LOS ANGELES 24, CALIFORNIA

[CONTRIBUTION FROM THE RESEARCH DEPARTMENT OF WESTVACO CHLOR-ALKALI DIVISION OF FOOD MACHINERY AND CHEMICAL CORPORATION]

The Synthesis of Monovinyl Esters of Phosphorus(V) Acids

BY J. FORREST ALLEN AND OSCAR H. JOHNSON

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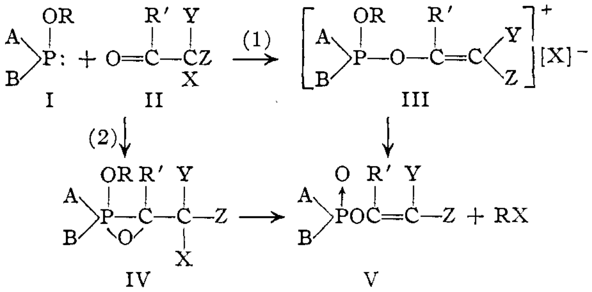
The reaction of completely esterified acids of trivalent phosphorus containing at least one alkyl ester group with α-halogenated aldehydes, ketones, and some carboxylic acid esters and amides produces a monovinyl ester of the corresponding pentavalent phosphorus acid.

Several investigators have attempted to use α-halo ketones[1] and esters[2] instead of alkyl halides in the Michaelis–Arbuzov reaction involving esters of phosphorus(III) acids, but in all cases the products have been assumed to be phosphonates of the type expected from a normal Michaelis–Arbuzov reaction. When this work was begun no one had reported the reaction of a polyhalogen compound of the type under consideration with a completely esterified acid of trivalent phosphorus, but recently ethyl trichloroacetate[2f] and chloral[3] have been reported to yield phosphonates, and even more recently chloral,[4a] bromal[4a] and methyl 2-chloroacetoacetate[4b] have been reported to yield vinyl phosphates. It has been shown in this Laboratory also that α-halogenated aldehydes, ketones, and the esters and amides of certain carboxylic acids react with completely esterified acids of trivalent phosphorus to form vinyl esters of the corresponding pentavalent phosphorus acid. The proof of structure of these compounds will be given in detail in another paper, but the structure assignment rests upon the following experimental facts: (a) In the independent synthesis of diethyl vinyl phosphate by the dehydrobromination of diethyl 2-bromoethyl phosphate the product obtained was identical with that obtained by the reaction of triethyl phosphite and chloroacetaldehyde. (b) The products show strong infrared absorption at 6.1 μ which is characteristic of the ethylenic double bond. (c) Diethyl vinyl phosphate, obtained from triethyl phosphite and chloroacetaldehyde, was hydrogenated over a nickel catalyst to triethyl phosphate. (d) The products add chlorine and bromine to form dihalides. (e) Hydrolysis of the product obtained from chloral and triethyl phosphite gave dichloroacetaldehyde.

The reaction may involve a nucleophilic attack by the phosphorus atom on the oxygen of the carbonyl compound (mechanism 1) and the simultaneous expulsion of a chloride ion from the latter. In most cases a stable intermediate is not obtained, but intermediates have been obtained when the phosphorus compound has phosphorus in a ring system (*e.g.*, I, A + B = OCH_2CH_2O). This mechanism is unusual in that it represents the normally nucleophilic oxygen atom of the carbonyl group as being electrophilic. Furthermore, this mechanism would be expected to involve an intermediate having the structure III, but the infrared spectrogram prepared from a mineral oil mull of the intermediate resulting from chloral and ethyl ethylene phosphite did not show the absorption at 6.1 μ which is characteristic of the vinyl or substituted vinyl phosphates, and chloride ion was not precipitated by methanolic silver nitrate. A second possible mechanism (2) involves a nucleophilic attack by the phosphorus atom on the carbonyl carbon and a similar attack by the carbonyl oxygen on the phosphorus to form a 3-membered ring (IV) of the type suggested by Conant and MacDonald.[5]



Of the various classes of phosphorus compounds which would be expected to enter into this reaction, only phosphites, amidophosphites, phosphonites and phosphinites have been investigated. The limitations of the reaction with respect to the phosphorus compound appears to be about the same as observed with the Michaelis–Arbuzov reaction. Aromatic esters do not react, at least under normal conditions, but mixed aliphatic and aromatic esters react readily. For example, triphenyl phos-

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[1] (a) A. E. Arbuzov and A. I. Razumov, *J. Gen. Chem.* (*U.S.S.R.*), **4**, 834 (1934); (b) A. I. Razumov and N. Petrov, *Trudy Kazan. Khim.-Tekhnol. Inst.*, **10**, 35 (1946); (c) B. A. Arbuzov, B. P. Lugovkin and N. P. Bogonostseva, *J. Gen. Chem.* (*U.S.S.R.*), **20**, (8) 1468 (1950); (d) Norman D. Dawson and Alfred Burger, THIS JOURNAL, **74**, 5312 (1952).

[2] (a) A. E. Arbuzov and A. A. Dunin, *J. Russ. Phys.-Chem. Soc.*, **46**, 295 (1914); (b) G. M. Kosolapoff, THIS JOURNAL, **68**, 1103 (1946); (c) A. E. Arbuzov and G. Kamai, *J. Gen. Chem.* (*U.S.S.R.*), **17**, 2149 (1947); (d) Richard H. Wiley, U. S. Patent 2,478,441 (1949); (e) G. Kamai and E. Sh. Bastanov, *Zhur. Obshchei Khim.* (*J. Gen. Chem.*), **21**, 2188 (1951); (f) Denham Harmon and Roy E. Thorpe, U. S. Patent 2,614,990 (1952).

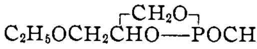
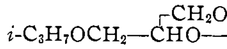
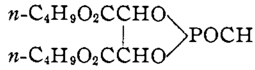
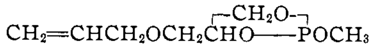
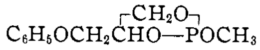
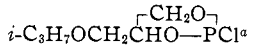
[3] (a) A. E. Arbuzov and P. I. Alimov, *Izvest. Akad. Nauk S.S.S.R.*, *Otdel. Khim. Nauk*, 530 (1951); (b) Elbert C. Ladd and Merlin P. Harvey, U. S. Patent 2,597,938 (1952); (c) Elbert C. Ladd and Merlin P. Harvey, U. S. Patent 2,631,162 (1953).

[4] (a) Werner Perkow, *Chem. Ber.*, **87**, 755 (1954); (b) Alan R. Stiles, U. S. Patent 2,685,552 (1954).

[5] J. B. Conant and A. D. MacDonald, THIS JOURNAL, **42**, 2337 (1920).

TABLE I

TRIVALENT PHOSPHORUS COMPOUNDS

Formula	Yield, %	Phosphorus, % Calcd.	Phosphorus, % Found	B.p., °C.	B.p., Mm.	$n^{35}D$
$(C_2H_5O)_2POC_6H_5$	50	14.5	14.3	63–85	1	1.4835
$(p\text{-}t\text{-}C_4H_9C_6H_4O)_2POCH_3$	69	8.6	8.6	173–179	0.1	....
 $C_2H_5OCH_2\overbrace{CHO\text{—}POCH_3}^{CH_2O}$	59	17.2	17.2	85–95	10	1.4378
 $i\text{-}C_3H_7OCH_2\text{—}\overbrace{CHO\text{—}POCH_3}^{CH_2O}$	88	16.0	15.6	90–100	10	1.4378
 $\left.\begin{array}{l} n\text{-}C_4H_9O_2CCHO \\ \quad\;\; \vert \\ n\text{-}C_4H_9O_2CCHO \end{array}\right\rangle POCH_3$	80	9.6	9.2	.....	..	....
 $CH_2{=}CHCH_2OCH_2\overbrace{CHO\text{——}POCH_3}^{CH_2O}$	89	16.1	16.2	74–76	1	1.4580
 $C_6H_5OCH_2\overbrace{CHO\text{—}POCH_3}^{CH_2O}$	76	13.6	13.2	118–135	1	....
$(CH_2)_3O_2POCH_3$	59	22.8	23.3	65–80	20	....
$(n\text{-}C_4H_9S)_3P$	65	10.4	10.5	145–168	2	....
 $i\text{-}C_3H_7OCH_2\overbrace{CHO\text{—}PCl}^{CH_2O}$[a]	71	15.6	15.6	82–92	5	1.4583

[a] Chlorine, calcd. 17.9; found 17.1.

phite and chloral did not react when equimolar quantities of the compounds were refluxed, but ethyl diphenyl phosphite reacted readily with chloral at temperatures above 45° to yield dichlorovinyl diphenyl phosphate and ethyl chloride. Esters of tertiary alcohols do not react normally but form an olefin instead, a behavior analogous to the reaction of alkyl halides and tri-*t*-butyl phosphite.[6] Trithiophosphites, which do not give a normal Michaelis–Arbuzov reaction, do not react with chloral to form dichlorovinyl thiophosphates, although alkyl chloride is a by-product of the reaction. An infrared trace of the product obtained from chloral and tributyl trithiophosphite did not show absorption at 6.1 μ, but the product obtained from chloral and triethyl dithiophosphite did absorb at 6.1 μ, indicating that at least some vinyl ester was formed.

A further similarity between the vinyl ester reaction and the Michaelis–Arbuzov reaction is to be found in the reactions involving phosphites containing phosphorus in a ring system. Arbuzov and co-workers[7] reported that alkyl ethylene phosphites (I, A + B = ethylenedioxy) reacted with alkyl halides by ring cleavage but that substitution in the ethylene radical stabilized the ring and alkyl halide was obtained. Similar results were reported by Mitchell and Lucas[8] who found that isopropyl propylene phosphite did not undergo ring cleavage in the reaction with 1-bromopentane. We have found that chloral reacts with ethyl ethylene phosphite by ring cleavage since no ethyl chloride is obtained as by-product but reaction of chloral with ethyl propylene phosphite gave a 22% yield of ethyl chloride. The alkyl radical, however, is important in determining the course of the reaction and methyl is cleaved more readily than ethyl and therefore favors retention of the ring structure. Chloral reacted with methyl ethylene phosphite and with methyl propylene phosphite to give, respectively, 22 and 68% yields of methyl chloride. Isopropyl ethylene phosphite, however, gave propylene and no isopropyl chloride. As would be expected, enlarging the ring increases the stability in both the reaction with alkyl halides[7] and with chloral, and in reactions with the latter methyl trimethylene phosphite gave 65% methyl chloride and methyl tetramethylene phosphite gave 45% methyl chloride. But substitution even in the larger rings increases the stability and methyl 1-methyltrimethylene phosphite gave 97% methyl chloride.

The formation of stable intermediates in the vinyl ester reaction has been observed only with alkyl ethylene phosphites. When chloral and triethyl phosphite are mixed at 0°, or even lower, a strongly exothermic reaction occurs and ethyl chloride can be obtained immediately by reducing the pressure, but the reaction of ethyl ethylene phosphite and chloral at ordinary temperatures, while exothermic, results in a liquid which soon becomes a waxy solid. Upon heating, the solid melts and at about 130–140° a second strongly exothermic reaction begins.

Of the halogenated carbonyl compounds which have been investigated, chloral and bromal react most readily and the reactivity decreases as the number of halogen atoms on the α-carbon atom decreases. Ketones react less readily than aldehydes and esters are considerably less reactive than ketones. Ethyl trichloroacetate at 50° gave a mildly exothermic reaction with triethyl phosphite to form diethyl 2,2-dichloro-1-ethoxyvinyl phosphate, but ethyl dichloroacetate reacted slowly with triethyl phosphite even at 160° to give a mixture boiling over a wide range and no identifiable product was isolated except ethyl chloride. Diethyl bromomalonate and diethyl dibromomalonate, however, reacted readily with triethyl phosphite at 25° to form the vinyl esters. There was a slight exothermic effect when N,N-diethyltrichloroacetamide and triethyl phosphite were mixed at ordinary temperature, but ethyl chloride was not obtained below 125° when the temperature was raised rapidly. The product was not obtained in pure form but an infrared spectrogram revealed intense absorption at 6.1 μ. An interesting example of vinylogy is in the reac-

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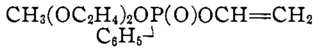
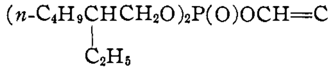
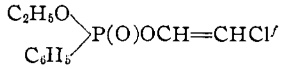
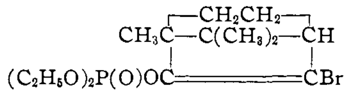
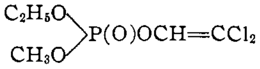
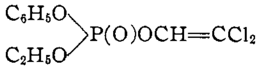
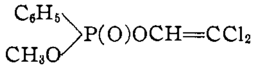
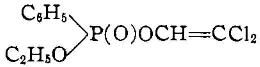
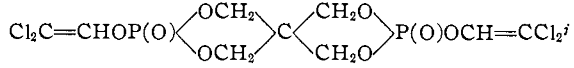
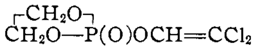
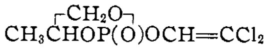
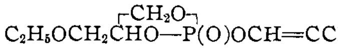
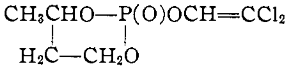
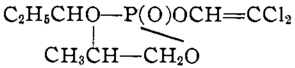
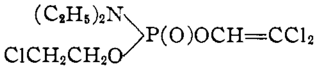
[6] G. M. Kosolapoff, THIS JOURNAL, **74**, 4953 (1952).

[7] A. E. Arbuzov, V. M. Zoroastrova and N. I. Rizpolozhenskii, *Bull. acad. sci. U.R.S.S., Classe sci. chim.*, 208 (1948).

[8] F. W. Mitchell, Jr., and H. J. Lucas, THIS JOURNAL, **72**, 5779 (1950).

TABLE II

VINYL ESTERS OF PHOSPHORUS(V) ACIDS

	Precursors[l]			Halogen, %		Phosphorus, %		B.p.,	
Formula	P cmpd.	Carbonyl cmpd.	Yield, %	Calcd.	Found	Calcd.	Found	°C.	Mm.
$(C_2H_5O)_2P(O)OCH{=}CH_2$	1	2	67	..	..	17.2	17.1	79	6
$(C_2H_5O)_2P(O)OC(CH_3){=}CH_2{}^{a}$	1	3	56	..	..	16.0	16.1	72–73	1
$(C_2H_5O)_2P(O)OC(CH_2Cl){=}CH_2$	1	4	82	15.5	16.0	13.6	13.7	76–89	1
$(C_2H_5O)_2P(O)OCH{=}CHCH_2Cl$	1	5	100	15.5	16.6	13.6	13.7	....	...
$(C_2H_5O)_2P(O)OCH{=}CHCHClC_6H_5$	1	6	100	11.6	12.0	10.2	10.6	......	..
 $\underset{C_6H_5}{CH_3(OC_2H_4)_2O}P(O)OCH{=}CH_2$	7	2	100	..	..	10.8	10.9	....	..
$(C_2H_5O)_2P(O)OCH{=}CHCl^{b}$	1	8	54	16.5	16.5	14.4	14.9	92–105	1–2
$(n\text{-}C_3H_7O)_2P(O)OCH{=}CHCl^{c}$	9	8	56	14.6	13.4	12.8	12.7	94–100	0.1
$(\text{Iso-}C_3H_7O)_2P(O)OCH{=}CHCl^{d}$	10	8	37	14.6	14.7	12.8	12.0	74–87	0.1
 $(n\text{-}C_4H_9\underset{C_2H_5}{CH}CH_2O)_2P(O)OCH{=}CHCl^{e}$	11	8	82	9.3	8.3	8.1	7.8	156–173	0.1
 $\begin{matrix}C_2H_5O\\C_6H_5\end{matrix}{>}P(O)OCH{=}CHCl^{f}$	12	8	79	14.4	14.4	12.6	12.1	118–134	0.1–0.4
$(ClCH_2CH_2O)_2P(O)OCH{=}CHCl$	13	8	70	37.5	37.5	10.9	11.1	152–157	1
	1	14	81	21.8	20.6	8.4	8.3	.....	..
$(C_2H_5O)_2P(O)OC(CH_3){=}CClCO_2C_2H_5$	1	15	68	11.8	11.3	10.3	10.5	120–128	1
$(C_2H_5O)_2P(O)OCH{=}CClCHClCH_3$	1	16	49	25.6	24.9	11.2	11.3	*ca.* 80	0.01
$(CH_3O)_2P(O)OCH{=}CCl_2$	18	17	53	32.1	31.2	14.0	14.5	74–87	2
 $\begin{matrix}C_2H_5O\\CH_3O\end{matrix}{>}P(O)OCH{=}CCl_2$	19	17	67	30.2	29.6	13.2	13.2	80–96	1
$(C_2H_5O)_2P(O)OCH{=}CCl_2$	1	17	38	28.5	28.6	12.4	12.4	114.5–115	5
$(n\text{-}C_3H_7O)_2P(O)OCH{=}CCl_2$	9	17	75	25.6	24.3	11.2	11.0	109–123	3
$(\text{Iso-}C_3H_7O)_2P(O)OCH{=}CCl_2{}^{g}$	10	17	62	25.6	25.5	11.2	11.4	96.5	2
$(n\text{-}C_4H_9O)_2P(O)OCH{=}CCl_2$	20	17	80	23.2	21.7	10.2	10.2	107–121	0.5
$(n\text{-}C_4H_9CH(C_2H_5)CH_2O)_2P(O)OCH{=}CCl_2$	11	17	100	17.0	16.7	7.4	7.4	....	..
$(ClCH_2CH_2O)_2P(O)OCH{=}CCl_2{}^{h}$	13	17	68	44.6	43.1	9.7	9.7	93–112	0.1
$[CH_3(OCH_2CH_2)_2O]_2P(O)OCH{=}CCl_2$	21	17	75	17.9	17.9	7.8	7.8	......	..
 $\begin{matrix}C_6H_5O\\C_2H_5O\end{matrix}{>}P(O)OCH{=}CCl_2$	22	17	84	23.9	24.6	10.4	10.3	116–130	0.5
$(p\text{-}t\text{-}C_4H_9C_6H_4O)_2P(O)OCH{=}CCl_2$	23	17	89	15.5	14.4	6.8	7.1	......	..
$(C_2H_5O)_2P(O)OCH{=}CBr_2$	1	24	48	47.3	45.1	9.2	9.2	*ca* 100	0.15
$(C_2H_5O)_2P(O)OC(OC_2H_5){=}CCl_2{}^{i}$	1	25	53	24.2	23.6	10.6	10.9	120–127	1
 $\begin{matrix}C_6H_5\\CH_3O\end{matrix}{>}P(O)OCH{=}CCl_2$	26	17	73	26.6	25.6	11.6	11.5	125–137	1
 $\begin{matrix}C_6H_5\\C_2H_5O\end{matrix}{>}P(O)OCH{=}CCl_2$	12	17	68	25.2	25.2	11.0	11.1	131–144	2–3
	27	17	68	31.5	30.2	13.8	13.6	.....	..
$(C_2H_5O)_2P(O)OC(C_6H_5){=}CH{-}CH{=}CCl_2$	1	28	100	20.2	20.2	8.8	8.8	.....	..
	29	17	24	32.4	32.2	14.1	13.8	110–117	0.5
	30	17	54	30.4	29.5	13.3	13.5	118–123	2
	31	17	99	25.6	26.3	11.2	10.8	.....	..
	32	17	97	28.7	29.1	12.5	12.6	132–140	1
	33	17	81	25.8	24.5	11.3	10.9	.....	..
$[(CH_3)_2N]_2P(O)OCH{=}CCl_2{}^{k}$	34	17	67	28.7	27.8	12.5	12.5	90–95	1
$[(C_2H_5)_2N]_2P(O)OCH{=}CCl_2$	35	17	74	23.4	22.8	10.2	10.6	115–125	1
 $\begin{matrix}(C_2H_5)_2N\\ClCH_2CH_2O\end{matrix}{>}P(O)OCH{=}CCl_2$	36	17	73	34.3	33.5	10.0	9.9	113–123	0.2

[a] n^{35}D 1.4135, d^{35}_4 1. 0579. [b] n^{35}D 1.4276. [c] n^{25}D 1.4364. [d] n^{25}D 1.4307. [e] n^{25}D 1.4492. [f] n^{25}D 1.5174. [g] n^{35}D 1.4372, d^{35}_4 1.1924. [h] n^{35}D 1.4820. [i] n^{25}D 1.4173. [j] M.p. 130–132° (uncor.; recryst. from 2-propanol). [k] n^{35}D 1.4708, d^{35}_4 1.2432. [l] Precursors: 1, triethyl phosphite; 2, chloroacetaldehyde; 3, chloroacetone; 4, sym-dichloroacetone; 5, 2,3-dichloropropanal; 6, 2,3-dichloro-3-phenylpropanal; 7, bis-(methoxyethoxyethyl) phenylphosphonite; 8, dichloroacetaldehyde; 9, tripropyl phosphite; 10, triisopropyl phosphite; 11, tris-2-ethylhexyl phosphite; 12, diethyl phenylphosphonite; 13, tris-chloroethyl phosphite; 14, dibromocamphor; 15, ethyl 2,2-dichloroacetoacetate; 16, 2,2,3-trichlorobutanal; 17, chloral; 18, trimethyl phosphite; 19, ethyl dimethyl phosphite; 20, tributyl phosphite; 21, trismethoxyethoxyethyl phosphite; 22, diethyl phenyl phosphite; 23, ethyl bis-*p*-*t*-butylphenyl phosphite; 24, bromal; 25, ethyl trichloroacetate; 26, dimethyl phenylphosphonite; 27, diethyl pentaerythrityl diphosphite; 28, phenyl 3,3,3-trichloropropenyl ketone; 29, ethylene methyl phosphite; 30, methyl propylene phosphite; 31, 3-ethoxypropylene methyl phosphite; 32, methyl 1-methyltrimethylene phosphite; 33, 1-ethyl-2-methyltrimethylene methyl phosphite; 34, ethyl tetramethylphosphorodiamidite; 35, ethyl tetraethylphosphorodiamidite; 36, ethylene diethylphosphoramidite.

tions of triethyl phosphite with phenyl trichloromethyl ketone and with its vinylog, phenyl 3,3,3-trichloropropenyl ketone.

Experimental

Preparation of Phosphorus(III) Esters.—The glycol esters were prepared by the two-step method of Lucas, Mitchell and Scully[9] which involves the use of methylene chloride as solvent in the preparation of the chlorophosphite. In the conversion of the latter to the tertiary ester we preferred triethylamine or diethylaniline as the base. The preparation of tertiary phosphites from phosphorus trichloride and monohydric alcohols made use of hexane as solvent and triethylamine or diethylaniline as base.[10] Phosphites with mixed radicals, $(RO)_2POR'$, were prepared from the appropriate dichlorophosphite, $R'OPCl_2$, and 2 moles of alcohol or phenol, ROH, in the usual manner. Many of these esters were not isolated in purified form and Table I contains only new compounds having a reasonable degree of purity.

Preparation of Vinyl Esters.—The following examples illustrate the preparation of vinyl phosphates, amidophosphates, phosphonates and phosphinates. Other examples are shown in Table II. *Caution: Many substituted vinyl phosphates are powerful cholinesterase inhibitors and therefore highly toxic.*

Diethyl Vinyl Phosphate.—Four moles (665 g.) of triethyl phosphite was added gradually with stirring to 4 moles (314 g.) of chloroacetaldehyde over a period of 40 minutes with sufficient cooling to keep the temperature at 50 to 60°. The mixture then was heated to 110° and 178 g. (70%) of ethyl chloride (b.p. 13°) obtained in a cold trap. Fractionation of the product by means of a 2-foot column packed with glass helices gave a 67% yield of diethyl vinyl phosphate, b.p. 79° (6 mm.), n^{35}D 1.4100, and d^{35}_4 1.0724.

Anal. Calcd. for $C_6H_{13}O_4P$: P, 17.2. Found: P, 17.1.

Bis-2-chloroethyl 2-Chlorovinyl Phosphate.—To 56.5 g. (0.5 mole) of technical dichloroacetaldehyde (containing about 15% of chloral) there was gradually added 134.8 g. (0.5 mole) of tris-2-chloroethyl phosphite at about 40°. Mild cooling of the reaction mixture was necessary until about 75% of the phosphite had been added. When addition was complete the temperature was raised gradually to 120° with distillation of ethylene chloride (37.8 g., 77% yield). Distillation of the product gave 100 g. (70% yield), of bis-2-chloroethyl 2-chlorovinyl phosphate, b.p. 152–157° (1 mm.).

Anal. Calcd. for $C_6H_{10}O_4Cl_3P$: Cl, 37.5; P, 10.9. Found: Cl, 37.2; P, 11.1.

Diethyl 2,2-Dichlorovinyl Phosphate.—Four moles (589.6 g.) of chloral was cooled to 8° and 4 moles (664.8 g.) of technical grade triethyl phosphite added over a two-hour period with cooling by an ice–salt-bath to keep the temperature below 26°. Gradual heating of the product led to the evolution of ethyl chloride (206 g., 80% yield) from 40 to 115°. Rectification of the product through a 20-inch column packed with glass helices gave a 38% yield of diethyl 2,2-dichlorovinyl phosphate, b.p. 114.5–115° (5 mm.), n^{35}D 1.4428, d^{35}_4 1.2821.

Anal. Calcd. for $C_6H_{11}O_4Cl_2P$· Cl, 28.5; P, 12.4. Found: Cl, 28.6; P, 12.4.

2,2-Dichlorovinyl Ethyl Phenylphosphonate.—Diethyl phenylphosphonite (0.37 mole) was added gradually with cooling to chloral (0.37 mole) at 23–28°. Distillation of the product gave 71.0 g. (68% yield) of dichlorovinyl ethyl phenylphosphonate, b.p. 131–144° (2–3 mm.).

Anal. Calcd. for $C_{10}H_{11}P_3Cl_2P$: Cl, 25.2; P, 11.0. Found: Cl, 25.2; P, 11.1.

Diethyl 1-(Chloromethyl)-vinyl Phosphate.—To 50 g. (0.4 mole) of *sym*-dichloroacetone cooled to 40 to 50° there was added gradually 66 g. (0.4 mole) of triethyl phosphite. The temperature then was raised to 100° and 21.6 g. of ethyl chloride (85% yield) obtained in a cold trap. Distillation of the product gave an 82% yield of diethyl 1-(chloromethyl)-vinyl phosphate, b.p. 76–89° (1 mm.). The sample analyzed was collected at 84°.

Anal. Calcd. for $C_7H_{14}O_4ClP$: Cl, 15.5; P, 13.6. Found: Cl, 16.0; P, 13.7.

2,2-Dichlorovinyl Tetraethylphosphorodiamidate.—Ethyl tetraethylphosphorodiamidite (0.35 mole) was added gradually to chloral (0.35 mole) with cooling at 15 to 25°. When the reaction mixture was heated to 45° ethyl chloride began collecting in the cold trap and at 100° the weight of ethyl chloride obtained was 15 g. (66% yield). Distillation of the product gave 78.3 g. of 2,2-dichlorovinyl tetraethylphosphorodiamidate (74% yield) from 115–125° (1 mm.).

Anal. Calcd. for $C_{10}H_{21}N_2O_2Cl_2P$: Cl, 23.4; P, 10.2. Found: Cl, 22.8; P, 10.6.

Ethylene 2,2-Dichlorovinyl Phosphate.—The gradual addition of 24.4 g. (0.2 mole) of methyl ethylene phosphite to 29.5 g. of chloral (0.2 mole) at 20–45° gave a strongly exothermic reaction, but methyl chloride was not obtained at 125°. Distillation gave 13 g. (24% yield) of 2,2-dichlorovinyl ethylene phosphate, b.p. 110–117° (0.5 mm.).

Anal. Calcd. for $C_4H_5O_4Cl_2P$: Cl, 32.4; P, 14.1. Found: Cl, 32.2; P, 13.8.

When this reaction was carried out on a larger scale (12 moles), the reaction mixture became solid when about one-third of the phosphite had been added. Upon heating, the solid melted at about 90° and at 140° an exothermic reaction occurred with the formation of methyl chloride (22% yield).

2,2-Dichloro-1-ethoxyvinyl Diethyl Phosphate.—One mole of triethyl phosphite (166 g.) was added rapidly to 1 mole (191.5 g.) of ethyl trichloroacetate at 25°. The temperature rose slowly and mild cooling was necessary to maintain the temperature at 75–80°. When heat was no longer evolved the reaction mixture was heated to 100° for 30 minutes. The yield of ethyl chloride was 87% and distillation of the main product followed by redistillation through a 10-inch Vigreux column gave 155 g. (53% yield) of 2,2-dichloro-1-ethoxyvinyl diethyl phosphate, b.p. 120–127° (1 mm.), n^{35}D 1.4437, and d^{35}_4 1.2485.

Anal. Calcd. for $C_8H_{15}O_5Cl_2P$: Cl, 24.2; P, 10.6. Found: Cl, 23.6; P, 10.9.

2-Chlorovinyl Diphenylphosphinate.—To 7.24 g. of dichloroacetaldehyde (0.064 mole) was added over a period of ten minutes 13.8 g. (0.064 mole) of ethyl diphenylphosphinite. The mixture was not cooled during the mixing operation and the temperature rose from 10 to 77°. The product then was heated to 115° and the ethyl chloride (72% yield) removed *in vacuo*. The yield of crude product was 17 g. (100.8%).

Anal. Calcd. for $C_{14}H_{12}O_2ClP$: Cl, 12.7; P, 11.1. Found: Cl, 13.0; P, 11.0.

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[9] H. J. Lucas, F. W. Mitchell, Jr., and C. N. Scully, THIS JOURNAL, **72**, 5491 (1950).

[10] Most of the triethyl phosphite used in this work was technical grade product obtained from the Virginia–Carolina Chemical Corporation.

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[CONTRIBUTION FROM THE WESTERN UTILIZATION RESEARCH BRANCH, AGRICULTURAL RESEARCH SERVICE, UNITED STATES DEPARTMENT OF AGRICULTURE]

Reaction-Inactivation of Polyphenol Oxidase: Catechol and Oxygen Dependence

BY LLOYD L. INGRAHAM

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Further studies of the reaction-inactivation of polyphenol oxidase have shown that both the reaction-inactivation and enzymatic oxidation of catechol have the same Michaelis–Menten dependence on catechol concentration and oxygen pressure. This is interpreted as meaning that the reaction-inactivation and oxidation mechanism are identical until the enzyme–semiquinone complex is formed. These results are in agreement with the previously proposed idea that the enzyme–semiquinone complex may decompose by either of two pathways: (1) to active enzyme and semiquinone or (2) to inactive enzyme.

During the polyphenol oxidase catalyzed aerobic oxidation of catechol the enzyme activity gradually decreases and finally disappears after about 20 minutes. This effect, called reaction-inactivation,[1] has been shown in previous research to depend upon the first power of the enzyme concentration.[2]

It has been proposed that the reaction-inactivation is due to the possibility that the enzyme–semiquinone complex may decompose by either of two pathways: (1) to active enzyme and semiquinone or (2) to inactive enzyme by an internal oxidation–reduction reaction. The over-all mechanism would be described by the reactions[3]

$$\mathrm{E} + \mathrm{O_2} \rightleftarrows \mathrm{EO_2} \text{ or } \mathrm{E_0} + \mathrm{H_2O}$$
$$\mathrm{E_0} + \mathrm{C} \rightleftarrows \mathrm{E_0C}$$
$$\mathrm{E_0C} \rightleftarrows \mathrm{ES}$$
$$\mathrm{ES} \longrightarrow \mathrm{E} + \mathrm{S}$$
$$\mathrm{ES} \longrightarrow \text{inactive enzyme}$$

where E is reduced enzyme, E_0 is oxidized enzyme, C is catechol, S is semiquinone and O_2 is oxygen. If this mechanism holds, the formation of product must have a Michaelis–Menten dependence on not only the catechol concentration but also the oxygen concentration. In addition, however, the reaction-inactivation must also have a Michaelis–Menten dependence on both catechol concentration and oxygen pressure. The integrated rate equation which includes the dependence on catechol concentration and oxygen pressure may be derived in the same manner as equation 1 which is only valid for the experimental conditions where the oxidation is zero order in catechol concentration and oxygen pressure.

$$Q = \frac{k_0'E_0}{}[1 - e^{-k_I't}] \qquad (1)$$

This equation shows how the amount of oxidation, Q, varies in time, t, at given initial concentration of enzyme, E_0. The "constants" k_0' and k_1' are the rate constants for oxidation and inactivation, respectively, which also include the catechol and oxygen dependence of each reaction. If we substitute $k_0' = k_0f(\mathrm{C,O})$ and $k_1' = k_1g(\mathrm{C,O})$ where $f(\mathrm{C,O})$ is the Michaelis–Menten dependence the oxidation reaction has on catechol and oxygen and $g(\mathrm{C,O})$ is the Michaelis–Menten dependence the inactivation has on catechol and oxygen in the rate equations used to derive equation 1, the integration of the rate equation is not affected. This is because the catechol concentration and oxygen pressure are kept constant during the reaction in our experiments. The catechol concentration is kept constant by adding enough ascorbic acid to the reaction mixture to continually reduce any semiquinones or *o*-quinones formed back to catechol and the oxygen pressure is kept constant by passing a slow stream of an oxygen–nitrogen gas mixture through the reaction mixture. Since the integration is not affected by the substitution one may in effect substitute the values for k_0' and k_1' in equation 1 to obtain equation 2

$$Q = \frac{k_0f(\mathrm{C,O})E_0}{k_Ig(\mathrm{C,O})}[1 - e^{-k_Ig(\mathrm{C,O})t}] \qquad (2)$$

which holds at all concentrations of catechol and all oxygen pressures. Equation 2 predicts, as one would expect, that the initial rate of reaction

$$\left(\frac{\mathrm{d}Q}{\mathrm{d}t}\right)_{t=0} = k_0E_0f(\mathrm{C,O}) \qquad (3)$$

has a Michaelis–Menten relationship on both catechol concentration and oxygen pressure. However, equation 2 also predicts that if our proposed mechanism is valid, then the ultimate amount of oxidation

$$\lim_{t\to\infty} Q = \frac{k_0f(\mathrm{C,O})E_0}{k_Ig(\mathrm{C,O})} = \frac{k_0E_0}{k_I} \qquad (4)$$

is independent of both the catechol concentration and oxygen pressure, since $f(\mathrm{C,O})$ is identical with $g(\mathrm{C,O})$ in the proposed mechanism.

Experimental values of the initial rates of oxidation catalyzed by mushroom enzyme at various percentages of oxygen–nitrogen mixtures are shown in Fig. 1. A locus of the experimental values is found to approximate the theoretical Michaelis–Menten curve corresponding to a maximum activity of 20 and a Michaelis constant of 9% oxygen.

[1] See I. Asimov and C. R. Dawson, THIS JOURNAL, **72**, 820 (1950) and preceding papers.

[2] L. L. Ingraham, J. Corse and B. Makower, *ibid.*, **74**, 2623 (1952).

[3] L. L. Ingraham, *ibid.*, **76**, 3777 (1954).