Tetrahedron. 1967, Vol. 23. pp. 1065 to 1078. Pergamon Press Ltd. Printed in Northern Ireland

SECONDARY PHOSPHINE OXIDES

THE EFFECT OF STRUCTURE ON ACID STRENGTH AND RATES OF CLEAVAGE OF DISULFIDES

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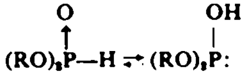
(*Received in U.S.A. 23 April 1966; accepted for publication 19 July 1966*)

Abstract—Second order rate constants for reaction of a series of symmetrical, substituted diarylphosphine oxides and several dialkylphosphine oxides with diphenyl disulfide and acidities of the former in t-butanol and 95% ethanol were measured. Catalysis of the disulfide cleavage by base was observed. Correlation with Hammett substituent constants of both rate and acidity data is reported. A mechanism in which a rapid equilibrium "enolization" of the nucleophilic secondary phosphine oxide group occurs prior to cleavage of the disulfide bond is proposed. The reaction was reversible in the presence of triethylamine.

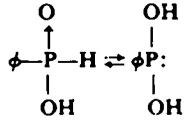
THE question of tautomeric ("keto-enol") equilibrium in the chemistry of dialkylphosphonates (1) and arylphosphinates (2) has been clarified in recent years by kinetic studies of deuterium exchange[1-4] and oxidation reactions.[3,5] Although these compounds are largely pentavalent ("keto") by spectral measurements[4] their exchange and oxidation reactions evidently proceed by prior enolization to the trivalent phosphite form. The analogy with acetone bromination is evident in neutral as well as acid and base catalyzed deuterium exchange and iodine oxidation reactions. The salts of dialkyl phosphonates appear to be entirely trivalent in character by IR[6] and P^{31} NMR[7] measurements, presumably accounting for their enhanced reactivity as compared to the neutral esters.

(1)



$$(RO)_2\overset{\overset{O}{\uparrow}}{P}-H \rightleftharpoons (RO)_2\overset{\overset{OH}{|}}{P}:$$

1



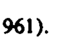
$$\phi-\underset{\underset{OH}{|}}{\overset{\overset{O}{\uparrow}}{P}}-H \rightleftharpoons \phi\underset{\underset{OH}{|}}{\overset{\overset{OH}{|}}{P}}:$$

2

Analogy between 1 and 2 and secondary phosphine oxides (3) has been cited in view of their common structural relation to phosphorous acid (4).[8] However, the

$$R_2\overset{\overset{O}{\uparrow}}{P}-H \rightleftharpoons R_2\overset{\overset{OH}{|}}{P}:$$

3



$$(HO)_2\overset{\overset{O}{\uparrow}}{P}-H$$

4

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[1] Z. Luz and B. L. Silver, *J. Amer. Chem. Soc.* **83**, 4518 (1961).

[2] J. Reuben, D. Samuel and B. L. Silver, *J. Amer. Chem. Soc.* **85**, 3093 (1963).

[3] D. Samuel, *Pure and Appl. Chem.* **9**, 449 (1964) and Refs cited.

[4] W. J. Bailey and R. B. Fox, *J. Org. Chem.* **28**, 531 (1963); *Ibid.* **29**, 1013 (1964); and earlier papers.

[5] P. Nylen, *Z. Anorg. Allgem. Chem.* **235**, 161 (1938).

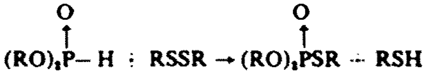
[6] L. W. Daasch, *J. Amer. Chem. Soc.* **80**, 5301 (1958).

[7] K. Moedritzer, *J. Inorg. and Nucl. Chem.* **22**, 19 (1961).

relevance of the prototropy of secondary phosphine oxides to their chemical reactivity has not been systematically investigated. IR evidence clearly indicates the dominant "keto" nature of the aryl and alkyl secondary phosphine oxides.

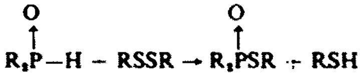
The reaction of secondary phosphine oxides with disulfides was selected as a model system for this investigation in view of the simplicity and clear-cut nature of the reaction as well as an interest in the biologically significant disulfide bond. Analogy between dialkyl phosphonates and secondary phosphine oxides in disulfide cleavage (Eqs 3 and 4) has been established.[9] Qualitatively, the secondary phosphine oxides appeared to be more reactive in that the sodium salt was not required for complete formation of products. The reaction between dialkyl phosphonate salts and disulfides has been reported.[10–12] Foss has in fact suggested that sodium dialkyl phosphonates may be better nucleophiles toward disulfides than cyanide ion.[10] Mechanistically, this type of displacement reaction on sulfur would be expected to proceed by straightforward colinear backside attack in the same manner as with other nucleophiles.[13,14]

(3)



$$(RO)_2\overset{O}{\overset{\uparrow}{P}}-H + RSSR \rightarrow (RO)_2\overset{O}{\overset{\uparrow}{P}}SR + RSH$$

(4)



$$R_2\overset{O}{\overset{\uparrow}{P}}-H + RSSR \rightarrow R_2\overset{O}{\overset{\uparrow}{P}}SR + RSH$$

RESULTS

The reaction of secondary aryl phosphine oxides with diphenyl disulfide was found to proceed smoothly in the absence of bases to give the expected products, thiophenol and the corresponding phenyl diarylphosphinothiolate ester, in good yield (Table 7 Exp. Section). The rates of reaction were followed conveniently by polarographic analysis for thiophenol. t-Butanol was selected as the solvent to permit direct determination of the acidity of the oxides in the same solvent by non-aqueous potentiometric titration. Satisfactory second order rate constants were obtained for each set of reactants at all initial concentration levels studied (0·05–0·4 m/l) up to essentially complete reaction. Acidities of the weaker *p*-methoxy, *p*-methyl and unsubstituted compounds were determined by titration in pyridine and extrapolation to t-butanol by correlation with those compounds which were acidic in both solvents. Kinetic results at equimolar initial concentrations of reactants and apparent p*Ka* data for the oxides are summarized in Table 1. Linear correlations of log k_2 *vs* $\Sigma\sigma p$ (with the exception of *p*-CF_3) and log k_2 *vs* p*Ka* were found as indicated in Figs 1 and 2, respectively (correlation of p*Ka* and σ is described in the Experimental).

When the rate of reaction of bis(*p*-tolyl)phosphine oxide with diphenyl disulfide

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[8] N. B. Colthup, L. H. Daly and S. E. Wiberley, *Introduction to Infrared and Raman Spectroscopy*, pp. 299–300, 402. Academic Press, N.Y. (1964).

[9] K. A. Petrov, N. K. Bliznyuk and I. Yu. Mansurov, *Zh. Obsch. Khem.* 31, 176 (1961).

[10] O. Foss, *Acta Chem. Scand.* 1, 307 (1947); also in *Organic Sulfur Compounds* (Edited by N. Kharasch) Vol. 1. Pergamon Press, London (1961).

[11] J. Michalski and J. Wasiak, *J. Chem. Soc.* 5056 (1962).

[12] R. G. Harvey, H. I. Jacobson and E. V. Jensen, *J. Amer. Chem. Soc.* 85, 1623 (1963).

[13] A. Fava, A. Iliceto and E. Camera, *J. Amer. Chem. Soc.* 79, 833 (1957).

[14] A. Fava and A. Iliceto, *J. Amer. Chem. Soc.* 80, 3478 (1958).

TABLE 1. APPARENT p*Ka* AND RATE DATA AT 30° IN t-BUTANOL

$(p\text{-}RC_6H_4)_2PHO + Ph{-}S{-}S{-}Ph \rightarrow PhSH + (p\text{-}RC_6H_4)_2P(O)S{-}Ph$

R	Conc.[a] m/l	$\Sigma\sigma p^{15,16}$	p*Ka* in t-BuOH	k_2, $1\ m^{-1}\ min^{-1}$	$k_2(R)/k_2(H)$
MeO	0·20	−0·54	30·0	$1{\cdot}7^c \times 10^{-2}$	0·43
Me	0·20	−0·34	29·0	$2{\cdot}15 \pm 0{\cdot}02 \times 10^{-2}$	0·56
H	0·20	0·00	28·0	$3{\cdot}87 \pm 0{\cdot}07 \times 10^{-2}$	1·0
Cl	0·20	+0·454	25·0	$14^c \times 10^{-2}$	3·6
Br	0·15[b]	+0·464	25·0	$17^c \times 10^{-2}$	4·3
CF_3	0·15[b]	+1·08	23·2	$32^c \times 10^{-2}$	8·3

[a] Both reactants.

[b] *k* values may be as much as 5% low compared to results at 0·20 m/l (See Table 2 and Fig. 3)

[c] Single run, otherwise duplicate runs were made.

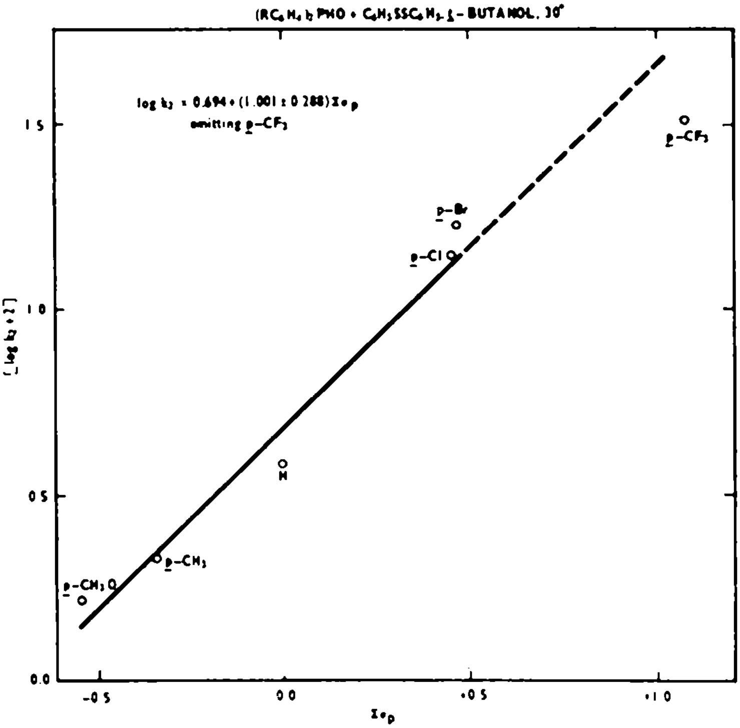

FIG. 1.

was studied as a function of concentration in t-butanol it was found that the second order rate constant was not independent of the concentration of the oxide (Table 2). The rate constant appeared to increase in a linear fashion by a factor of two with an eight-fold increase in concentration (Fig. 3). Doubling the disulfide concentration, on the other hand, produced a slight drop in specific rate which is within the experimental error (ca. 3–5%). Changing the solvent to 95% ethanol suppressed this effect of phosphine oxide concentration markedly. The variation of k_2 with secondary phosphine oxide concentration is still linear in 95% ethanol but the rate of change is

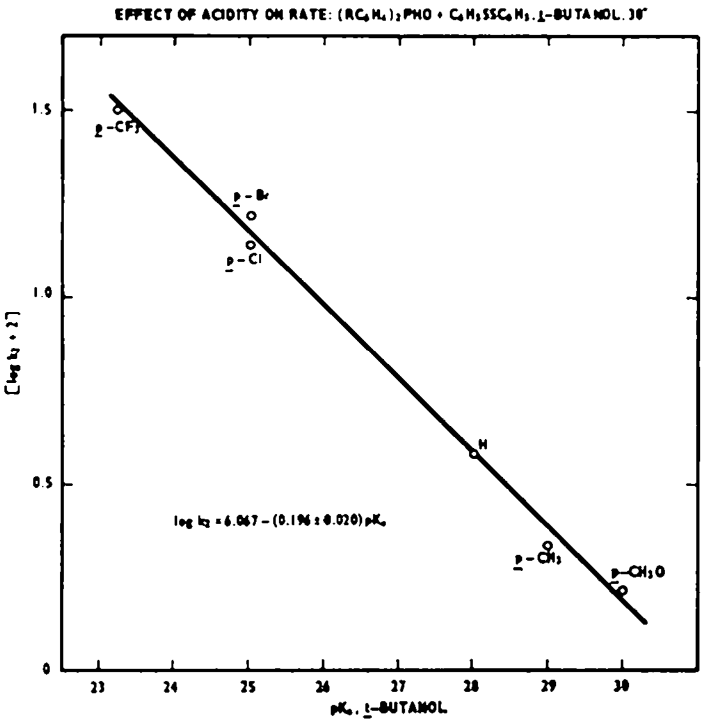

FIG. 2.

TABLE 2. VARIATION OF RATE CONSTANT WITH CONCENTRATION AT 30° IN t-BUTANOL

$(p\text{-}MeC_6H_4)_2PHO + PhSSPh \rightarrow PhSH + (p\text{-}MeC_6H_4)_2P(O)SPh$

$(p\text{-}MeC_6H_4)_2PHO$	PhSSPh	k_2, l m^{-1} min^{-1}
0·40 m/l.	0·10 m/l.	3·13 × 10^{-2}
0·20	0·20	2·17
0·20	0·20	2·13
0·10	0·20	1·83
0·10	0·10	1·96
0·05	0·20	1·52

quite low since a six-fold increase produced only a 20% rise in specific rate (Table 3). In fact, extrapolation to zero concentration indicates that no appreciable further drop in k_2 would be expected below the lowest concentration tested (0·05 m/l, Fig. 3). As a result, rate and acidity measurements were repeated in 95% ethanol with the addition of the extremely acidic compound bis(3,5-bistrifluoromethylphenyl)phosphine oxide as well as bis(*m*-trifluoromethylphenyl)phosphine oxide and three dialkylphosphine oxides (Table 4). As shown in Fig. 4 and Table 4, the ethanol results give a linear free energy correlation with the standard substituent constants for aromatic compounds[15] (log k_2 *vs* $\Sigma\sigma$) with the exception of the p-CF_3 value.[16] It appears that the few aliphatic compounds measured tend to give a similar correlation with inductive substituent constants[17] (log k_2 *vs* $\Sigma\sigma^*$) with parallel slope ($\rho = 1{\cdot}168$) to the aromatic phosphine

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[15] L. P. Hammett, *Physical Organic Chemistry*, p. 188. McGraw-Hill, N.Y. (1940).

[16] H. H. Jaffé, *Chem. Rev.* 53, 222 (1953).

[17] R. W. Taft, Jr. in Newman, *Steric Effects in Organic Chemistry* p. 619. J. Wiley, New York (1956).

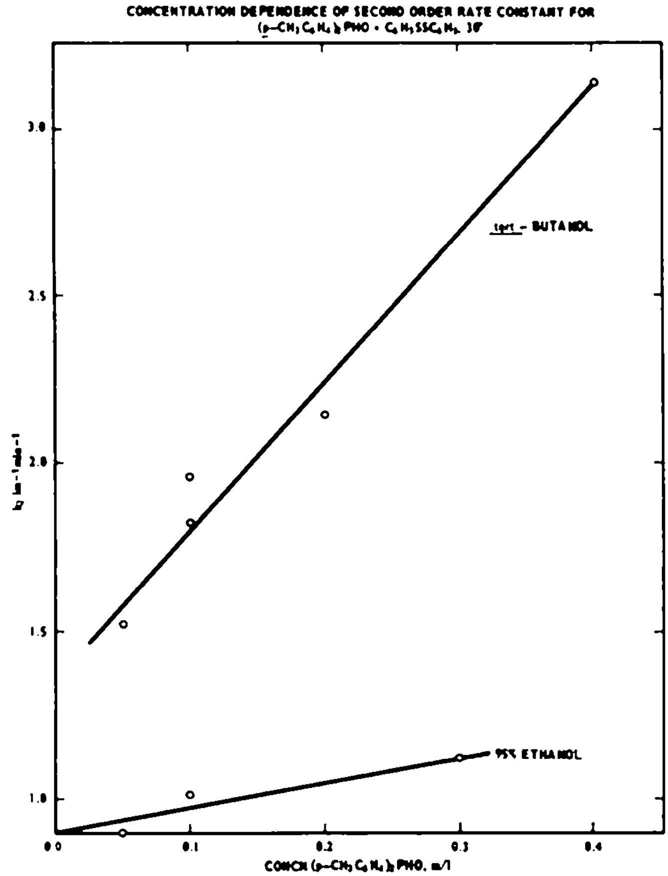

FIG. 3.

TABLE 3. EFFECT OF CONCENTRATION ON RATE CONSTANT AT 30° IN 95% ETHANOL

$(p\text{-}MeC_6H_4)_2PHO + PhSSPh \rightarrow PhSH + (p\text{-}MeC_6H_4)_2P(O)SPh$

$(p\text{-}MeC_6H_4)_2PHO$	PhSSPh	k_2, l m^{-1} min^{-1}
0·30 m/l.	0·10 m/l.	$1{\cdot}08 \times 10^{-3}$
0·30	0·10	1·16
0·10	0·10	1·01
0·10	0·10	1·01
0·05	0·20	0·89
0·05	0·20	0·90
		av. 1·01 ± 0·09

oxide plot. However, more data would be required before this relationship could be considered firmly established.

An observation of considerable mechanistic significance was the great increase in rate obtained in the presence of base. For example, a 50-fold increase in rate occurred with bis(*p*-tolyl)phosphine oxide and phenyl disulfide (0·01 m/l each) in the presence of a large excess (0·16 m/l) of triethylamine in 95% ethanol at 30° ($k_2^B = 50 \pm 5 \times$

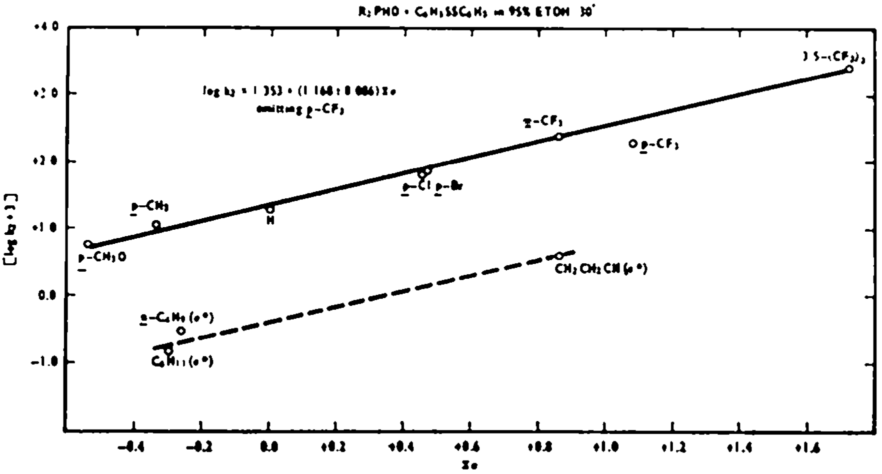

FIG. 4.

TABLE 4. RATE DATA AT 30° IN 95% ETHANOL

$(R_1R_2C_6H_3)_2PHO + PhSSPh \rightarrow PhSH + (R_1R_2C_6H_3)_2P(O)SPh$

0·20 m/l. 0·20 m/l.

R_1	R_2		k_2, l m^{-1} min^{-1} [g]	$k_2(R_1R_2)/k_2(H)$
p-Me	H	−0·54	6·11 ± 0·04 × 10^{-2}	0·32
p-Me	H[a]	−0·34	10·1 ± 0·90	0·53
H	H[b]	0·0	19·05 ± 0·20	1·0
p-Cl	H[b]	+0·454	64·8 ± 0·40	3·4
p-Br	H[b]	+0·464	72·4 ± 0·60	3·8
p-CF_3	H[c]	+1·08	197 ± 22[h]	10·3
m-CF_3	H[d]	+0·86	235 ± 4	12·3
3-CF_3	5-CF_3[e]	+1·72	2575 ± 80	135
		Aliphatic Compounds (R_1R_2PHO)		
CH_2CH_2CN	CH_2CH_2CN	+0·86[f]	4·04 ± 0·05 × 10^{-2}	0·21
n-C_4H_9	n-C_4H_9	−0·26[f]	0·311 ± 0·003	0·016
C_6H_{11}	C_6H_{11}	−0·30[f]	0·157 ± 0·002	0·0082

[a] Conc. varied from 0·05 to 0·30 m/l. (Table 3).
[b] Conc. was 0·10 m/l.
[c] 0·04 m/l.
[d] 0·07 m/l.
[e] 0·01 m/l.
[f] σ^* values.
[g] Average of duplicate values.
[h] Average of three runs.

10^{-2} l m^{-1} min^{-1}). The rate constant was calculated as a reversible second order reaction[18] since it was found unexpectedly that equilibrium was established in this system in the presence of base at about 50% reaction. The back reaction was confirmed by following the consumption of thiophenol in the presence of phenyl diphenylphosphinothiolate and excess triethylamine under the kinetic conditions

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[18] A. A. Frost and R. G. Pearson, *Kinetics and Mechanism* (2nd Edition) p. 188. J. Wiley, New York (1961).

(Eq. 5). It is presumed that thiophenoxide ion is the actual nucleophilic species in the presence of the base. Equilibrium was attained in a few hr. Further consumption of

$$\text{PhSH} + (\text{Ph})_2\text{P(O)SPh} \overset{\text{Et}_3\text{N}}{\rightleftharpoons} (\text{Ph})_2\text{PHO} + \text{PhSSPh} \qquad (5)$$

thiophenol was exceedingly slow. It therefore seems reasonable to draw a parallel between the secondary phosphine oxides and the acetone-like enolization of **1** which has a pH-rate profile resulting from both acid and base catalysis of deuterium exchange and oxidation.[3,4] This will be discussed further in the next section.

In considering this system as a model for reaction with the disulfide bond of various proteins, the relative reactivity of diphenyl disulfide and aliphatic disulfides, especially combined cystine is of interest. Reactivity comparisons were made with N,N′ diacetyl-L-cystine diethylester[19] (Cys) and di-n-octyl disulfide with bis(*p*-tolyl) phosphine oxide in the presence of triethylamine. The reactivity order $(\text{PhS})_2 >$ Cys $> (\text{n-C}_8\text{H}_{17}\text{S})_2$ (8·6:1·0:0·21) was observed. With bis(*p*-chlorophenyl)phosphine oxide in the absence of the base, reaction with di-n-octyl disulfide was too slow for convenient measurement (~2·5% in 24 hr) and the order $(\text{PhS})_2 >$ Cys $\gg (\text{n-C}_8\text{H}_{17}\text{S})_2$ was observed again (4·6:1·0:?).

DISCUSSION

It is evident from the linear variation of second order rate constant with the phosphine oxide concentration described in Fig. 3 and Tables 2 and 3 for both t-butanol and 95% ethanol that the reaction is indeed second order but complicated by a solvent dependent concentration effect. The fact that the increase in rate constant with oxide concentration is sharply reduced by carrying out the reaction in 95% ethanol instead of t-butanol suggests as one might expect that highly polar or ionic species are being formed prior to or during the transition state. It seems likely that the polar phosphoryl group of the secondary phosphine oxide is capable of association through hydrogen bonding or otherwise assists the acidic ionization which precedes the transition state by ion-dipole interactions (*vide infra*). There is some indication from the titration curves that the secondary phosphine oxide exists in anhydrous t-butanol to some extent at least as a dimer or that there is strong anion-acid association so that one of the species present during the titration has the form $(\text{AHA})^-$. This is quite reasonable in the light of previously observed behavior of weak acids in low dielectric media.[20] However, there is no comparable evidence for association in 95% ethanol. The reduction of this effect in a medium of higher dielectric and better hydrogen donor properties such as 95% ethanol is in keeping with this interpretation.

The acceleration of reaction by electron withdrawing groups as well as the additional acceleration by base provide substantial support for a mechanism involving rapid establishment of equilibrium between the "keto" and reactive trivalent "enol" or ionized "enol" forms of the secondary phosphine oxide prior to the rate determining attack on the disulfide by the anion (in 95% EtOH) or anion complex (AHA^-) (in t-butanol) discussed above.

The first equilibrium step (Eq. 6, below) is written both on the evidence of the obvious acidity of the secondary phosphine oxides, the acceleration of reaction by base and the evident analogy with the dialkyl phosphonates (**1**). A similar enolization

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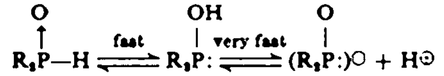
[19] E. Cherbuliez and P. Plattner, *Helv. Chem. Acta.* **12**, 317 (1929).

[20] L. W. Marple and J. S. Fritz, *Analyt. Chem.* **35**, 1223 (1963); *Ibid.* **34**, 921 (1962).

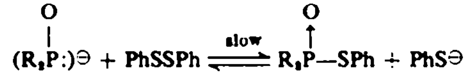
mechanism has been proposed[2,4] on the basis of deuterium exchange and iodine oxidation kinetics with 1. The analogy to acetone enolization in bromination, etc. appears to be valid.[2,4] The reversibility of Eq. 7 has been established separately (Eq. 5). The nucleophilic properties of both the anion of 1 and secondary phosphine oxides toward saturated and unsaturated carbon as well as sulfur are amply attested to by a host of alkylation, carbonyl and Michael addition reactions as well as sulfur abstraction processes and documentation here seems unnecessary. Eq. 7 is written as a

(6)



$$R_2\overset{\overset{O}{\uparrow}}{P}-H \overset{\text{fast}}{\rightleftharpoons} R_2\overset{\overset{OH}{|}}{P}: \overset{\text{very fast}}{\rightleftharpoons} (R_2\overset{\overset{O}{|}}{P}:)^{\ominus} + H^{\oplus}$$

(7)



$$(R_2\overset{\overset{O}{|}}{P}:)^{\ominus} + PhSSPh \overset{\text{slow}}{\rightleftharpoons} R_2\overset{\overset{O}{\uparrow}}{P}-SPh + PhS^{\ominus}$$

(8)

$$PhS^{\ominus} + H^{\oplus} \overset{\text{fast}}{\rightleftharpoons} PhSH$$

reversible reaction although it is clear that the overall reaction is largely irreversible in neutral alcoholic systems where thiophenol is little ionized. It is likely that mercaptide ion attacks the sulfur of the thiolate ester directly in the reverse of Eq. 7 although it has been established that hydrolytic reactions of phosphorus esters proceed by way of attack on the phosphoryl group.[21] Formation of disulfide from an adduct of the type $R_2\overset{\overset{O^{\ominus}}{|}}{P}(SPh)_2$ cannot be excluded but does not appear likely. Obviously ordinary dealkylation via attack on carbon (to give diphenyl sulfide) is extremely unfavorable with the aromatic esters.

The correlation of observed rate with increased electronegativity of the substituents on the secondary phosphine oxides indicated in Figs. 1 and 3, tells us that the equilibrium constant or constants of Eq. 6 (K_1) dominates the kinetics (e.g. $k_{obs.} = K_1k_2$, where k_2 is the forward rate of Eq. 7). In other words, the anion is an extremely reactive intermediate and the free energy of the reaction is largely a function of K_1. Were this not the case, electron withdrawing groups on the phosphine oxide would reduce the rate of reaction since the nucleophilicity of the anion would be correspondingly reduced.

As can be seen from Figs. 1 and 4, especially the latter, either the σ_p or k_2 value for bis(*p*-trifluoromethylphenyl)phosphine oxide is inaccurate. However, the good agreement obtained in the plot of p*Ka* versus log k_2 for the trifluoromethyl compound (Fig. 2) makes it unlikely that experimental errors in k_2 are involved. It has been shown[22] that the σ_p value for trifluoromethyl may vary widely from the one determined with benzoic acids depending on the reaction type and presumably the electron demand. On the other hand, σ_m values are invariant with reaction type. The σ_m and σ_I values are nearly identical.[23] Use of either of these values restores the agreement between *p*-CF_3 and the other substituents. From this we may conclude that forms such as the following make very little contribution to the acidity of the secondary phosphine oxides. However, since the *p*-methoxy group appears to make its normal contribution here as a donor, some structures from which ring-P overlap can occur must be

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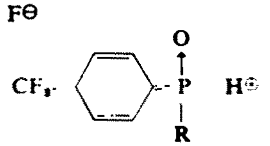
[21] J. R. Cox, Jr. and O. B. Ramsay, *Chem. Rev.* **64**, 317 (1964); P. Haake and C. Diebert, private comm.

[22] J. D. Roberts, R. L. Webb and E. A. McElhill, *J. Amer. Chem. Soc.* **72**, 408 (1950).

[23] R. W. Taft, Jr. and I. C. Lewis, *J. Amer. Chem. Soc.* **80**, 2436 (1958).

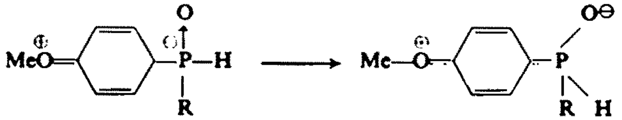
contributing to reactivity[24] as in (10) (in this case reduced acidity of the phosphine oxide). Conceivably this type of interaction increases with donor strength[25] which

(9)



would account for the reduced participation of fully overlapped forms with trifluoromethyl substitution.

(10)



To assess qualitatively the general extent of C—P pi bond overlap in aromatic phosphorus acids, it is interesting to compare the reaction constant, ρ, with related systems. A value for ρ of 0·83 was found[26] for the ionization of substituted phosphonous acids [$X\text{-}C_6H_4PH(O)(OH)$] compared to the value of 1·168 found here for the neutral system in 95% ethanol. A value of ρ found for the first ionization of phenylphosphonic acid in water was 0·76.[27] In agreement with this, it was concluded[28] that $d\pi$–$p\pi$ bonding in aromatic phosphorus acids is quite small since the σ^* correlation

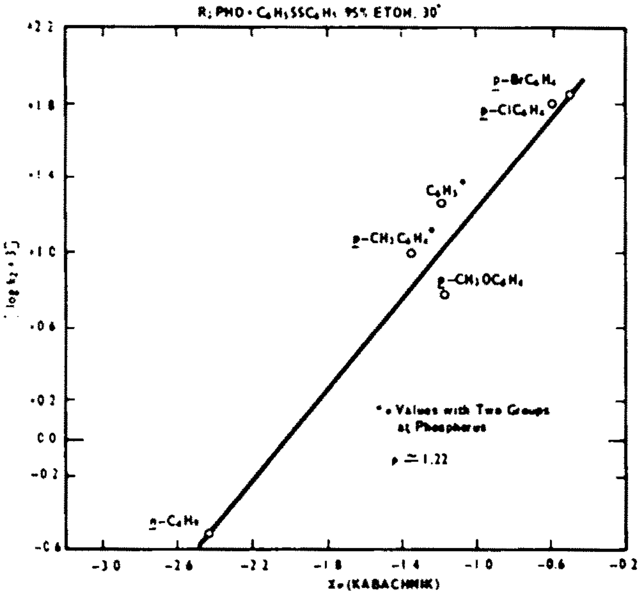


Fig. 5.

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[24] D. E. Bissing, *J. Org. Chem.* 30, 1296 (1965).

[25] H. Goetz, F. Nerdel and K. H. Wiechel, *Liebig's Ann.* 665, 1 (1963).

[26] L. D. Quin and M. R. Dysart, *J. Org. Chem.* 27, 1012 (1962).

[27] H. H. Jaffé, L. D. Freedman and G. O. Doak, *J. Amer. Chem. Soc.* 75, 2209 (1953); H. H. Jaffé and L. D. Freedman, *Ibid.* 74, 1069 (1952); L. D. Freedman and G. O. Doak, *Ibid.* 77, 6221 (1955).

[28] D. J. Martin and C. E. Griffin, *J. Organometallic Chem.* 1, 292 (1964).

for alkylphosphonic acids applied equally well to the aromatic compounds using $\sigma^*C_6H_5$. Added confirmation for this was obtained when log k_2 was plotted *vs* $\Sigma\sigma$ using Kabachnik's values for alkyl as well as aryl groups[29] (Fig. 5). A ρ of 1·22 was found which compares well with the values reported by Kabachnik for phosphinic and phosphonic acids in 80% ethanol (1·219).

EXPERIMENTAL

Symmetrical diaryl phosphine oxides were prepared by the given method[30,31] with several modifications. Grignard reagents were prepared from aryl bromides in dry THF and filtered to remove excess Mg. Following reaction with diethyl phosphonate (molar ratio 3:1), the reaction mixture was hydrolyzed with an equimolar amount of 20% H_2SO_4. After separation of layers and extraction of the water with benzene, the combined organic phases were evaporated *in vacuo* and the residue redissolved in benzene. After washing with 5% bicarbonate and drying over $MgSO_4$, the solvent was evaporated and the crude product was recrystallized from benzene (diethyl ether was used for trifluoromethyl-containing compounds). Yields are reported for the pure products (Table 5).

TABLE 5. SECONDARY PHOSPHINE OXIDES, R_2PHO

R	M.P. (°C) Found*	M.P. (°C) Lit.	Ref.	Yield %	Analysis Found C	Analysis Found H	Analysis Found P	Analysis Calc. C	Analysis Calc. H	Analysis Calc. P
C_6H_5	53–55	53–56	30	63	—	—	—	—	—	—
p-ClC_6H_4	131–133	132–133	30	73	53·24	3·45	11·48	53·17	3·35	11·43
p-BrC_6H_4	139–141	141	30	31	39·55	2·79	8·70	40·04	2·52	8·60
p-$CH_3OC_6H_4$	125–126	126·5–127·5	30	47	64·28	5·86	11·72	64·12	5·77	11·81
p-$CH_3C_6H_4$	102–103	—	—	48	72·70	6·68	13·60	73·03	6·57	13·46
p-$CF_3C_6H_4$	65–67	-	—	5	49·51	2·93	9·40	49·72	2·68	9·16
m-$CF_3C_6H_4$	53·5–54·5		—	21	49·46	3·17	9·38	49·72	2·68	9·16
3,5-$(CF_3)_2C_6H_3$	122–125	—	--	50	41·16	2·08	6·79	40·53	1·49	6·53
C_6H_{11}	72·5–74·5	76–77	30	20	67·64	10·91	14·40	67·26	10·82	14·45
n-C_4H_9	53–56	58–60	31	49	—	—	---	—	—	--
CH_2CH_2CN	95–96·5	98–99	31	64	- ·	—	....	---	—	—

* Uncorrected

Dicyclohexyl-, di-n-butyl- and bis(2-cyanoethyl)phosphine oxide were prepared by air oxidation of the corresponding secondary phosphines.[32] Di-n-octyl disulfide was prepared by I oxidation of the mercaptan followed by distillation. Diphenyl disulfide (Aldrich Chemical Company) was recrystallized from 95% EtOH. t-Butanol was refluxed several hr with Na and distilled. 95% EtOH was distilled before use.

Kinetic procedure. A typical procedure is as follows: 5·4002 g (0·015 mole) of bis(p-bromophenyl)-phosphine oxide and 45 ml t-butanol were placed in a 100 ml volumetric flask. To a second 100 ml volumetric flask was added 3·2750 g (0·015 mole) diphenyl disulfide, 45 ml t-butanol and 0·0220 g (0·0003 mole) hydroquinone. Both flasks were swirled to effect soln, purged with dry N, stoppered and immersed in a water bath maintained at 30·00 ± 0·05° for at least ½ hr before combining. At zero

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[29] M. I. Kabachnik, *Dokl. Akad. Nauk SSSR* **110**, 393 (1956); T. A. Mastrukova, A. E. Shipov, T. A. Melentyeva and M. I. Kabachnik, *Zh. Obshch. Khem.* **29**, 2178 (1959); M. I. Kabachnik, T. A. Mastrukova, A. E. Shipov and T. A. Melentyeva, *Tetrahedron* **9**, 10 (1960); M. I. Kabachnik, T. A. Mastrukova and T. A. Melentyeva, *Ibid.* **17**, 239 (1962).

[30] R. H. Williams and L. A. Hamilton, *J. Amer. Chem. Soc.* **74**, 5418 (1952); *Ibid.* **77**, 3411 (1955).

[31] W. Lorenz and G. Schrader, unpublished. Cited in K. Sasse, Houben-Weyl, *Methoden der Organischen Chemie*, (Edited by E. Muller) Vol. 12 (part 1); p. 197. Georg. Thieme, Stuttgart (1963).

[32] M. M. Rauhut, I. Hechenbleikner and H. A. Currier, USP 2,953,596 (1958) to American Cyanamid Company; M. M. Rauhut and H. A. Currier, *J. Org. Chem.* **26**, 4626 (1961).

time, the contents of the flasks were rapidly combined and diluted to 100 ml with t-butanol (10–20 sec) followed by thorough mixing. The reaction samples were quenched by direct dilution to a mercaptan concentration of less than $0{\cdot}5 \times 10^{-3}$ mole with a minimum dilution ratio of 50:1 in the polarographic solvent (Eastman Kodak Spectograde acetonitrile containing 0·10 molar tetrapropylammonium perchlorate as supporting electrolyte was used for phenyl mercaptan and the cysteine derivative; dimethylsulfoxide with the same salt was used for n-octyl mercaptan). Results are tabulated below ($k_2t = (1/C) - (1/C_0)$ where C is the disulfide concentration).

TABLE 6. TYPICAL KINETIC RUN AT 30° IN t-BUTANOL
$(p\text{-}BrC_6H_4)_2PHO$ + PhSSPh

Time (min)	C_6H_5SH	C	k_2 l. m^{-1} min^{-1}
0	0·0 m/l.	0·1500 m/l.	...
15	0·0400	0·1100	$16{\cdot}2 \times 10^{-2}$
30	0·0628	0·0872	16·0
60	0·0918	0·0582	17·5
90	0·1057	0·0443	17·6
120	0·1118	0·0382	16·3
150	0·1187	0·0313	16·8
			av. 16·7 ± 0·6

Reaction products were isolated directly from the kinetic runs in a number of cases (Table 7). Where a material balance was attempted, yields were essentially quantitative.

TABLE 7. PHENYL DIARYLPHOSPHINOTHIOLATES
$R_2P(O)SPh$

		Analysis %							
		Found				Calc.			
R	M.P.*	C	H	P	S	C	H	P	S
C_6H_5	89–90°	69·50	5·28	9·95	10·24	69·66	4·87	9·98	10·33
$p\text{-}BrC_6H_4$	120–122·5°	46·11	2·92	6·83	6·97	46·18	2·80	6·62	6·85
$p\text{-}ClC_6H_4$	122·5–123°	57·13	3·56	8·36	8·29	57·01	3·46	8·12	8·45
$p\text{-}CH_3C_6H_4$	125–126°	70·78	5·45	9·16	9·61	70·98	5·66	9·15	9·48
$p\text{-}CH_3OC_6H_4$	69·5–71·5°	64·94	5·26	8·55	8·65	64·85	5·17	8·36	8·66
$p\text{-}CF_3C_6H_4$	113–114°	—	—	7·08	7·07	—	—	6·94	7·18
$3,5\text{-}(CF_3)_2C_6H_3$	115–116·5°	45·45	2·22	5·61	—	45·37	1·90	5·32	—
C_6H_{11}	91–93·5°	—	—	9·43	10·23	—	—	9·61	9·94

* Uncorrected

Determination of acidities

A. *Acidity of secondary phosphine oxides in t-butanol.* If a compound which is weakly acidic is titrated potentiometrically with a base it can be shown that the potential of the indicator electrode during the titration is a measure of the hydrogen ion concentration of the solution and under favorable circumstances can be related directly to the ionization constant of the acid. In low dielectric solvents salt and concentration effects may cause some difficulties. However, if these factors are held within reasonable limits, a direct correlation between the half neutralization potential of the acid and the apparent pK_{HX} value may be obtained. The method described (*vide infra*) was used for both standards and the secondary phosphine oxides.

Approximately 1 meq. of acid was dissolved in 100 ml of redistilled t-butanol and this solution titrated potentiometrically with 0·1M tetrabutylammonium hydroxide also dissolved in redistilled t-butanol. The titrant was obtained by diluting 50 ml of M tetrabutylammonium hydroxide dissolved in methanol with 50 ml of redistilled t-butanol and then vacuum evaporating this solution until all the methanol was removed. The residue was then diluted to 50 ml with the purified t-butanol. The titrant was standardized against benzoic acid.

All titrations were made using a Precision Dow Recordomatic Titrator. The indicating system consisted of a Beckman glass electrode and a modified Leeds and Northrup calomel electrode. The modified electrode is essentially the same as a standard calomel electrode with the exception that the aqueous potassium chloride solution was replaced with t-butanol which had been saturated with tetramethylammonium chloride. It was hoped in this way to produce stable liquid junction potentials.

TABLE 8. EXPERIMENTAL HNP AND APPARENT pK_{HX} VALUES IN t-BUTANOL

Compound	mmoles Titrated	HNP	pK_{HX} (exp.)
Perchloric Acid	0·960	−312 mv	3·94[10]
Picric Acid	0·242	−280	4·96[10]
	0·560	−274	4·96
2,4-Dinitrophenol	0·823	−29	10·58[10]
	0·823	−27	10·58
Benzoic Acid	1·142	177	15·27[10]
	0·867	184	15·27
$[3,5(CF_3)_2C_6H_3]_2PHO$	0·897	259	17·07
	0·838	254	16·95
		(205)*	*ave.* 17·0 ± 0·08
$(m\text{-}CF_3C_6H_4)_2PHO$	0·794	537	23·38
	0·871	528	23·18
		(447)*	*ave.* 23·3 ± 0·1
		(446)*	
$(p\text{-}CF_3C_6H_4)_2PHO$	0·728	530	23·22
	0·643	531	23·24
			ave. 23·2 ± 0·01
$(p\text{-}BrC_6H_4)_2PHO$	0·826	613	25·11
	0·823	602	24·86
			ave. 25·0 ± 0·2
$(p\text{-}ClC_6H_4)_2PHO$	0·892	603	24·88
	0·822	610	25·04
		(605)*	*ave.* 25·0 ± 0·1
		(635)*	
$(Ph)_2PHO$	0·964	(749)*	28†
	0·791	(754)*	28†
$(p\text{-}CH_3C_6H_4)_2PHO$	0·853	(818)*	29†
	0·918	(814)*	29†
$(p\text{-}CH_3OC_6H_4)_2PHO$	0·739	(846)*	30†
	0·727	(833)*	30†

* Measured in pyridine.

† Calculated from pyridine data.

The four acids previously investigated[10] were titrated in this manner. Data are given in Table 8. A correlation between apparent pK_{HX} and half neutralization potentials was made by the method of least squares (Eq. 11). The algebraic solution of the least squares equations is

$$\text{p}K_{HX} = 11{\cdot}18 + 0{\cdot}0227\,(\text{HNP}) \tag{11}$$

where pK_{HX} is the value for the acid in t-butanol and (HNP) is the half neutralization potential for the acid in the same solvent.

The secondary phosphine oxides were then titrated under the same conditions and HNP values for most of them obtained. Apparent pK_{HX} values for these compounds in t-butanol were calculated using the above equation and the aforementioned HNP values. Data and calculated results are also given in Table 8.

A number of the secondary phosphine oxides, specifically the bis(p-methyl)-, bis(p-methoxy)-, and the diphenyl derivatives were too weak to be titrated as acids in this solvent system. However, they were titrated in pyridine and a correlation between pK_{HX} values in t-butanol and HNP values in pyridine made for those compounds which were acidic in both solvents. The equation relating the values in the two solvents is

$$pK_{HX(t\text{-}BuOH)} = 13 + 0{\cdot}02\,(\mathrm{HNP})_{\mathrm{Pyridine}} \tag{12}$$

Values for the acids not titratable in t-butanol were then obtained by extrapolation of this data. Data and calculated values are given in Table 8. It is believed this method is valid inasmuch as the relative acidities of the secondary phosphine oxides should not vary with solvent changes since all the solute molecules are of the same molecular type. The accuracy of the calculated pKa values, however, will be reduced, because of the inclusion of greater experimental errors through the indirect determination.

As can be seen from the calculated data, all the secondary phosphine oxides are extremely weak acids in t-butanol, although the bis(3,5-bistrifluoromethylphenyl) derivative is only two orders of magnitude weaker than benzoic acid. These values should be considered in light of those for acids which are ordinarily completely dissociated in water such as perchloric acid. In t-butanol even perchloric is a weak acid with a pK_{HX} of 3·94. The inability of t-butanol to solvate ions effectively and the low dielectric constant ($\varepsilon = 11{\cdot}23$) of this solvent probably account for the low ionization and dissociation of the acids.

Excellent correlation of pK_{HX} values and σ values is obtained if only data for the acids determined in t-butanol are used. This correlation also implies that the acidity value for the bis(4-trifluoromethyl) compound is too low or the σ value is too high. The values for the pyridine data also appear to be an order of magnitude low and this is quite probably a true condition since it was necessary to extrapolate the data in order to obtain pK_{HX} values.

The least squares solution for the data ignoring the compounds noted is

$$pK_{HX} = 28{\cdot}06 - 6{\cdot}349\,\sigma \tag{13}$$

B. *Acidity of secondary phosphine oxides in 95% ethanol.* This solvent has a dielectric constant of approximately 26·5 at 20° and contains a sufficient amount of water to solvate both anions and cations present in dilute solution. However, there are strong interactions between the alcohol and water molecules and pK values in ethanol-water mixtures are not necessarily linear functions of the concentration of either solute.

To determine pK values in 95% ethanol, a system similar to that used for tertiary butanol was used. Tetrabutylammonium hydroxide was the titrant and was dissolved in 95% ethanol, the original methanol being removed by vacuum evaporation. A glass/calomel electrode system was employed. The calomel was modified by replacing the aqueous potassium chloride solution with 95% ethanol saturated with potassium chloride. All titrations were performed using a Precision-Dow Recordomatic Titrator.

Only a few of the secondary phosphine oxides were sufficiently strong acids to be titrated in this solvent. A number of other compounds were titrated for comparison purposes and pK values calculated for all of them. These are listed in Table 9. The calculation method is based on equilibrium

TABLE 9. pK VALUES FOR VARIOUS ORGANIC ACIDS IN 95% ETHANOL AND IN WATER

Compound	pK (95% EtOH), app.	pK (H_2O)
PhCOOH	7·19 ± 0·08	4·20
MeCOOH	7·13	4·76
p-ClC_6H_4COOH	11·33 ± 0·01	3·98
$(PhNH)_2C{-}NH_2^+$	8·80 ± 0·08	10·00
$PhNH_3^+$	3·6 ± 0·2	5·22
$(Et)_3NH^+$	8·16 ± 0·10	10·72
$N(CH_2CH_2)_3NH^+$	6·98 ± 0·06	8·68
Bu_3NH^+	7·18	10·5
Bu_3PH^+	4·78	8·4

considerations which are applicable to aqueous systems and most probably are valid for 95% ethanol. The expression relating hydrogen ion concentration and the K_a of the acid is

$$[H^+]^3 + (K_a + xa)[H^+]^2 - (aK_a(1 - x) + K_s)[H^+] - K_aK_s = 0 \tag{14}$$

where a is the formal concentration of the acid, xa is the amount titrated at any time and K_s is the dissociation constant of the solvent.

To determine K_a for benzoic acid in 95% ethanol where $K_s = 10^{-18.88}$ let us consider data for $[H^+]$, xa, and a from three different points on a titration curve. Values are given in Table 10.

TABLE 10. APPARENT pK OF BENZOIC ACID IN 95% ETHANOL

No.	x	a	$[H^+]$	K_a	pK_a
1	0·300	$9{\cdot}16 \times 10^{-3}$	$10^{-6.89}$	$10^{-7.26}$	7·26
2	0·500	$9{\cdot}008 \times 10^{-3}$	$10^{-7.21}$	$10^{-7.21}$	7·21
3	0·800	$8{\cdot}776 \times 10^{-3}$	$10^{-7.70}$	$10^{-7.10}$	7·10

The average value for pKa is 7·19 and the value for $s = \pm 0{\cdot}08$. The value of (a) changes because of dilution effects.

In a similar manner pK values were calculated from titration curves for bis(3,5-bistrifluoromethylphenyl)-, bis(m-trifluoromethylphenyl)-, and bis(p-bromophenyl)phosphine oxide and the compounds listed in Table 9. Data and calculated values for the phosphine oxides are given in Table 11.

TABLE 11. APPARENT pK VALUES FOR SECONDARY SUBSTITUTED ARYL PHOSPHINE OXIDES IN 95% ETHANOL

Compound	x	a	$[H^+]$	K_a	pK_a
$[3,5\text{-}(CF_3)_2C_6H_3]_2PHO$	0·300	$5{\cdot}22 \times 10^{-3}$	$10^{-9.33}$	$10^{-9.67}$	9·67
	0·500	$5{\cdot}16 \times 10^{-3}$	$10^{-9.64}$	$10^{-9.64}$	9·64
	0·800	$5{\cdot}08 \times 10^{-3}$	$10^{-10.20}$	$10^{-9.59}$	9·59
					$ave. = 9{\cdot}63$
					$s = 0{\cdot}04$
$(m\text{-}CF_{36}CH_4)_2PHO$	0·500	$5{\cdot}43 \times 10^{-3}$	$10^{-12.18}$	$10^{-12.41}$	12·41
	0·500	$5{\cdot}31 \times 10^{-3}$	$10^{-12.89}$	$10^{-12.68}$	12·68
					$ave. = 12{\cdot}5$
					$s = 0{\cdot}2$
$(p\text{-}BrC_6H_4)_2PHO$	0·500	$3{\cdot}327 \times 10^{-3}$	$10^{-12.90}$	$10^{-12.66}$	12·7

Only these three compounds were acidic enough and available in sufficient quantities to make the determinations.

Acknowledgement—The authors are indebted to Mr. W. Jura for polarographic analyses used in this work.