867. *Strength of Chloro-substituted Phenoxyacetic and Related Phosphorus-containing Acids.*

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Dissociation constants are reported for a number of chloro-substituted phenoxyacetic and phosphorus-containing analogues. Generally chloro-substitution increases acidic strength except with 2 : 6-disubstituted derivatives, whose anomalous behaviour is attributed to steric hindrance. Contrary to predicted statistical and inductive effects, both phosphinic acids and ethyl phosphonates are stronger than the corresponding phosphonic acids. The relative strength of the acid types studied is in the order phenyl dihydrogen phosphates > ethyl hydrogen (phenoxymethyl)phosphonates > phenoxymethylphosphinic acids > phenoxymethylphosphonic acids > phenoxyethyl dihydrogen phosphates > phenoxyacetic acids.

CHLORINATED phenoxyacetic acids and related compounds are of interest because of their effect on plant growth.[1] However, no systematic investigation of their acidic strength has been reported, although such data may be required for the study of their mode of action and in correlations of biological activity and chemical structure. The dissociation constants reported here refer to a number of chloro-substituted phenoxyacetic acids $Ph{\cdot}O{\cdot}CH_2{\cdot}CO_2H$, phenoxymethylphosphonic acids $Ph{\cdot}O{\cdot}CH_2{\cdot}P(\colon O)(OH)_2$ and their ethyl half-esters, phenoxymethylphosphinic acids $Ph{\cdot}O{\cdot}CH_2{\cdot}PH(\colon O)OH$, phenoxyethyl dihydrogen phosphates $Ph\,O{\cdot}CH_2{\cdot}CH_2{\cdot}O{\cdot}P(\colon O)(OH)_2$, and phenyl dihydrogen phosphates $Ph{\cdot}O{\cdot}P(\colon O)(OH)_2$. The growth-regulating and toxic properties of some of the phosphorus-containing acids have been reported elsewhere.[2]

EXPERIMENTAL

The applicability of potentiometric titration to the determination of dissociation constants is limited here by the poor solubility in water of di- and tri-chlorophenoxyacetic acids and by the strongly acidic nature of the first dissociating group of phosphorus-containing acids. It has however been used to determine the relative strength of the chlorophenoxyacetic acid series in 50% (w/v) ethanol and of some of its more soluble members in water. It has also been used to determine second dissociation constants in water of the phenoxymethylphosphonic acids, and of the phenoxyethyl and phenyl dihydrogen phosphates. 25 ml. of 0·01M-acid in the appropriate solvent were titrated with 0·05M-sodium hydroxide (carbonate free). The solution was maintained at 20° and was magnetically stirred throughout the titration. The pH was determined with a standard Cambridge pH-meter. Agreement between theoretical and experimental end points was within 2%. In some instances the compound was supplied as its sodium salt, in which case a back titration was carried out with standardised hydrochloric acid, and the theoretical end point assumed.

For a monobasic acid the apparent dissociation constant (K') was calculated from a number of points on each titration curve from the relation

$$\mathrm{p}K' = \mathrm{pH} - \log\,(\alpha c + [\mathrm{H}^+])/\{(1 - \alpha)c - [\mathrm{H}^+]\} \quad . \quad . \quad . \quad . \quad (1)$$

where α is the degree of neutralisation of the weak acid and c its total concentration. For a

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[1] Leaper and Bishop, *Bot. Gazette*, 1951, **112**, 250.

[2] Greenham, *Austral. J. Sci.*, 1953, **16**, 66; *Austral. J. Biol. Sci.*, 1957, **10**, 180.

dibasic acid pK'_1 and pK'_2 were determined by applying eqn. (1) to each of the two ionisation steps.

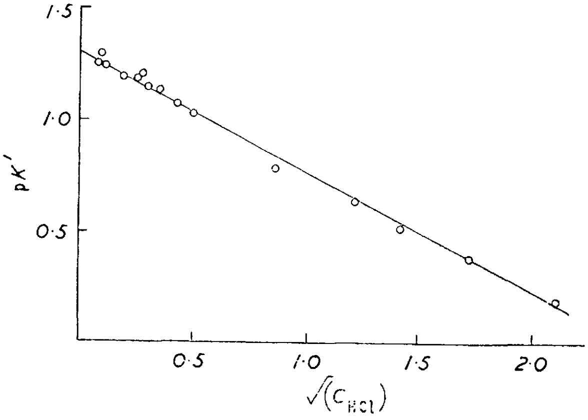
A more promising technique for aqueous solution is spectroscopic titration. There is a shift[3] in the ultraviolet spectra associated with the ionisation of aryloxyalkyl-substituted acids so that dissociation constants can be determined from the effect of pH on the spectra at concentrations considerably less than those necessary for potentiometric titration. Spectrophotometry has the further advantage of being equally applicable to weak or strong acids, whilst potentiometry is effectively limited to the former because of the high concentrations necessary to avoid corrections for hydrolysis. The optical density–pH relationship was measured at a number of wavelengths selected to give the maximum change between the two species in a Beckman spectrophotometer at 20°. The concentration of the solution (usually 5×10^{-4}M) was chosen so that Beer's law was obeyed.

pK' values were calculated from the relation

$$\mathrm{p}K' = \mathrm{pH} - \log[(\varepsilon_{\mathrm{pH}}{}^{\lambda} - \varepsilon_1{}^{\lambda})/(\varepsilon_2{}^{\lambda} - \varepsilon_{\mathrm{pH}}{}^{\lambda})] \quad . \quad . \quad . \quad . \quad . \quad (2)$$

where $\varepsilon_1{}^{\lambda}$ and $\varepsilon_2{}^{\lambda}$ refer to the molar extinction coefficient for the undissociated acid and the ionic species respectively at wavelength λ and $\varepsilon_{\mathrm{pH}}{}^{\lambda}$ refers to the molar extinction coefficient at wavelength λ for an intermediate pH.

The maximum change between the undissociated and the ionised form generally occurred in the far ultraviolet region where, because of the relatively steep slope of the ε–λ curve, a small displacement of the spectrum gave rise to a large change in absorption at a given wavelength. Because of this it was undesirable to use only one wavelength, and we normally determined the optical density–pH curve for 4 wavelengths separated by 10 Å intervals and calculated an average pK for each wavelength from a number of points on it, the mean value for the 4 wavelengths being accepted as the pK'. pK values calculated at the various wavelengths and from the different points at the one wavelength usually agreed to within $\pm 0{\cdot}05$ pK unit.



Plot of pK' *against* $\sqrt{(C_{\mathrm{HCl}})}$ *for the first dissociation constant* (K'_1) *of* 2 : 4-*dichlorophenoxymethylphosphonic acid.*

The pH of the solutions was adjusted by means of 0·01M-phosphate buffer in the region 5—8 and otherwise with hydrochloric acid solutions. pH values above 2 were determined with a glass electrode and Cambridge pH meter.

For phosphorus-containing acids the effective pH values were calculated from the known activities[4] of the various hydrochloric acid solutions used, by replacing pH by $-\log_{10}\sqrt{(a_{\mathrm{HCl}})}$. When such values were substituted into eqn. (2), however, the calculated pK' varied with degree of ionisation, as would be expected owing to the variation in ionic strength with hydrochloric acid concentration.

This difficulty was overcome by determining the H_- acidity function[5] for hydrochloric acid solutions under these conditions so that thermodynamic pK° values could be determined. 2 : 4-Dichlorophenoxymethylphosphonic acid was chosen as the standard. The optical density

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[3] Phillips, *Austral. J. Chem.*, in the press.

[4] Harned and Owen, " Physical Chemistry of Electrolyte Solutions," Reinhold Publishing Corporation, New York, 1943, pp. 547, 577.

[5] Paul and Long, *Chem. Rev.*, 1956, **56**, 1.

was measured as a function of hydrochloric acid concentration (C_{HCl}) and the apparent pK' determined from a number of points on the curve by substituting $-\log_{10}\sqrt{(a_{\text{HCl}})}$ for pH in eqn. (2). A plot of pK' against $\sqrt{(C_{\text{HCl}})}$ (Figure) is straight, with slope 0·53, surprisingly close to the theoretical Debye–Hückel slope (0·50), and intercept 1·30 ± 0·05, corresponding to the thermodynamic pK° value. The H_- acidity function was calculated for a particular hydrochloric acid concentration from the relation

$$H_- = -\log_{10}\sqrt{(a_{\text{HCl}})} + \text{p}K^\circ - \text{p}K' \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

The usefulness of the H_- function is illustrated in Table 1 which summarises the pK values calculated as a function of degree of ionisation for 2 : 4-dichlorophenyl dihydrogen phosphate. Whereas pK° calculated from H_- is constant, pK' calculated by putting pH = $-\log_{10}\sqrt{(a_{\text{HCl}})}$ varies with the degree of ionisation.

TABLE 1. 2 : 4-*Dichlorophenyl dihydrogen phosphate at* 20°.

C_{HCl} (mole/l.)	7·5	6·0	4·5	1·5	0·375	0·225	0·150	0·075
α *	0·12	0·17	0·23	0·42	0·64	0·70	0·77	0·84
$-\log_{10}\sqrt{(a_{\text{HCl}})}$ ...	−1·59	−1·31	−0·97	−0·14	+0·53	+0·76	+0·92	+1·22
pK'	−0·73	−0·62	−0·45	0	+0·28	+0·39	+0·40	+0·50
H_-	−0·16	−0·01	+0·14	+0·53	+0·85	+1·00	+1·13	+1·36
pK°	+0·70	+0·68	+0·66	+0·67	+0·60	+0·63	+0·61	+0·64

* α calculated for λ = 2350 Å.

TABLE 2.

Compound	pK' (H_2O), 20° Pot. I ~0·005 *	Spectr. I ~0·001 *	λ_{mean} † (Å)	pK' (H_2O), 20° Lit. values	pK' (50% ethanol), 20° Pot. I ~0·005 *	ΔpK'	Source ‡
Phenoxyacetic acid	3·11	3·12	2260	3·12 [a]; 3·17 [b]	4·30	1·18	
2-Cl- ,,	2·96	2·96	2300	2·99 [a]; 3·06 [b]	4·23	1·27	
3-Cl- ,,	2·97	2·97	2310	3·07 [b]	4·14	1·17	
4-Cl- ,,	2·99	3·00	2370	3·02 [a]; 3·10 [b]; 3·01	4·15	1·15	
2 : 4-Cl_2- ,,	—	2·86	2390	3·27 [d]; 2·81 [e]; 2·96 [f]; 3·00 [g]; 2·90 [c]; 2·64 [h]	4·10	1·24	
2 : 5-Cl_2- ,,	—	2·94	2500	—	4·13	1·19	
2 : 6-Cl_2- ,,	—	3·30	2300	—	4·22	0·92	*A*
3 : 4-Cl_2- ,,	—	2·92	2400	—	4·10	1·18	
2 : 3 : 4-Cl_3 ,,	—	2·60	2340	—	3·92	1·32	*A*
2 : 3 : 6-Cl_3 ,,	—	§	—	—	4·10	—	*A*
2 : 4 : 5-Cl_3 ,,	—	2·85	2450	2·58 [e]; 2·84 [c]	4·01	1·16	*B*
2 : 4 : 6-Cl_3 ,,	—	§	—	—	4·20	—	
α-(2 : 4-Cl_2-phenoxy)-propionic acid	—	2·86	2410	—	4·30	1·44	
β-(2 : 4-Cl_2-phenoxy)-propionic acid	—	4·42	2410	—	5·50	1·08	*C*
γ-(2 : 4-Cl_2-phenoxy)-butyric acid	—	§	—	—	5·89	—	*D*

* Mean ionic strength at half-neutralisation point.

† Mean of wavelength region from which pK values were calculated.

‡ *A*, Supplied by Timbrol Ltd., Sydney. *B*, Supplied by Dr. M. H. Maguire, Sydney. *C*, Synthesised by Mr. P. I. Mortimer, Division of Plant Industry, Canberra. *D*, Supplied by Professor Wain, Wye College, England.

§ Spectral shift too small to be measured.

[a] Behaghel, *J. prakt. Chem.*, 1926, **114**, 287. [b] Hayes and Branch, *J. Amer. Chem. Soc.*, 1943, **65**, 1555. [c] Matell and Lindenfors, *Acta Chem. Scand.*, 1957, **11**, 324. [d] Audus, *New Phytologist*, 1949, **48**, 97. [e] Van Overbeek, Blondeau, and Horne, *Plant Physiol.*, 1951, **26**, 687. [f] Wedding, Erickson, and Brannaman, *Plant Physiol.*, 1954, **29**, 64. [g] Burstrom, Sjoberg, and Hansen, *Acta Agr. Scand.*, 1956, **6**, 155. [h] Ketelaar, Gersmann, and Beck, *Rec. Trav. chim.*, 1952, **71**, 497.

The phenoxyacetic acids were supplied commercially except where otherwise stated (see Table 2). The phosphorus analogues [6] were supplied by Drs. M. H. Maguire and G. Shaw of the University of Technology, Sydney.

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[6] Maguire and Shaw, *J.*, 1953, 1479; 1955, 1756; 1957, 311.

RESULTS

Table 2 records pK' values determined in water by potentiometric (Pot.) and spectral (Spectr.) titration and in 50% ethanol by potentiometric titration for phenoxyacetic acid and a number of mono-, di-, and tri-chlorinated derivatives as well as for some 2 : 4-dichloro-substituted homologues. Where comparison is possible the agreement between the potentiometric and the spectroscopic technique is satisfactory.

Table 3 summarises pK values determined for a number of chloro-substituted phenoxymethylphosphonic acids, phenoxymethylphosphinic acids, and ethyl hydrogen (phenoxymethyl)phosphonates as well as for some phenoxyethyl and phenyl dihydrogen phosphates. In general the strongly acidic dissociation constants were determined spectroscopically. For the phenyl dihydrogen phosphates the potentiometric pK'_2 values reported in the literature agree well with those determined here spectroscopically, whilst the potentiometric pK'_1 values show very poor agreement with the spectroscopic values. The literature values were determined by potentiometric titration of a 0·02M-solution and were termed " approximate." No details as to the method of calculation were given.

TABLE 3.

			pK_1 (Spectr.), 20°		pK_2, 20°		Lit. values §	
		λ_{mean}			pK'_2 (Pot.)	pK'_2 (Spectr.)		
Parent	Subst.	(Å)	pK'_1 *	pK°_1 †	I ‡ ~0·02	I ‡ ~0·01 → 0·02	pK'_1	pK'_2
Phenoxymethyl-phosphonic acid	—	2290	1·22	1·37	6·84	6·82	—	—
	2-Cl-	2320	1·30	1·43	6·83	6·80	—	—
	4-Cl-	—	*a*	—	6·82 [c]	*a*	—	—
	2 : 4-Cl_2-	2420	1·15	1·30	6·72	6·75	—	—
	2 : 6-Cl_2-	—	*b*	—	7·11	*b*	—	—
	2 : 4 : 5-Cl_3-	2450	1·10	1·26	6·59	6·56	—	—
	2 : 4 : 6-Cl_3-	—	*b*	—	7·07	*b*	—	—
Ethyl hydrogen (phenoxy-methyl)-phosphonate	—	—	*a*	—	—	—	—	—
	2-Cl-	2310	0·71	0·96	—	—	—	—
	4-Cl-	2380	0·66	0·93	—	—	—	—
	2 : 4-Cl_2-	2400	0·65	0·92	—	—	—	—
	2 : 6-Cl_2-	—	*b*	—	—	—	—	—
	2 : 4 : 5-Cl_3-	2450	0·55	0·86	—	—	—	—
	2 : 4 : 6-Cl_3-	—	*b*	—	—	—	—	—
Phenoxymethyl-phosphinic acid	—	—	*a*	—	—	—	—	—
	4-Cl-	2380	0·77	1·00	—	—	—	—
	2 : 4-Cl_2-	2400	0·73	0·98	—	—	—	—
	2 : 4 : 5-Cl_3-	2450	0·67	0·94	—	—	—	—
Phenoxyethyl dihydrogen phosphate	—	—	*a*	—	*a*	*a*	—	—
	2-Cl-	—	*b*	—	6·58	*b*	2·03	6·55
	4-Cl-	—	*b*	—	6·58	*b*	2·03	6·50
Phenyl dihydrogen phosphate	—	—	*a*	—	*a*	*a*	—	—
	4-Cl-	2320	0·37	0·70	5·89	5·83	2·02	5·80
	2 : 4-Cl_2-	2350	0·28	0·65	5·76	5·68	2·03	5·63
	2 : 4 : 5-Cl_3-	2940	−0·1	0·53	5·47	5·48	2·03	5·30

[a] Compound not available. [b] Spectral shift too small to permit measurement. All this compound was used up in the potentiometric titration.

* pK' is equal to the pH at half-neutralisation. † Determined at various degrees of ionisation by use of H_- values.

‡ Approximate ionic strength at the point of half neutralisation.

§ Maguire and Shaw, *J.*, 1953, 1479.

In the case of the phenoxyethyl dihydrogen phosphates the spectral change associated with ionisation was too small for the spectroscopic method to be applied so that pK_1 values could not be determined. It was however readily applicable to the phenyl dihydrogen phosphates.

DISCUSSION

The relative acid-strengthening effect of the phenoxy-group is shown in Table 4, which summarises pK'_1 values for various substituted acetic acids and methylphosphonic acids. This enhancement of acid strength arises primarily from the negative inductive effect of the phenoxy-group, which is of the same order as that of the iodo-group and considerably greater than that of the phenyl or hydroxyl groups.

The insertion of methylene groups between the phenoxy- and the ionising group markedly affects the acidic strength as would be expected from a consideration of the inductive field effect. Thus β-(2 : 4-dichlorophenoxy)propionic acid is *ca.* 1·5 pK units weaker than the corresponding acetic or α-substituted propionic acid and the insertion of another methylene group weakens it by a further 0·4 pK unit to a value corresponding to that for butyric acid. Similarly chloro-substituted phenoxyethyl dihydrogen phosphates are weaker than the corresponding phenyl dihydrogen phosphates and are equivalent in strength to ethyl dihydrogen phosphate (pK'_1 = 1·60, pK'_2 = 6·62).[7] It appears therefore that the inductive effect of the phenoxy-group is almost eliminated by the insertion of two methylene groups and completely so by the insertion of three or more.

TABLE 4.

R		CH_3	H	C_6H_5	HO	C_6H_5O †	I	Br	Cl
$R{\cdot}CH_2{\cdot}CO_2H$	pK'_1 ...	4·87 [a]	4·74 [a]	4·25 [a]	3·31 [b]	3·12	3·13 [a]	2·86 [a]	2·81 [a]
$R{\cdot}CH_2{\cdot}P(\colon O)(OH)_2$ *	pK'_1 ...	2·43 [c]	2·38 [c]	1·85 [e]	1·91 [d]	1·22	1·30 [d]	1·14 [d]	1·40 [d]
,,	pK'_2 ...	8·05 [c]	7·74 [c]	7·4 [e]	7·15 [d]	6·84	6·72 [d]	6·52 [d]	6·30 [d]

* See Freedman and Doak, *Chem. Rev.*, 1957, **57**, 479, for other pK values for substituted phosphonic acids. † Determined here.

[a] Watson, "Modern Theories of Organic Chemistry," Oxford Univ. Press, 1941, Table I, p. 27. [b] International Critical Tables, Vol. VI, p. 262. [c] Ref. 13. [d] Crofts and Kosolapoff, *J. Amer. Chem. Soc.*, 1953, **75**, 5738. [e] Lesfauries and Rumpf, *Bull. Soc. chim.*, 1950, 542.

Chloro-substitution in the phenyl ring generally enhances the acidic strength, the magnitude depending on the number of chloro-groups and the distance of separation between the aromatic nucleus and the ionising group. In the phenoxyacetic acids and their phosphorus analogues the effect is so small as to be partially swamped by solvent effects [cf. the different order of strength of substituted phenoxyacetic acids in water and in 50% ethanol (Table 2)].

2 : 6-Disubstituted derivatives are exceptional in being weaker acids than their isomers and in some cases than their unsubstituted parent acid, *e.g.*, 2 : 6-dichloro- and 2 : 4 : 6-trichloro-phenoxyacetic acids and phenoxymethylphosphonic acids. This anomaly is reflected in a smaller intensity of the ultraviolet absorption bands than with other isomers.[3] It has been attributed [8] to steric hindrance's preventing the oxygen–methylene carbon bond's lying in the plane of the benzene ring with a consequent reduction in conjugation between the side-chain and the aromatic nucleus. This weakens the inductive pull of the phenoxy-group on the electrons associated with the acidic group and leads to an acid-weakening effect.

It is noteworthy that 2 : 6-disubstituted phenoxyacetic acids are generally inactive as auxins and have been claimed [9] to act as anti-auxins. Although such behaviour has been attributed to the chemical blocking of both *ortho*-positions, the fact that the substitution of the smaller fluoro-group for one of the *ortho*-chloro-groups in 2 : 4 : 6-trichlorophenoxyacetic acid restores auxin activity [10] suggests that the anomalous biological as well as physicochemical behaviour can be attributed to stereochemical factors.

The ethyl hydrogen phosphonates are *ca.* 0·4 pK unit stronger than the free acids, a similar effect having been observed [7] with phosphoric acid and its simple alkyl esters. This could not be attributed to an inductive or statistical effect, both of which would be acid-weakening, but rather, as in the case of the phosphate esters, to a solvation effect's stabilising the free acid relative to its ion more than the ester relative to its ion.

Substituted phosphinic acids are stronger than the corresponding phosphonic acids by *ca.* 0·3 pK unit. No accurate comparison of the relative strength of phosphinic and phosphonic acids has been reported previously, although Lesfauries and Rumpf's results [11]

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[7] Kumler and Eiler, *J. Amer. Chem. Soc.*, 1943, **65**, 2355.

[8] Wiles, *Chem. Rev.*, 1956, **56**, 329; Burawoy and Chamberlain, *J.*, 1952, 2310.

[9] McRae and Bonner, *Plant Physiol.*, 1952, **27**, 834.

[10] Wain, *Science Progress*, 1956, **176**, 604.

[11] Lesfauries and Rumpf, *Compt. rend.*, 1949, **228**, 1018.

on the strength of substituted phenylphosphinic and phenylphosphonic acids are consistent with ours. This trend is again contrary to what would be expected from inductive and statistical considerations so that a solvation effect may be responsible, although in this case the possibility of differing resonance stabilisation energies cannot be ignored.

Unfortunately direct comparison is not possible between the phosphonic and phosphinic acids studied and the corresponding phosphates because of difficulties in preparing phenoxymethyl dihydrogen phosphates. The pK' values for *p*-chlorophenyl dihydrogen phosphate (0·37 and 5·83) can however be compared with that for *p*-chlorophenylphosphonic acid[12] (pK'_1 = 1·66 and pK'_2 = 6·75) from which it is clear that the phosphate is the stronger acid. A similar conclusion can be drawn from comparison in the alkyl series, *e.g.*, ethyl dihydrogen phosphate, pK'_1 = 1·60; pK'_2 = 6·62,[7] and ethylphosphonic acid, pK'_1 = 2·43; pK'_2 = 8·05.[13]

The spectral change accompanying the ionisation of the strong phosphorus-containing acids has a particular application to the measurement of the H_- acidity function in strongly acidic media. Some preliminary data for aqueous hydrochloric acid solutions pertinent to this investigation are shown in Table 1, and more detailed results will be discussed elsewhere.[3]

The pK values reported indicate that of the phosphorus-containing acidic groups the order of strength is phosphate > ethyl phosphonate > phosphinic acid > phosphonic acid.

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[12] Jaffe, Freedman, and Doak, *J. Amer. Chem. Soc.*, 1953, **75**, 2209.

[13] Crofts and Kosolapoff, *J. Amer. Chem. Soc.*, 1953, **75**, 3379.