7. (*o*-Hydroxyphenyl)methylphosphonic acids: Synthesis and Potentiometric Determinations of their pK_a Values

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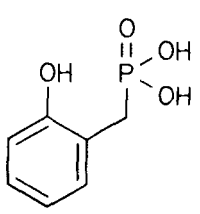
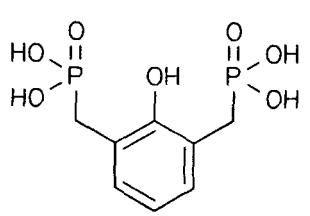
(*o*-Hydroxyphenyl)methylphosphonic acids are readily obtained from *o*-(bromomethyl)- or *o*-(hydroxymethyl)phenols and trialkyl phosphites. Subsequent hydrolysis leads to the corresponding phosphonic acids. For a series of such compounds, the pK_a values have been determined by potentiometry. Their dependence on additional substituents in the aromatic ring is discussed in terms of electronic and steric effects.

Introduction. – Organic phosphates, for example tributyl phosphate or di(2-ethylhexyl) phosphate, are known for their affinity for heavy metal cations, and, therefore, they are widely used as extractants [1]. One disadvantage of these compounds is that they are principally sensitive to hydrolytic attack. In contrast, phosphonic acids, with the P–C bond as the essential structure, are resistant to hydrolysis and are, therefore, superior to phosphoric-acid derivatives, especially for longer lasting applications under aggressive conditions. The same holds for phosphinic acids and for phosphin oxides. Consequently, a large number of such compounds has been examined with respect to their complexing properties and their suitability as extractants, and some are commercially available and used in industrial applications (for reviews, see [1]).

A general concept to improve the complexing properties is introduction of further functional groups which can cooperate with the phosphonate structure to form stronger and perhaps more specific complexes. Such a structure can be realized with the (*o*-hydroxyphenyl)methylphosphonic acids in which one or two methylphosphono groups are combined with a phenolic OH group at a suitable intramolecular distance, leading to the tridentate or pentadentate ligands, **1** or **2**, respectively. Compound **1** may be described as



1



2

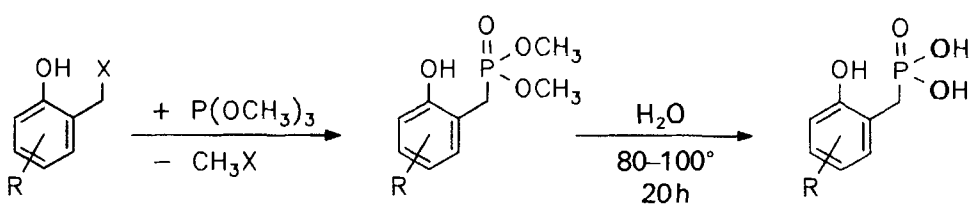
o-hydroxybenzylphosphonic acid. Compound **2** is a 2-hydroxy-1,3-phenylenebis-(methylphosphonic acid). In this paper, compounds of type **1** and type **2** will be described as 'mono-' and 'bis-phosphonic acids' for convenience.

Benzylphosphonic acids (phenylmethylphosphonic acids) are usually obtained from reaction of benzyl halides with trialkyl phosphites, according to the *Michaelis-Arbuzov* reaction. For phenolic benzylphosphonic acids, especially with the phenolic OH in *o*-position relative to the phosphonomethyl group, the direct reaction of *o*-hydroxybenzyl alcohols with trialkyl phosphites [2] [3] is also possible. The dialkyl esters formed by these reactions are readily hydrolyzed under acidic conditions.

Based on **1**, we recently obtained a cation-exchange resin which clearly discriminates between different metal cations [4], but the use of **2** seems even more promising. To incorporate these ligands into polymer networks, at least one of the ring positions is needed. The remaining ones are free for other substituents, by which the properties of the acidic function can be modulated. Besides incorporation of such structures into highly cross-linked (and inevitably not so well defined) products for practical purposes, it is desirable to study the low-molecular-weight models also. In this paper, we present a detailed potentiometric study of the acid/base properties of various mono- and bis-phosphonic acids. These results are the basis for an understanding of their complexation properties with various metal cations as a function of pH, and for the development of improved ionophores, extractants, and ion-exchange resins. In a second part, we will complete and support these results by spectrophotometric results.

Synthesis and General Properties. – All compounds used for this study, were obtained according to the general reaction *Scheme*. The overall yields for phosphonylation and subsequent hydrolysis of the phosphonic ester intermediates range between 40 and 80%.

Scheme



X = Br, OH

The *o*-(halomethyl)- or *o*-(hydroxymethyl)phenol is mixed with a slight excess of $(MeO)_3P$ at room temperature. Spontaneously or with gentle heating, a vigourous reaction starts with evolution of MeBr or MeOH, respectively. Normally, it is finished after some minutes. In many cases, the product crystallizes spontaneously on cooling. If not, the volatile constituents are removed in vacuum at 50°, and crystallization is performed by addition of Et_2O and cooling in a refrigerator. The crude material is recrystallized from AcOEt. Crystallization failed sometimes, especially when two alkyl groups were present.

The ester intermediates are readily hydrolyzed by H_2O or H_2O/MeOH. Addition of mineral acid as catalyst is not necessary. The *ortho*-OH group acts as an intramolecular

catalyst for the hydrolysis, a process well known for salicylates. It is a similar neighboring-group effect, which is also responsible for the modulation of pK_a values, discussed later in this paper.

A delicate problem is the characterization of the free acids of type **2** which contain two phosphonomethyl groups in the 2,6-positions relative to the phenolic OH. Most of them crystallize with one or two molecules of H_2O (as confirmed by an X-ray structure of **11**). Strong drying conditions remove this H_2O of crystallization. However, it is not possible to do this in a controlled way, because at 100°, even with gradual heating, H_2O is lost also by a chemical reaction, probably between the acidic and the phenolic OH. Due to this fact, a definite stoichiometric composition is difficult to obtain.

Evidently, the elemental analysis is affected by this problem of sample preparation. In addition, these compounds have bad combustion properties. For these reasons, the elemental analysis is not as precise and reliable as usual and consequently only of limited value. Due to this behavior, the melting points are not well defined and in practice also useless for characterization. Microscopic observation shows that partial melting, partial resolidification and eventually definite melting occur over a temperature range of 100 to 250°.

In this situation, individuality and purity are best proven by a combination of ^{1}H-NMR and alkalimetric titration. For all samples used for pK_a determinations, the NMR (200 MHz) showed purity of better than 99% and titration experiments gave NaOH consumptions within ±0.5% of the expected values.

Titration Experiments and pK_a Values Determination. – Details of the method are described in the *Exper. Part.* The *Figure* shows the titration curves of compounds **1** and **2** as typical examples of mono- and bis-phosphonic acids.

The mono-acid is characterized by two equivalent points for the two P–OH groups. The phenolic OH group cannot be seen as an inflexion of the curve, but the shape is

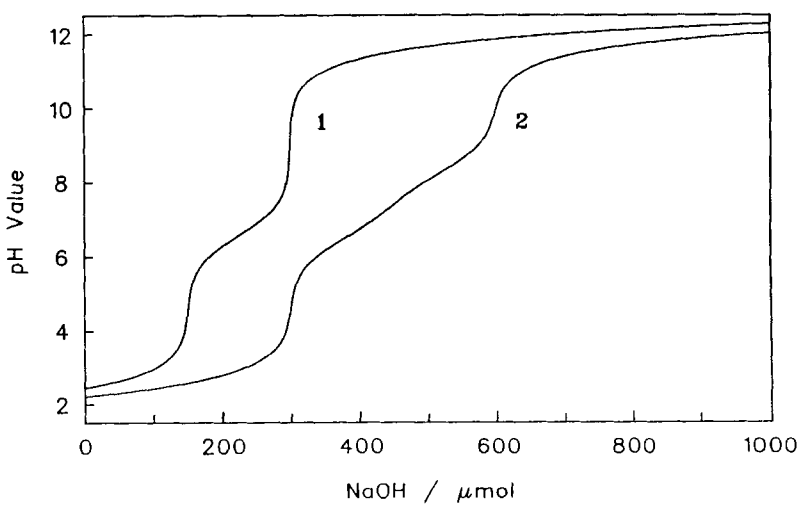
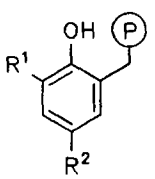


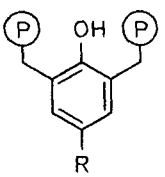
Figure. *Titration curves of (o-hydroxyphenyl)methyl phosphonic acid* (**1**) *and 2-hydroxy-1,3-phenylenedimethylbis(phosphonic acid)* (**2**)

precisely enough defined, to enable determination of the third pK_a value. The bis-acid shows only three of five possible inflexion points, at two, three, and four equivalents of base. The first one for P(O) $(OH)_2$ and the last one for the phenolic OH cannot be seen. But as in the case of the mono-acid, all five pK_a values can be obtained by computational methods.

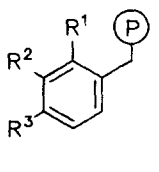
The purpose of this study was to establish a relationship between pK_a values and the substituent pattern of the aromatic ring for compounds derived from **1** (**3–10**), **2** (**11–15**), and some related compounds (**16–20**). For this purpose, exact thermodynamic pK_a values are not necessary. It is sufficient to compare the compounds under precisely controlled conditions.



	R_1	R^2
1	H	H
3	CH_3	CH_3
4	*t*-Bu	CH_3
5	*t*-Bu	*t*-Bu
6	H	NO_2
7	CH_3	NO_2
8	*t*-Bu	NO_2
9	NO_2	CH_3
10	NO_2	NO_2



	R
2	H
11	CH_3
12	*t*-Bu
13	NO_2
14	Cl
15	OCH_3



	R^1	R^2	R^3
16	H	H	H
17	H	H	OH
18	CH_2Ⓟ	H	H
19	H	CH_2Ⓟ	H
20	H	H	CH_2Ⓟ

Ⓟ = $-PO(OH)_2$

The standard conditions used during this study were: concentration of the acids, $5 \cdot 10^{-3}$ M; supporting electrolyte, 0.1M $NaClO_4$; temperature: 25.0 ± 0.1°; and standard solution: 1M NaOH.

At least four titration curves were registrated for each compound, and at least 200 data pairs of pH *vs.* NaOH consumption were collected during each experiment. These data were treated off line with a computer program briefly described in the *Appendix* (*Method 1*). The pH electrode was calibrated using buffer solutions. That means, the data are based on the 'practical pH scale' as recommended by *Sigel et al.* [5], leading to apparent deprotonation constants.

For convenience, we use the notation pK_1, pK_2, *etc.* for the pK_a of the first, the second, and so on dissociation step. Some of the dissociation constants were additionally determined using an electrode which was calibrated with 10^{-2} and 10^{-3} M solutions of perchloric acid (of the same ionic strength as for the measurements) and, thus, referring to hydronium ion concentrations of 10^{-2} to 10^{-3} M, respectively. Computation was accomplished in this case with the general MINIQUAD program (*Method 2*). This leads to deprotonation constants based on the 'concentration scale' [5].

As pointed out by *Sigel et al.* [5] pK_a values obtained on the basis of the 'practical pH scale' (*Method 1*) should be higher by *ca.* 0.03 pK units compared to those obtained *via* the 'concentration scale' (*Method 2*). In practice, some larger deviations are found, which

we deliberately report. They must be caused by the different treatment (calibration, titration, and computation) of exactly the same samples and illustrate the difficulties in comparing results obtained by different laboratories. This is especially the case for pK_a values below 2 and above 11, where the limits of the potentiometric method are reached.

For the following discussion, exlusively data obtained by *Method 1* are used, which are strictly comparable. The results are compiled in *Tables 1* and *2*.

Table 1. *p*K$_a$ *Values of Mono-phosphonic Acids*[a])

Compound	pK_1	pK_2	pK_3
1	2.00 (1.80)	6.52 (6.35)	11.78 (11.21)
3	1.64	6.49	11.84
4	1.56	6.50	11.84
5	1.52	6.55	11.82
6	1.85 (1.68)	6.08 (6.00)	9.35 (9.10)
7	1.53 (1.51)	5.88 (5.76)	9.80 (9.56)
8	1.34	5.90	10.12
9	1.92	6.67	9.78
10	1.64 (1.10)	4.39 (4.22)	7.92 (7.96)
16	2.03	7.51	
17	2.07 (1.91)	7.54 (7.43)	10.33 (10.05)

[a]) Values in brackets determined by *Method 2*.

Table 2. *p*K$_a$ *Values of Bis-phosphonic Acids*[a])

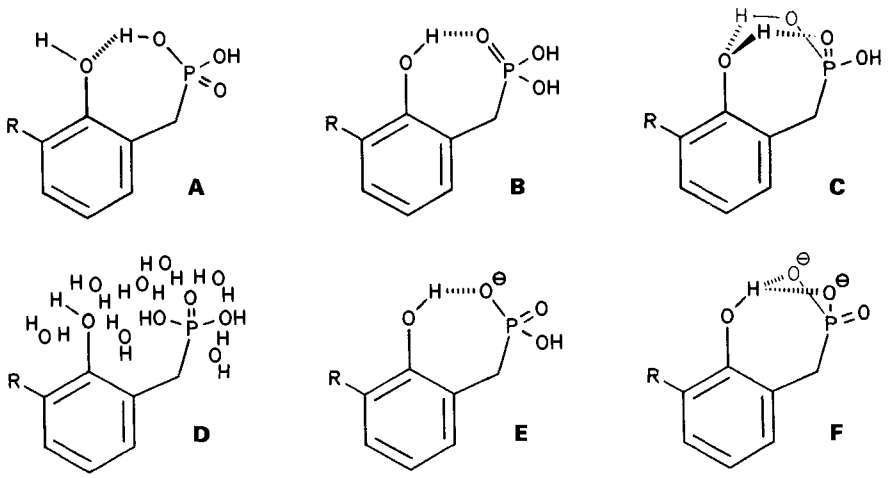
Compound	pK_1	pK_2	pK_3	pK_4	pK_5
2	1.36 (1.50)	2.48 (2.24)	6.45 (6.24)	8.29 (8.04)	12.06 (11.76)
11	1.46 (1.60)	2.47 (2.33)	6.51 (6.36)	8.30 (8.08)	11.88 (11.86)
12	1.50	2.38	6.50	8.38	11.89
13	1.01 (1.65)	2.20 (2.00)	5.88 (5.78)	7.90 (7.75)	10.54 (10.30)
14	1.45 (1.73)	2.34 (2.13)	6.29 (6.13)	8.11 (7.87)	11.94 (11.74)
15	1.26 (1.81)	2.36 (2.26)	6.41 (6.30)	8.19 (8.00)	11.87 (11.70)
18	1.49	2.75	7.07	8.93	
19	1.73	2.44	7.27	8.27	
20	1.76	2.49	7.34	8.16	

[a]) Values in brackets determined by *Method 2*.

The pK_a values obtained by a given method are reproducible within a standard deviation of ±0.05 in the middle of the scale ranging from 3 to 10 and increasingly worse below and above (*cf.* the *Exper. Part*).

Mono-phosphonic Acids. – Among these compounds, the unsubstituted benzylphosphonic acid (**16**; $pK_1 = 2.03$, $pK_2 = 7.51$) and the (4-hydroxybenzyl)phosphonic acid (**17**; $pK_1 = 2.07$, $pK_2 = 7.54$) are the weakest. pK_1 and to an even greater extent pK_2 decrease by introducing an OH group in the *ortho*-position (**1**), and the introduction of further substituents causes a further decrease in comparison with **1**. These observed effects must be explained by intramolecular H-bonds, since the phosphonic-acid group is separated by a CH_2 group from the aromatic ring system, and, therefore, mesomeric effects can be ruled out.

There are several possibilities to formulate interactions by H-bonds within the undissociated (*o*-hydroxybenzyl)phosphonic acids.



A: One of the P–OH groups is the proton donor and the phenolic OH is the acceptor.
B: The phenolic OH is the donor and the phosphoryl O-atom (P=O) is the acceptor.
C: The situations of **A** and **B** are combined assuming a cyclic array of two H-bonds of 'opposite polarity', similar to the common formulation for the dimers of carboxylic acid or to the cyclic array of H-bonds in calixarenes [6].
D: Taking into account the fact that huge amounts of H_2O are present as solvent, formulation **D** may be regarded as the most realistic one. This means, that the phosphonic acid and the phenolic OH are included into a cluster of H_2O molecules, within which interactions are transferred by 'a fluctuating network of H-bonds' over more or less long distances.

Intramolecular H-bonds are even more important in the anions, which are stabilized thus by partial compensation of the negative charge. UV-Spectroscopic studies (which are described in a second part of this series) clearly show, that in all cases (except the dinitro compound **10**) the phenolic OH group is dissociating last, which leads to the structures **E** and **F**.

E: For the monoanion a formulation with a H-bond directed from the phenolic OH group to the phosphonate oxygen (like in **B**) is the most probable structure, although in principal H-bonds like in **A** or **C** are still possible.
F: A 'three-center H-bond' [7] may be the best characterization of the situation in the dianion.

The pK_a value of a given acid H_nL reflects the difference of the *Gibbs* free energy (in standard states) between H_nL and its corresponding conjugated base $H_{n-1}L^-$ ($pK_a = \Delta G_0/(2.303 \cdot RT)$). A lower pK_a in comparison to a reference compound may be caused, therefore, either by a relative stabilization of the base or by a relative destabilization of the acid. The following results will be discussed according to these arguments.

Effect of the OH Groups in Benzylphosphonic Acid. Introduction of an *ortho*-OH group scarcely changes pK_1, but pK_2 decreases by 0.99 pK units (compounds **16** and **1**). Intramolecular H-bonds do not stabilize the monoanion more than the acid, but stabilize the dianion more than the monoanion, if **1** is compared with **16**. This stabilization by a structure like **F** is evident also in pK_3 for the dissociation of the phenolic OH which in **1** is higher by 1.45 in comparison to **17** and by 1.6 in comparison to *o*-cresol (10.2 [8]).

Introduction of the OH group in the *para*-position (**17**) has no influence on the dissociation behavior of the phosphonic acid group. Both pK_a values are practically equal for **17** and for benzylphosphonic acid (**16**). Further, the dissociation of the phenolic *p*-OH group is independent of the presence of the phosphonic structure. The value found (10.33) is practically the same as for *p*-cresol (10.26 [8]). Without the possibility of a H-bond, both functional groups behave completely independent.

A behavior similar to **1** and **17** with respect to pK_2 and pK_3 is well known for salicylic acid ($pK_1 = 2.8$, $pK_2 = 12.4$) and *p*-hydroxybenzoic acid ($pK_1 = 4.6$, $pK_2 = 9.3$) [8].

Effect of the p-*Nitro Group in Hydroxy-monophosphonic Acids.* A NO_2 group in *p*-position relative to the phenolic OH group (**6**) not only lowers pK_3, which is related to the dissociation of this OH group (*–M* effect of NO_2) but in comparison to **1** lowers pK_2 also (–0.44). With its increased acidity, the phenolic OH group becomes a better donor for an intramolecular H-bond which leads to a stronger stabilization of the dianion as indicated in **F**. This '*p*-nitro effect' is not very dramatic, but it is also observed in the pairs **3**/**7** and **4**/**8**. The pK_3 of **6**, **7**, or **8** of course is much higher than in the corresponding *p*-nitrophenols (*e.g.* $pK_a = 7.2$ for 2,6-dimethyl-4-nitrophenol), since the proton not only is involved in a strong intramolecular H-bond, but also has to split from a dianion.

Effect of Substituents ortho *to the Phenolic OH Group.* Mono-acids **6**, **7**, and **8** differ only in their substituents in *o*-position to the phenolic OH group. They show a continuous decrease in pK_1 and a continuous increase in pK_3, while pK_2 remains nearly constant. This can be explained by the increasing bulkiness of the *o*-substituent which directs the phenolic OH group towards the phosphonomethyl group, thus favoring structures like **B** (which facilitate the dissociation of the first proton), and **E** and **F** (which stabilize the mono- and dianion). The hindered solvation of the phenolic O-atom in the trianion by the *o*-alkyl group may be an additional reason for the increase in pK_3. An analogous relation between size of the *o*-substituents and acidity of remote phenolic OH groups was observed in linearly connected oligophenols [9]. The situation as described for the *p*-NO_2 series is analogous for compounds with unpolar *p*-substituents, where the pK_1 values also decrease slightly with increasing bulkiness (**1** > **3** > **4**, **5**).

The *o*-NO_2 compounds **9** and **10** require a special mention.The electron-withdrawing *o*-NO_2 group will increase the acidity of the phenolic OH group similar to the *p*-NO_2 group, but will also act as a potential acceptor for an intramolecular H-atom from the adjacent phenolic OH group. This must be a reason for the different pK_1 and pK_2 values of **9** in comparison to the isomeric compound **7** where just the NO_2 and the Me groups have changed their positions. A more detailed discussion would require more examples.

Compound **10** is the only one where pK_2 refers to the dissociation of the phenolic OH and pK_3 to the second P–OH. This follows unambiguously from UV-spectroscopic studies (*cf.* the second part of this series) and can be easily understood by the strong acidifying effect of two NO_2 groups. Therefore, a comparison with the other compounds seems meaningless.

Bis-phosphonic Acids. – The pK_a values of the bis-phosphonic acids studied are collected in *Table 2*. Surprisingly, the five pK_a values are very similar for all phenolic bis-acids (except the *p*-NO_2 compound). The ranges are: $pK_1 = 1.3$ to 1.5, $pK_2 = 2.3$ to 2.5, $pK_3 = 6.3$ to 6.5, $pK_4 = 8.1$ to 8.4, $pK_5 = 11.9$ to 12.1.

Within the experimental error the pK_a values for the acids with the unpolar *p*-substituents H, Me, and *t*-Bu are equal. The *p*-Cl and the *p*-MeO compounds show pK_a values on the lower limit of the pK_a ranges mentioned above, but these deviations are hardly significant.

The only clear exception is the *p*-NO_2 compound **13** (the data of which are the average of 16 measurements). Compared with the mean values for the *p*-H, *p*-Me, and *p*-(*t*-Bu) compounds, its pK_a values are lower by 0.4, 0.2, 0.6, 0.4, and 1.4 pK units. Even here, with the most acidic phenolic unit of the series, the last proton (pK_5) dissociates from the phenolic OH group, which is clearly demonstrated by UV-spectroscopic evidence. Thus, pK_1 and pK_2 refer to the dissociation of the first proton of each $PO(OH)_2$ group, and pK_3 and pK_4 to the dissociation of the second proton.

The phenolic OH group in **2** lowers pK_1 by 0.4 and pK_3 by 0.8 units compared with the parent non-phenolic diacid **19**. This latter effect has the same order of magnitude as found for pK_2 of the monoacids **1** and **16** (1.0 units), and the explanation is the same in both cases, namely the stabilization of a phosphonate dianion PO_3^{2-} (for **2**, at one of the two P-centers) by a H-bond involving the phenolic OH.

Interaction of Both Phosphonic Groups in Bis-Phosphonic Acids. An important question for the bis-acids is whether both phosphonic groups interact or not. For statistical reasons the two pK_a values of a dibasic (diprotonic) acid, in which two (chemically identical) acidic groups are completely independent, differ by

$$pK_2 - pK_1 = \log 4 \; (= 0.602).$$

This difference is found for instance as limiting value for aliphatic dicarboxylic acids $HOOC-(CH_2)_n-COOH$ with increasing chain length *n* [8]. (Treatment as a monobasic acid of double concentration then leads to $pK_a = (pK_1 + pK_2)/2$.)

Due to the observed large difference between pK_2 and pK_3 all bis-phosphonic acids studied here may be regarded as diprotonic with two acidic centers below pH 4, where each $P(O)(OH)_2$ group looses one proton. In analogy, their dianions again are two centered diprotonic acids in the pH range between 4.5 and 9.5, where each $P(O_2)PH^-$ group looses the second proton. The deviation of $(pK_2 - pK_1)$ and $(pK_4 - pK_3)$ from 0.602 then reflects the strength of the interaction of the two acidic groups, regardless of the kind of this interaction. The difference $(pK_2 - pK_1)$ increases in the order: 0.73 (**20**), 0.71 (**19**) < 1.12 (**2**) < 1.26 (**18**). For **20** and **19**, where no direct interaction of the acidic functions is possible, the difference, slightly higher than 0.6, may be explained by electrostatic attraction. The somewhat higher difference for **2** in comparison to **19**, however, indicates an interaction by intramolecular H-bonds *via* the phenolic OH group. Stabilization by intramolecular H-bond directly between the phosphonic groups may be present in **18**.

The same order is found for the differences $(pK_4 - pK_3)$: 0.82 (**20**) < 1.00 (**19**) < 1.84 (**2**), 1.86 (**18**). They are slightly higher than $pK_2 - pK_1$ for **20** and **19**. The distinctly higher differences for **2** and **18** are due to the stabilization of the trianion by strong intramolecular H-bonds, which in the case of **2** again include the phenolic OH.

In conclusion it can be said, that an interaction between the two phosphonic-acid groups exists in diacids of type **2**, which is mediated by the phenolic OH group. This interaction is more pronounced in the second dissociation step of the phosphonic groups $((pK_4 - pK_3) > (pK_1 - pK_2))$.

Experimental Part

The synthetic procedures are not optimized for all the compounds mentioned, but as a general rule one can state: *a*) the whole synthesis works best with halogen-substituted compounds or with mononitro compounds; *b*) with dinitro compounds the yield drops to *ca.* 30%, probably because partial reduction by the trivalent phosphorus occurs; *c*) esters of phosphonic acids with exclusively alkyl substituents are especially sensitive towards hydrolysis. Solvents for recrystallization must be carefully dried. Some esters of this type do not crystallize, and purification must be done at the acid stage.

Synthesis. Phosphonylation Reaction. The following general procedure is the same for *o*-hydroxybenzyl halides and for *o*-hydroxybenzyl alcohols as the starting materials. Since the reactions are very exothermic, not more than 0.1 mol per batch should be used. The trialkyl phosphite can be diluted by an equal volume of toluene, but sometimes the yield drops under these conditions. $(MeO)_3P$ in general is better suited than other esters, because the products are mostly crystalline and the ^{1}H-NMR spectra are much more straightforward.

Procedure. Benzyl compound (0.1 mol) is placed in a two-necked 500-ml vessel equipped with a reflux condenser; 0.105 mol $(MeO)_3P$ per CH_2OH group (0.12 per halomethyl group) is added in one portion. The reaction starts spontaneously or on slow and careful heating to *ca.* 70°. Once started, it becomes very vigorous. When the reaction ceases, the mixture is held at 80 to 100° for ½ h and the solvents are then removed *in vacuo*. In most cases, the product crystallizes spontaneously or on addition of the 5- to 10-fold volume of Et_2O and cooling in a refrigerator for some h. If not, the crude mixture is submitted to hydrolysis. In most cases AcOEt was the most suitable solvent for recystallization of the esters. The yields of pure products range between 40 and 80%.

Hydrolysis. The alkyl esters of (*o*-hydroxyphenyl)methylphosphonic acids are readily hydrolyzed within a few h by pure H_2O. In this respect they behave quite differently compared with analogues without the phenolic *o*-OH group, which need conc. HCl and several days heating for total splitting.

Procedure. A slurry of the ester in H_2O is diluted with MeOH so that at least a part of the sample is dissolved. That mixture is heated in a closed vessel at 80°. In most cases, the hydrolysis is finished within 10 h, but in order to be certain one should let the reaction run for 20–30 h. The solvent is removed *in vacuo*.

The free acids behave very differently on recrystallization attempt. In most cases, (few) H_2O can be used, but sometimes with low recovery. For **1** and **5**, we could not find a suitable solvent. Therefore, it is strongly recommended to purify the esters carefully before hydrolysis.

Titration (*Method 1, Mainz*). The standard conditions are reported in the main part. At least four titration curves were registrated for each compound and at least 200 data pairs of pH *vs.* NaOH consumption were collected during each experiments.

For all titration experiments, a computer-controlled assembly of our own design was used. It consisted of a *Dosimat 655* with 1-ml piston burette (*Metrohm*) and a precision pH-meter (resolution 0.001 pH) with combined glass electrode, which was connected to a personal computer *via* an analog/digital converter. Function control, dosage of NaOH, data collection, and pK_a evaluation were performed by a program package specially designed for that equipment. All original data were collected on disc for further off-line treatment. 125 to 150 μmol of the acids were used for each titration experiment.

Determinations of pK_a values by potentiometric titration require some special precautions: *a*) The temp. in the titration vessel was adjusted to 25.0 ± 0.1°. The burette was kept at the same temp. by a water jacket supplied from the same thermostat. *b*) The titration vessel was swept by a slow stream of N_2 to exclude pertubations by CO_2. *c*) The standard 1N NaOH was stored not in a glass bottle, but in a polyethylene container equipped with a CO_2 trap. That container was directly connected to the *Dosimat via* 1/16″ *Teflon* tubing. The quality, predominantly the absence of CO_2, was checked periodically by test titrations of HCl and inspection of the titration curve at extended spreading. *d*) Only high quality deionized and CO_2-free H_2O was used for all solns. *e*) The glass electrode was adjusted daily with *Bates* buffers 4.005 and 9.180 (using special buffer substances for pH measurements supplied by *Merck Co.*, Darmstadt) under exact the same conditions as for the measurements, and controlled after each series.

Deviations never exceeded 0.01 pH units for both fix points within 8 h. *f*) To supress errors by diffusion of base during the waiting time for potential equilibration after each addition, the dosage trip for NaOH, dipping into the soln., had a diameter of less than 0.1 mm over the last 10 mm. *g*) One could expect a pertubation due to precipitation of $KClO_4$ in the diaphragm where KCl from the reference electrode and $NaClO_4$ from the soln. meet. Such clogging would result in alterations of the diffusion potential and in an increase of the electric resistance. We never observed such effects. Electric noise or response time of the combined electrode never increased even during extended measurements. The calibration was stable (*cf. e*) and the reproducibility, especially in the range around $pK_a = 7$, was well within maximal ±0.05 pK units (*cf.* later).

The precision of the pK_a values obtained is basically determined by the possible precision of pH measurements which we assume to be ±0.02 pH units over the whole scale from 2 to 12 covered during the titrations. The reproducibility of measured curves of the same kind, performed during a period of several months and with changing electrodes, is in the range of ±0.05. This range is mainly due to imperfection of the glass electrodes (aging, deviations between different species) and possibly by errors in the buffer solns. used for electrode adjustment or errors connected with the calibration process. For measurements carried out within a few days, the observed reproducibility is in the range of ±0.02 pH units.

For pK_a values between *ca.* 3 and 10, the possible error (due to our computing method) is numerically the same as for the pH values (±0.02 to ±0.05). But below and above these values, pK_a reacts increasingly more sensitively to uncertainties in the pH measurement. For $pK_a < 1.5$ the deviation can reach a multiple of the actual pH error. Accepting these considerations, pK_a values obtained by potentiometric measurements are reproducible within a standard deviation of ±0.05 units in the middle and increasingly worse at the ends of a scale ranging from 1 to 12.

Example. For six measurements with the bis-phosphonic acid **11**, the following results were obtained over a period of 6 month (extremata in brackets): $pK_1 = 1.46 \pm 0.09$ (1.26 to 1.74); $pK_2 = 2.47 \pm 0.05$ (2.43 to 2.58); $pK_3 = 6.51 \pm 0.02$ (6.44 to 6.59); $pK_4 = 8.30 \pm 0.02$ (8.25 to 8.39); $pK_5 = 11.88 \bullet 0.08$ (11.68 to 12.27).

Titration (Method 2, Strasbourg). The conditions are very similar to *Method 1*: *a*) The concentration of phosphonic acids was 10^{-2} M. *b*) The ionic strength was maintained constant with 0.1M $NaClO_4$. *c*) The standard NaOH soln. used (1M) was stored in a polyethylene container equipped with a CO_2 trap. *d*) The soln. was kept under a permanent Ar flow to exclude interferences due to CO_2. *e*) All experiments were performed using a 1-ml piston burette (*Metrohm, E635*), and a combined class electrode dipping into a doubled jacket glass cell. The temp. was kept constant at 25.0 ± 0.1°. The measurements were controlled by an automatic *Titroprocessor E636* (*Metrohm*) in the dynamic mode: the increments of added base change with the slope of the neutralization curve. Generally sets of 80 to 120 data points were collected. The experiments were repeated several times. *f*) The electrolyte used in the reference half cell of the combined glass electrode was 0.09M in $NaClO_4$ and 0.01M in NaCl. That means it was very similar to the base electrolyte used for calibration and for titrations. This provision minimizes the diffusion potential. *g*) The calibration of the electrode system was made using 10^{-2} and 10^{-3} M $HClO_4$ solns. (in 0.1M $NaClO_4$ as for the measurements). That means, calibration is based on H^+ concentration [5].

The pK_a values were evaluated using the well known MINIQUAD program [10].

With the data of two individual measurements with **11** and **16**, obtained by *Method 1*, the pK_a values were recalculated by MINIQUAD. The results are as follows (MINIQUAD values in brackets): **11**: 1.51 (1.55); 2.48 (2.46); 6.53 (6.50); 8.41 (8.37); 11.97 (11.88). **16**: 2.01 (1.98); 7.50 (7.49). Within the range of possible errors, both calculations yield identical results. The greatest deviations occur for pK_a values > 10.

Appendix. – *Short Description of the Program Used for* pK_a *Computation by* Method 1. The exact concentration of the acids was determined from the most distinct equivalent point of the titration curve. Nine data pairs around each 'half neutralization point' (at 0.5, 1.5,... equiv. of NaOH consumed) were used to interpolate the pH at exactly these points by fitting with a third order polynomial. These half neutralization points were used to evaluate as many pK_a values as acidic OH groups present. For this purpose, an iteration procedure was used, with the 'half equivalent pH values' as the starting set of assumed pK_a values. In the first step during a first fitting cycle all pK_a values except pK_1 are kept constant, and pK_1 is varied systematically as long a a calculated pH (for the corresponding half neutralization NaOH consumption) deviates from the 'measured' (the interpolated) one by at most ±0.0001 pH. Proceeding through all possible pK_a, in the second step pK_2 is varied, in the third pK_3 and so on. Eventually, the first cycle ends with a set of better adjusted pK_a values. 3 to 6 such cycles over all possible pK_a are needed to refine them all so that they become constant within a (computing) precision of ±0.0001 pK units. As described above, this is of course by far not the precision of the real pK_a values.

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