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Prediction of pK_a Vlaues of Alkylphosphonic Acids

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Synopsis. The pK_a values of unsubstituted and substituted alkylphosphonic acids in aqueous solution were found to have a good linear correlation with the electron densities of the phosphorus atom of the corresponding phosphonic acids, which are calculated using the PM3 method. This enabled us to predict the pK_a values of this class of compounds.

Many studies[1-11] concerning ionizations of alkylphosphonic acids have been carried out, due to the various bioligical interests of this class of compounds.[12] However, big discrepancies have been noted regarding the pK_a values reported by various workers, especially when they are for alkylphosphonic acids which are substituted with an electron-withdrawing group, and are expected to be relatively strong acids. This might be due because any measurement of pK_a is greatly influenced by various experimental conditions when measured by simple potentiometric titration in a lower pH range.[9,13] It is of great help if the pK_a values can be predicted without conducting any experiments, in the case that experimentally obtained pK_a values are not quite reliable. Along this line, various methods have been attempted in order to estimate the pK_a values. The acidity in the gas phase can be estimated by calculating the free energy-changes between neutral and dissociated species of the corresponding acid using ab initio[14] and semiempirical[15-17] molecular orbital methods. In most cases, however, except for only limited examples,[18] acidity in the gas phase has little correlation with the acidity in the aqueous phase due to strong hydration to an acidic moiety in the aqueous solution. Attempts have also been made to estimate the acidity in the aqueous phase in combination with estimating the acidity in the gas phase and the differences in free energies of hydration.[19] Alternatively, the electron densities of atoms, such as acidic hydrogen, oxygen adjacent to acidic hydrogen, or nitrogen, have been found to have some correlation with the acidity in the gas phase,[15,20] and in some cases even in the aqueous phase.[21]

This paper deals with a simple method used to predict the pK_a value of unsubstituted and substituted alkylphosphonic acids from the electron density of hydrogen, oxygen, and phosphorus atoms, which are component atoms of phosphonic acid.

Experimental

Calculations of the electron densities were performed using the MOPAC program[22] (ver. 6) with MNDO, AMI, and PM3 semiempirical methods. All of the structures were optimized by minimizing the energy with respect to the geometry. The results concerning the most stable conformers were used in this study.

Results and Discussion

The electron densities of hydrogen, oxygen, and phosphorus atoms were calculated for neutral molecules of phosphonic acids with MNDO, AM1, and PM3 semiempirical molecular orbital methods. Those densities were then compared with the reported experimental p$K_\mathrm{a}1$ values of the corresponding acids (listed in Table 1). The results showed that the p$K_\mathrm{a}1$ values have no linear correlation with the electron densities of the oxygen atom, though reasonably good correlations were observed regarding the electron densities of the hydrogen atom for all three methods with correlation coefficients[23] of 0.887—0.894. The highest correlation was found for those of the phosphorus atom with the PM3 method (r=0.918), as shown in Fig. 1a. However, it is clear from Fig. 1a that some of the data points for halogenoalkylphosphonic acids did not fit, since the reported p$K_\mathrm{a}1$ values found by various workers were scattered over a wide range. When halogenoalkylphosphonic acids were excluded, the electron densities of the hydrogen atom

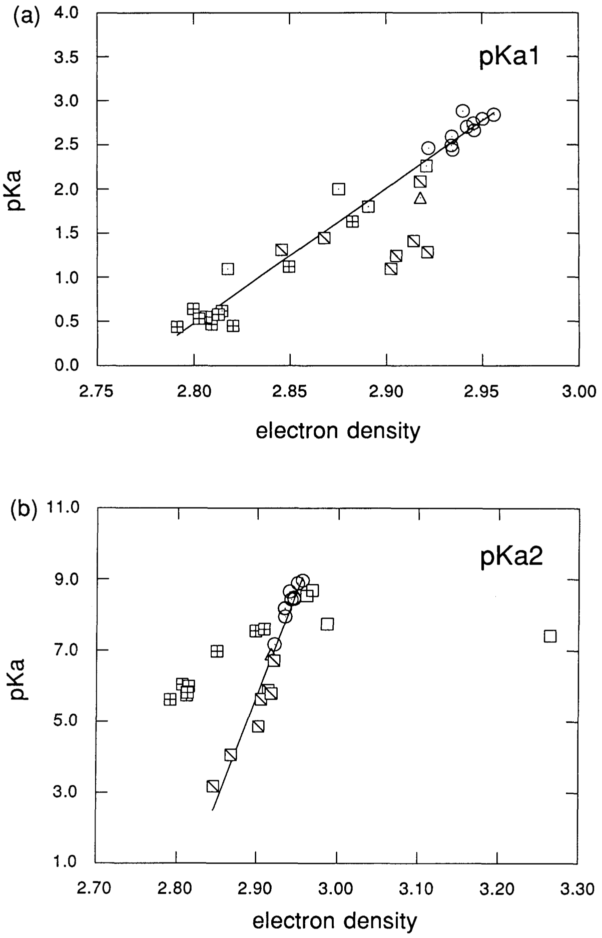

Fig. 1. Relationship between pK_a values and electron densities of phosphorus atoms. ○, unsubstituted alkyl; △, hydroxyalkyl; ⧅, halogenoalkyl; □, carboxyalkyl; ⊞, aminoalkyl.

appeared to have good linear correlations with the pK_a1 values using all the three methods. However, when regression analyses were performed for each individual substituted group, such as unsubstituted and substituted with halogeno, carboxy, hydroxy, and ammonium groups, the slopes and intercepts of the regression lines for each individual substituent group were found to be quite inconsistent (slope 50.0—195; intercept −36.5—(−149) for MNDO; 45.8—81.6 and =−30.5—(−56.4) for AM1; 51.7—251 and −37.0—(−191) for PM3). These results indicate that the linear correlations of the individual substituent groups are very much dependent on the nature of the substituent groups when the electron densities of the hydrogen atom are used for the parameter, even though the correlation coefficients for linear correlations including all the substituent groups except for the halogenoalkyl substituent, are in an acceptable level with all three methods (r=0.950—0.971).

On the other hand, when halogenoalkylphosphonic acids were similarly excluded for the phosphorus atom with the PM3 method, the slopes and intercepts for each individual substituent group stay within an acceptably narrow range (11.0—13.1 and −29.7—(−36.4) respectively) for all the substituent groups. The correlation coefficient without halogenoalkyl substituent was improved to be quite an acceptable level of 0.983. This indicates that the linear correlation between the pK_a1 values and the electron densities of the phosphorus atom is quite independent on the nature of the substitutent groups. It is interesting to note that the electron densities of the phosphorus atom were found to be significantly correlated, better than those of the hydrogen or oxygen atoms, which were found to be good indices in other classes of compounds.[16] This may be suggesting that the pK_a1 values of alkylphosphonic acids are a simple function of electronic effects of an unsub-

Table 1. Comparison of Experimental Values versus Estimated pK_a Values of Alkylphosphonic Acids

Alkyl	pK_a1		pK_a2		Electron density[a]
	Experimental	Estimated	Experimental	Estimated	
CH_3–	2.35[b] 2.68[c] 2.38[d] 2.48[e] 2.41[f]	2.31	7.10[b] 6.32[c] 7.74[d] 7.34[e] 7.35[f]	7.28	2.9221
CH_3CH_2–	2.43[d] 2.45[b]	2.50	8.05[d] 7.85[b]	8.03	2.9348
$CH_3CH_2CH_2$–	2.49[d]	2.49	8.18[d]	8.00	2.9342
$(CH_3)_2CH$–	2.66[d]	2.67	8.44[d]	8.70	2.9460
$CH_3CH_2CH_2CH_2$–	2.59[d]	2.50	8.19[d]	8.01	2.9344
$CH_3CH_2CH(CH_3)$–	2.74[d]	2.67	8.48[d]	8.67	2.9456
$(CH_3)_2CHCH_2$–	2.70[d]	2.62	8.43[d]	8.48	2.9423
$(CH_3)_3C$–	2.79[d]	2.74	8.88[d]	8.96	2.9504
$CH_3CH_2C(CH_3)_2$–	2.84[d]	2.83	8.96[d]	9.30	2.9562
$(CH_3)_3CCH_2$–	2.88[d]	2.59	8.65[d]	8.35	2.9402
$HOCH_2$–	2.21[c] 1.70[g] 1.91[h] 1.79[i]	2.24	5.65[c] 7.15[h] 7.90[i]	7.03	2.9178
CF_3–	1.46[c] 1.16[e]	1.14	2.43[c] 3.93[e]	2.76	2.8458
CH_2Cl–	1.04[g] 1.40[h] 1.51[f] 1.70[c]	2.19	6.30[h] 5.22[c] 6.17[f]	6.81	2.9141
$CHCl_2$–	0.70[g] 1.14[h] 1.44[c]	2.01	5.61[h] 4.12[c]	6.11	2.9024
CCl_3–	0.78[g] 1.63[h] 1.93[c]	1.48	4.81[h] 3.31[c]	4.07	2.8679
CH_2Br–	1.15[g] 1.14[h] 1.44[c]	2.05	6.52[h] 4.75[c]	6.27	2.9051
CH_2BrCH_2–	1.62[g] 2.55[c]	2.24	5.80[c]	7.03	2.9178
CH_2I–	1.27[g] 1.30[h]	2.30	6.72[h]	7.24	2.9214
HOOC–	0.49[c] 1.70[j]	0.71	7.27[c] 7.56[j]	27.58	2.8179 (3.2644)
$HOOCCH_2$–	ca. 2.0[j]	1.59	8.69[j]	10.00	2.8754 (2.9680)
$HOOCCH(CH_3)$–	1.80[j]	1.83	8.54[j]	9.60	2.8907 (2.9612)
$HOOCCH_2CH_2$–	2.26[j]	2.29	7.75[j]	11.11	2.9210 (2.9867)
$NH_3^+CH_2$–	0.44[g] 1.85[k] 2.35[b]	0.31	5.35[k] 5.90[b]	−0.48	2.7913
$CH_3CH(NH_3^+)$–	0.47[g]	0.58	—[m]	0.59	2.8092
$CH_3CH_2CH(NH_3^+)$–	1.95[l]	0.62	5.75[l]	0.74	2.8118
$(CH_3)_2CH(NH_3^+)$–	0.55[g] 2.09[l]	0.54	6.05[l]	0.41	2.8063
$(CH_3)CHCH(NH_3^+)$–	0.62[g] 2.04[l]	0.66	6.00[l]	0.91	2.8146
$CH_3CH_2CH_2CH(NH_3^+)$–	1.95[l]	0.63	5.83[l]	0.78	2.8124
$CH_3CH_2CH_2CH_2CH(NH_3^+)$–	0.58[g] 1.83[l]	0.64	5.82[l]	0.80	2.8128
$H_3N^+CH_2CH_2$–	1.12[g] 2.45[b] 2.11[l]	1.20	7.00[b] 6.97[l]	2.99	2.8497
$H_3N^+CH_2CH_2CH_2$–	1.63[g]	1.70	—[m]	4.93	2.8824
$H_3N^+CH_2CH_2CH_2CH_2$–	2.55[b]	1.94	7.55[b]	5.87	2.8983
$H_3N^+CH_2CH_2CH_2CH_2CH_2$–	2.60[b]	2.11	7.60[b]	6.50	2.9090
$CH_3NH_2^+CH_2$–	0.64[g]	0.44	—[m]	0.02	2.7997
$(CH_3)_2NH^+CH_2$–	0.45[g]	0.75	—[m]	1.24	2.8203
$CH_3CH_2NH_2^+CH_2$–	0.53[g]	0.48	—[m]	0.19	2.8026

a) The electron densities are for phosphorus atom of neutral molecule calculated with PM3 method. Numbers in parenthesis were calculated for carboxy anion form with PM3 method. b) Ref. 1. c) Ref. 11. d) Ref. 5. e) Ref. 3. f) Ref. 7. g) Ref. 9. h) Ref. 6. i) Ref. 8. j) Ref. 10. k) Ref. 2. l) Ref. 4. m) Data are not available.

stituted or substituted alkyl group on the phosphorus atom; the electron densities calculated using the PM3 method are therefore a good index of the electronic effect of the alkyl groups.

The $\mathrm{p}K_{\mathrm{a}}2$ values were also examined using the electron densities of hydrogen, oxygen, and phosphorus atoms for the corresponding mono anionic species. The calculations were carried out only using the PM3 method. Regression analyses showed that linear correlations with all of the compounds listed in Table 1 were found to be very poor for all three component atoms (correlation coefficient: 0.377—0.662); the slopes and intercepts were quite inconsistent among the individual substituent groups. Moreover, an unsubstituted alkyl substituent group showed a rather reverse correlation between the $\mathrm{p}K_{\mathrm{a}}2$ values and the electron densities. The $\mathrm{p}K_{\mathrm{a}}2$ values were thus found to have a good linear correlations with the electron densities of the phosphorus atom calculated for the corresponding neutral molecules,[24] better than or at least almost equal to those of the corresponding mono anionic species, as shown in Fig. 1b. This strongly suggests that the $\mathrm{p}K_{\mathrm{a}}2$ values of alkylphosphonic acids are also a simple function of the electronic effect of substituents. Regression analyses showed that the slopes and intercepts of ionic substituent groups such as ammonium (18.9 and −46.0, respectively) and carboxy (−3.29 and 18.1, respectively), are quite different from those (41.0—49.4 and −133—(−137), respectively) of the non ionic substituent groups. This might indicate that the $\mathrm{p}K_{\mathrm{a}}2$ values of the aminoalkyl and carboxyalkylphosphonic acids are still a function of the electronic effect of the substituents. However, it is likely that those groups have an ionic center in the substituents, so that the electronic effect is influenced by another ionic center of the dissociated phosphonic acid moiety in the same molecule; these might change the electronic effect of the substituents in actual molecules. Regression analyses without ionic substituent groups showed that the correlation coefficient is much improved to a quite acceptable level (r=0.962).

Table 1 summarizes the $\mathrm{p}K_{\mathrm{a}}$ values estimated based on the linear regression lines[25] shown in Fig. 1; they were compared with the $\mathrm{p}K_{\mathrm{a}}$ values reported in the literature. The results showed that the estimated $\mathrm{p}K_{\mathrm{a}}$ values have an excellent agreement with the experimental $\mathrm{p}K_{\mathrm{a}}$ values. Even many of the data points for halogenoalkylphosphonic acids agree very well with the corrresponding estimated values, even though they were estimated without a halogeno substituent group. In the case of $\mathrm{p}K_{\mathrm{a}}2$, it seems necessary to either handle aminoalkyl and carboxyalkylphosphonic acids separately or to incorporate additional term(s) into the linear regression equation.

It has been demonstrated that the electron densities of the phosphorus atom are a very good index of the acid strength of alkylphosphonic acids when the electron densities are calculated by the PM3 method. It appears that this correlation can be used to predict the intrinsic acidities of alkylphosphonic acids.

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23) Performing regression analyses, an average value was used when multiple $\mathrm{p}K_{\mathrm{a}}$ data points are available for a compound, and data in Ref. 9 were used for $\mathrm{p}K_{\mathrm{a}}1$ values of aminoalkylphosphonic acids due to unreliability of other data points.

24) Since carboxy group is expected to be fully ionic in the $\mathrm{p}K_{\mathrm{a}}$ range, the electron densities of carboxyalkylphophonic acids were recalculated with PM3 method for the structures which are ionic in the carboxy moiety and non ionic in the phosphonic acid moiety.

25) The slopes and the intercepts are 49.5 and −143 for $\mathrm{p}K_{\mathrm{a}}1$, and 15.3 and −42.4 for $\mathrm{p}K_{\mathrm{a}}2$, respectively.