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Prediction of pK_a values of phenolic and nitrogen-containing compounds by computational chemical analysis compared to those measured by liquid chromatography

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Abstract

The pK_a values of 64 phenolic and 50 nitrogen-containing compounds were obtained by reversed-phase liquid chromatography and computational chemical calculation. The chromatographically obtained values of phenolic compounds were equal to pK_a values from references and Hammett's equation, and those of nitrogen-containing compounds were lower than the reference values. It appeared difficult to calculate the properties of the *ortho* effect and nitro group by the computational calculation method. However, the calculation was simpler than selecting different constants of Hammett's equation for a variety of compounds.

Keywords: Dissociation constants; Hammett's equation; Phenolic compounds; Nitrogen-containing compounds

1. Introduction

The prediction of the dissociation constant is important for drug design and optimization in biomedical and environmental analysis [1–4]. Prediction of dissociation constants has usually been based on Hammett's equation, $pK_a = A + B\Sigma\sigma$, where A and B are constants for different groups of compounds, and σ is Hammett's constant [5]. A and B values were proposed for prediction of the retention times of aromatic acids [6]. The pK_a values can be measured by liquid chromatography. However, due to the instability of octadecyl-bonded silica gels, the retention time of phenolic and nitrogen-containing compounds cannot be measured in an eluent with a pH value that is higher than 8. This problem was

overcome by developing stable and inert bonded silica gels. The retention times of 51 phenolic compounds and 50 nitrogen-containing compounds were measured in eluents with pH values ranging from 2–10. Their dissociation constants were calculated using the following equation [7]:

$$k = (k_m + k_i[K_a]/[H^+]) / (1 + [K_a]/[H^+]) \quad (1)$$

where k_m is the maximum retention factor related to $\log P$ values, k_i is the minimum retention factor and $[H^+]$ is the hydrogen ion concentration. The pK_a values obtained by liquid chromatography have been used for the evaluation of a prediction method of pK_a values, based on a combination of empirical and theoretical approaches. The pK_a values were calculated by Hammett's equation and the CACheTM pK_a program based on the partial charge of atoms. The

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pK_a values obtained by these methods were correlated with each other.

2. Experimental

A Macintosh 8100/100 computer was used for the calculations and the software used was the CAChe™ pK_a program, including ProjectReader™ from Sony-Tektronix (Tokyo, Japan), Cricket-Graph™ from Computer Associates and TK-Solver™ from Universal Technical Systems (IL, USA). The liquid chromatograph was a model HP1090 from Hewlett-Packard (Los Angeles, CA, USA) and the octadecyl-bonded silica gel column, Luna C₁₈ (15 cm × 4.6 mm I.D.) was from Phenomenex (Torrance, CA, USA). Chemicals used were from Aldrich and ChemService. HPLC-grade acetonitrile was from Fisher Scientific and HPLC-grade water was from Merck.

The retention times of the 51 phenolic compounds listed in Table 1 were measured by reversed-phase liquid chromatography at 40°C in 70% aqueous acetonitrile containing 20 mM sodium phosphate buffer, pH 2–10. The retention times of the 50 nitrogen-containing compounds listed in Table 2 were measured at 40°C in 60% aqueous acetonitrile containing 20 mM sodium phosphate buffer, pH 2–10.

Furthermore, the pK_a values of 13 phenolic compounds that did not have completed retention times were calculated by hand and using a computer program. These calculated and predicted values of pK_a are summarized in Tables 1 and 2, with their reference values.

3. Results and discussion

The elution times of many of these compounds in ionized form were shorter than that of the void volume measurement marker, fructose, due to the ion-exclusion effect. Since the negative values of retention factor could not be used for the theoretical study, the retention factors of these compounds were therefore considered as zero. The compounds are 25, 27, 28, 31–35, 39, 44, 46, 53–55, 57 and 58 in Table 1 and 18, 19, 28 and 31–41 in Table 2. The measurement of pK_a values (pK_a [III] in Table 1) of phenolic compounds by liquid chromatography was still difficult because their expected pK_a values were

higher than 10. Their retention times could be measured in pH 10.5 and 11.0 eluent, but their k_i values could not be obtained. The expected pK_a values of several nitrogen-containing compounds were too low. Their retention times were measured phosphoric acid solution containing acetonitrile at pH 1.5. Therefore, the pK_a values were calculated with the k_i value set to zero. However, the pK_a values of 2,6-dimethyl-, 2,3,6-trimethyl- and 2,4,6-trimethylphenols, 2- and 4-nitroanilines and of pyrazine were not obtained due to their being no significant difference in their measured retention factors. The relationship between chromatographically measured and reference pK_a values for phenolic compounds is given by the following equation, based on data collected in Table 1.

$$pK_a[\text{III}] = 1.010 \times pK_a[\text{I}] + 0.220,$$

$$r^2 = 0.955, (n = 39),$$

The chromatographically measured pK_a values were equal to those from Ref. [8]. The retention behavior of nitrogen-containing compounds on an octadecyl-bonded silica gel column was different from that on a polymethacrylate gel [9], where retention times which were supposed to be constant became shorter in eluents with higher pH values. Such an unexpected phenomenon was not observed on the octadecyl-bonded silica gel column.

The relationship between chromatographically measured pK_a [II] in Table 2, and reference pK_a values (pK_a [I] in Table 2), for nitrogen-containing compounds is given by the following equation. Some pK_a values were calculated where the k_i value was zero, due to a lack of experimental data. The compounds are 9–14, 16, 23 and 42–45 in Table 2.

$$pK_a[\text{II}] = 0.895 \times pK_a[\text{I}] + 0.061,$$

$$r^2 = 0.907, (n = 29)$$

The compounds not included in this calculation are 6, 8, 12, 13, 15, 17, 19, 22–25, 27, 28, 33, 38, 40, 41, 44, 45 and 50 in Table 2. The chromatographically measured pK_a values were smaller than the reference values, even when the pH of the eluent was measured before mixing with the organic modifier, acetonitrile. Similar results were observed on the polystyrene gel where the pH was measured after mixing with acetonitrile.

Table 1
 pK_a Values of phenolic compounds obtained by different methods

	Chemicals	pK_a (I)	pK_a (II)	pK_a (III)	pK_a (IV)	pK_a (V)
1	Phenol	10.02	10.47	9.92	10.36	9.93
2	2-Methylphenol	10.32	10.50	10.21	9.94	10.26
3	3-Methylphenol	10.09	10.57	10.05	10.15	10.10
4	4-Methylphenol	10.27	10.57	10.23	10.36	10.10
5	2,3-Dimethylphenol	10.54	10.60	10.34	10.15	10.75
6	2,4-Dimethylphenol	10.60	10.69	10.52	10.15	10.26
7	2,5-Dimethylphenol	10.41	10.70	10.34	10.15	10.42
8	2,6-Dimethylphenol	10.63	–	10.50	10.15	10.10
9	3,4-Dimethylphenol	10.36	10.55	10.37	10.36	10.10
10	3,5-Dimethylphenol	10.19	10.60	10.19	10.36	10.26
11	2,3,4-Trimethylphenol	–	–	10.66	10.56	10.42
12	2,3,5-Trimethylphenol	–	10.59	10.48	10.56	10.42
13	2,3,6-Trimethylphenol	–	–	10.63	10.15	10.42
14	2,4,6-Trimethylphenol	10.88	–	10.81	10.15	10.10
15	2,3,4,5-Tetramethylphenol	–	–	10.79	10.36	11.07
16	2,3,5,6-Tetramethylphenol	–	–	10.77	10.15	10.91
17	Pentamethylphenol	–	–	11.08	10.36	11.56
18	2-Ethylphenol	10.20	10.58	10.12	9.74	10.42
19	3-Ethylphenol	9.90	10.59	10.08	10.36	10.10
20	4-Ethylphenol	10.00	10.61	10.25	10.36	10.10
21	4- <i>tert.</i> Butylphenol	–	10.67	10.25	10.36	9.93
22	2-Chlorophenol	8.48	9.44	8.40	7.88	8.79
23	3-Chlorophenol	9.02	9.83	9.10	9.53	9.28
24	4-Chlorophenol	9.38	10.08	9.39	9.74	9.28
25	2,3-Dichlorophenol	7.45	8.04	7.58	7.47	8.31
26	2,4-Dichlorophenol	7.89	8.33	7.87	7.47	7.98
27	2,5-Dichlorophenol	7.50	7.53	7.58	7.27	7.98
28	2,6-Dichlorophenol	6.79	7.32	6.89	7.06	6.35
29	3,4-Dichlorophenol	8.39	9.00	8.56	9.12	8.63
30	3,5-Dichlorophenol	8.18	8.43	8.27	8.91	8.47
31	2,3,4-Trichlorophenol	7.59	7.27	7.04	7.06	7.65
32	2,3,5-Trichlorophenol	7.23	6.82	6.75	6.86	7.49
33	2,3,6-Trichlorophenol	6.12	6.29	6.06	6.65	5.86
34	2,4,5-Trichlorophenol	7.33	7.08	7.04	6.86	7.49
35	2,4,6-Trichlorophenol	6.42	6.42	6.35	6.65	5.70
36	3,4,5-Trichlorophenol	7.74	–	7.74	8.50	7.98
37	2,3,4,5-Tetrachlorophenol	6.96	–	6.22	6.65	7.00
38	2,3,5,6-Tetrachlorophenol	5.44	–	5.24	6.24	5.54
39	Pentachlorophenol	5.26	4.84	4.70	6.03	5.05
40	2-Bromophenol	8.44	8.90	8.36	7.47	8.63
41	3-Bromophenol	9.03	9.67	9.05	9.53	9.28
42	4-Bromophenol	9.36	10.22	9.43	9.53	9.12
43	2,4-Dibromophenol	7.80	8.20	8.36	7.06	8.14
44	2,6-Dibromophenol	6.60	7.05	6.80	6.65	6.19
45	1,2-Dihydroxybenzene	–	–	9.83	11.18	6.19
46	1,3-Dihydroxybenzene	9.81	9.78	9.63	9.53	9.77
47	1,4-Dihydroxybenzene	10.35	9.97	10.77	10.56	9.93
48	1-Hydroxynaphthalene	–	10.54	–	9.74	9.93
49	2-Hydroxynaphthalene	–	10.70	–	9.94	9.93
50	2-Hydroxyacetophenone	–	11.04	–	10.36	13.35
51	4-Hydroxybutylbenzoate	–	–	–	9.12	8.63
52	4-Hydroxypropylbenzoate	–	–	–	9.12	8.63

(Continued overleaf)

Table 1 (continued)

	Chemicals	p <i>K</i> _a (I)	p <i>K</i> _a (II)	p <i>K</i> _a (III)	p <i>K</i> _a (IV)	p <i>K</i> _a (V)
53	2-Nitrophenol	7.23	7.29	6.80	8.30	2.12
54	3-Nitrophenol	8.40	8.56	8.27	8.71	7.98
55	4-Nitrophenol	7.15	7.23	8.18	7.88	7.49
56	2,4-Dinitrophenol	4.09	–	5.06	–2.21	6.35
57	2,5-Dinitrophenol	5.22	5.39	5.15	–1.38	7.00
58	2,6-Dinitrophenol	3.71	4.93	3.68	–2.21	1.31
59	3,4-Dinitrophenol	5.43	–	6.53	6.65	5.86
60	1-Hydroxy-2,4-dinitronaphthalene	–	–	–	–3.03	6.84
61	2-Chloro-5-methylphenol	–	9.73	8.54	9.12	7.82
62	4-Chloro-2-methylphenol	–	10.53	9.68	9.53	9.77
63	4-Chloro-3,5-dimethylphenol	–	10.63	9.65	9.94	9.44
64	4-Chloro-3-methylphenol	–	9.57	9.52	9.74	9.44

p*K*_a(I): from reference [8]; p*K*_a(II): chromatographic data; p*K*_a(III): by Hammett's equations; p*K*_a(IV): CAChe p*K*_a values calculated from the partial charge of hydrogen; p*K*_a(V): CAChe p*K*_a values calculated from the partial charge of oxygen.

trile and the measured p*K*_a values were normalized to those in a 100% aqueous solution. The measured p*K*_a values were converted into p*K*_a values in pure water using the following equation.

$$pK_a(\text{water}) = pK_a(\text{aqueous acetonitrile}) - 0.022(\% \text{ acetonitrile}).$$

Such a phenomenon was not observed for aromatic acids whose p*K*_a values were measured in reversed-phase liquid chromatography using polystyrene gel, and the p*K*_a values measured by titration were equivalent to their reference values [10].

Further study was carried out using Hammett's equation [5] and the CACheTM p*K*_a calculation method [11]. Tables 1 and 2 summarize the calculated values. The calculated results using Hammett's equations for different compounds from Ref. [1] were:

Hammett's equation p <i>K</i> _a	=A	+BΣσ
Phenolic compounds	=9.92	–2.23Σσ
Anilines	=4.58	–2.88Σσ
Pyridines(1)	=5.25	–5.90Σσ
Pyridines(2)	=5.39	–5.70Σσ
Quinolines (2-substituted)	=5.12	–9.04Σσ
Quinolines (8-substituted)	=4.64	–3.11Σσ
α-Naphthylamines	=3.85	–2.81Σσ
β-Naphthylamines	=4.29	–2.81Σσ
Benzylamines (ring substituted)	=9.39	–1.05Σσ
N,N-Dimethylanilines	=5.06	–3.46Σσ
1-Aminoanthracene	=aniline	+0.17Σσ
Quinoline	=pyridine(1)	=0.06

where σ is Hammett's σ constant.

The calculated p*K*_a values are similar to the reference values, as expected. These values are given in Tables 1 and 2, as p*K*_a[III]. However, several p*K*_a values could not be calculated, due to the lack of Hammett's equations. The correlation between Hammett's p*K*_a values (p*K*_a[III]) and those determined by liquid chromatography (p*K*_a[II]) and reference values (p*K*_a[I]) is given by the following equations.

For phenolic compounds:

$$pK_a[\text{III}] = 0.974 \times pK_a[\text{I}] + 0.228, \\ r^2 = 0.965, (n = 46),$$

$$pK_a[\text{III}] = 0.958 \times pK_a[\text{II}] + 0.028, \\ r^2 = 0.945, (n = 45).$$

The p*K*_a values calculated by Hammett's equation, p*K*_a[III], were a little larger than the reference values, p*K*_a[I]. However, the correlation coefficients for the two equations above were excellent, and p*K*_a[III] can be used for the optimization of liquid chromatography, if reference values are not available.

For nitrogen-containing compounds:

$$pK_a[\text{III}] = 0.918 \times pK_a[\text{I}] + 0.399, \\ r^2 = 0.965 (n = 26),$$

$$pK_a[\text{III}] = 1.017 \times pK_a[\text{II}] + 0.395, \\ r^2 = 0.775, (n = 35).$$

Table 2
 pK_a Values of nitrogen-containing compounds obtained by different methods

	Chemicals	pK_a (I)	pK_a (II)	pK_a (III)	pK_a (IV)	pK_a (V)
1	Benzylamine	9.33	8.99	9.39	9.02	2.94
2	Aniline	4.63	3.86	4.58	4.66	4.21
3	2-Methylaniline	4.44	4.16	4.29	4.66	4.54
4	3-Methylaniline	4.73	4.71	4.75	4.91	4.43
5	4-Methylaniline	5.08	5.29	4.98	4.91	4.65
6	2,4-Dimethylaniline	–	4.46	4.70	4.79	4.65
7	4-Methoxyaniline	5.34	5.01	5.39	5.39	5.43
8	2,5-Diethoxyaniline	–	3.31	4.23	2.85	6.32
9	2-Chloroaniline	2.65	2.49	2.65	2.61	3.87
10	3-Chloroaniline	3.46	3.46	3.15	3.94	4.10
11	4-Chloroaniline	4.15	3.47	3.89	4.06	3.98
12	2,5-Dichloroaniline	–	3.87	1.58	1.76	3.43
13	3,4-Dichloroaniline	–	3.02	2.82	3.33	3.65
14	4-Bromoaniline	3.58	3.10	3.95	3.58	3.54
15	2-Nitroaniline	–	–	1.04	0.26	–0.46
16	3-Nitroaniline	2.466	2.86	2.45	2.73	3.65
17	4-Nitroaniline	1.00	–	2.33	0.55	0.98
18	5-Aminoindan	–	4.13	–	4.61	4.43
19	1-Aminoindan	9.21	9.26	–	9.14	3.65
20	1-Aminonaphthalene	3.92	3.43	3.85	4.42	4.32
21	2-Aminonaphthalene	4.16	3.99	4.29	3.58	4.32
22	1-Aminoanthracene	–	4.06	4.09	4.42	4.54
23	1-Aminopyrene	–	3.57	–	3.58	3.87
24	Dibenzylamine	–	6.10	–	6.48	4.98
25	N-Metylaniline	–	3.62	–	3.70	8.65
26	N-Ethylaniline	5.12	5.54	–	0.07	1.54
27	N-Butylaniline	–	3.35	–	3.94	8.88
28	5-Aminoindol	–	5.33	–	5.93	16.44
29	N,N-Dimethylaniline	5.15	4.69	5.06	–	20.14
30	N,N-Diethylaniline	6.61	6.18	–	–	29.28
31	Pyridine	5.25	5.26	5.25	–	5.62
32	2-Aminopyridine	6.82	5.81	6.93	–	3.58
33	3-Aminopyridine	–	5.24	5.25	–	4.18
34	4-Aminopyridine	9.114	8.39	8.64	–	2.85
35	2-Methylpyridine	5.97	4.85	6.02	–	6.21
36	3-Methylpyridine	5.68	4.90	5.60	–	5.39
37	4-methylpyridine	6.02	4.72	6.08	–	6.09
38	4- <i>tert.</i> Butylpyridine	–	5.85	6.14	–	5.97
39	2,4-Dimethylpyridine	6.99	5.60	6.93	–	6.56
40	2,5-Dimethylpyridine	–	5.78	6.37	–	5.86
41	2,6-Dimethylpyridine	–	4.97	6.78	–	6.44
42	Pyrazine	0.65	–	–	–	0.64
43	2-Methylpyrazine	1.45	1.91	–	–	0.37
44	2,5-Dimethylpyrazine	–	2.82	–	–	1.71
45	2,6-Dimethylpyrazine	–	2.75	–	–	1.77
46	Quinoline	4.9	3.92	4.90	–	4.80
47	8-Hydroxyquinoline	5.017	3.34	4.24	–	–0.04
48	2-Methylquinoline	5.83	4.94	5.66	–	5.39
49	4-Methylquinoline	5.67	4.45	5.72	–	5.27
50	8-Methylquinoline	–	2.64	4.83	–	4.92

pK_a (I): from reference [8]; pK_a (II): obtained by liquid chromatography; pK_a (III): by Hammett's equations; pK_a (IV): CAChe pK_a values calculated from the partial charge of hydrogen; pK_a (V): CAChe pK_a values calculated from the partial charge of nitrogen.

The exception from Hammett's calculation seems to be 2,5-dichloroaniline, due to *ortho* effect. However, the correlation coefficient of the above equation was only slightly improved to 0.841 ($n=34$).

The CACheTM pK_a calculation method was based on the correlation between the reference pK_a values and the atomic partial charge calculated using MOPAC (molecular orbital package). The pK_a values of phenolic compounds can be predicted using either the partial charge of hydrogen (pK_a [IV] in Table 1) or of the oxygen (pK_a [V] in Table 1) of an hydroxyl group. Those pK_a values of nitrogen-containing compounds can also be predicted using either the partial charge of hydrogen (pK_a [IV] in Table 2) or the nitrogen (pK_a [V] in Table 2) of an amino group. Those of derivatized pyridines and pyradines were calculated using the partial charge of nitrogen of their aromatic ring (pK_a [V] in Table 2). The following equations were used to predict pK_a values from partial charge. Nitrogen-containing compounds were classified in two groups, due to their structure. The first group contains compounds 1–28 and the second group contains compounds 31–50 in Table 2.

Eq. (4) was used for compounds 1–28 and Eq. (5) was used for compounds 31–50. Eq. (6) was also used for compounds 1–28. N,N-dialkylanilines (29 and 31 in Table 2) were eliminated from the calculations.

For phenolic compounds:

$$pK_a[\text{IV}] = -205.928 \times (\text{partial charge of H}) + 55.042, r^2 = 0.907, \quad (2)$$

$$pK_a[\text{V}] = -162.784 \times (\text{partial charge of O}) - 31.089, r^2 = 0.959, \quad (3)$$

For nitrogen-containing compounds:

$$pK_a[\text{V}] = 111.200 \times (\text{partial charge of N}) + 40.680, r^2 = 0.920 \quad (4)$$

$$pK_a[\text{V}] = -116.774 \times (\text{partial charge of N}) - 10.496, r^2 = 0.969 \quad (5)$$

$$pK_a[\text{IV}] = -120.930 \times (\text{partial charge of H}) + 26.794, r^2 = 0.981 \quad (6)$$

The predicted pK_a values (pK_a [V]) of 2-nitroaniline, 8-hydroxyquinoline, 5-aminoindole, N,N-dimethylaniline and of N,N-diethylaniline were unacceptable. The values were less than zero or more than sixteen. Other exceptions were benzylamine, N-ethylamine, 1-aminoindan and aminopyridines. Phenolic compounds whose pK_a values were unpredictable by this method were *ortho*-nitro-substituted compounds, with some pK_a values being less than zero. 1,2-Dihydroxybenzene was also an exception. The prediction of pK_a values from the partial charge of the atom seemed to be difficult to handle with nitro-substituted compounds, especially those having an *ortho* effect. After excluding these exceptions, the predicted pK_a values of phenolic and nitrogen-containing compounds were correlated with their reference values.

For phenolic compounds from Table 1:

$$pK_a[\text{IV}] = 0.882 \times pK_a[\text{I}] - 1.047, \\ r^2 = 0.907, (n = 41),$$

$$pK_a[\text{V}] = 0.959 \times pK_a[\text{I}] - 0.353, \\ r^2 = 0.959, (n = 41).$$

For nitrogen containing compounds from Table 2:

$$pK_a[\text{IV}] = 0.941 \times pK_a[\text{I}] - 0.048, \\ r^2 = 0.710, (n = 16),$$

$$pK_a[\text{V}] = 0.905 \times pK_a[\text{I}] + 0.296, \\ r^2 = 0.905, (n = 23),$$

Furthermore, the predicted pK_a values were correlated with those obtained by Hammett's equation and liquid chromatography.

For phenolic compounds:

$$pK_a[\text{IV}] = 0.854 \times pK_a[\text{II}] + 1.047, \\ r^2 = 0.890, (n = 43),$$

$$pK_a[\text{V}] = 0.880 \times pK_a[\text{III}] - 0.745, \\ r^2 = 0.905, (n = 43),$$

$$pK_a[\text{IV}] = 0.867 \times pK_a[\text{III}] + 1.202, \\ r^2 = 0.920, (n = 53),$$

$$\text{p}K_{\text{a}}[\text{V}] = 0.954 \times \text{p}K_{\text{a}}[\text{III}] + 0.392,$$

$$r^2 = 0.942, (n = 53).$$

For nitrogen-containing compounds:

$$\text{p}K_{\text{a}}[\text{IV}] = 0.972 \times \text{p}K_{\text{a}}[\text{III}] + 0.287,$$

$$r^2 = 0.879, (n = 26),$$

$$\text{p}K_{\text{a}}[\text{V}] = 0.803 \times \text{p}K_{\text{a}}[\text{III}] + 1.508,$$

$$r^2 = 0.262, (n = 38),$$

$$\text{p}K_{\text{a}}[\text{IV}] = 1.012 \times \text{p}K_{\text{a}}[\text{III}] - 0.148,$$

$$r^2 = 0.881, (n = 20),$$

$$\text{p}K_{\text{a}}[\text{V}] = 0.726 \times \text{p}K_{\text{a}}[\text{III}] + 1.426,$$

$$r^2 = 0.718, (n = 30).$$

The poor correlation between $\text{p}K_{\text{a}}[\text{IV}]$ and $\text{p}K_{\text{a}}[\text{III}]$ of nitrogen-containing compounds may be due to the poor $\text{p}K_{\text{a}}[\text{III}]$ values measured at low pH. The further elimination of N-alkylamine and dibenzylamine improved the slope and correlation coefficients from 0.803 and 0.262 ($n = 38$) to 1.036 and 0.589 ($n = 35$), respectively. For the calculations of correlation for phenolic compounds, 1,2-dihydroxybenzene and all of the nitro-substituted compounds were eliminated. When the values of 3-, 4-nitrophenols and 3,4-dinitrophenol were included, the correlation coefficients were improved to 0.867 and 0.954 ($n = 55$) from 0.862 and 0.935 ($n = 52$), respectively. This computational calculation system has not been perfected for predicting $\text{p}K_{\text{a}}$ values. It may not be used to calculate the properties of the *ortho* effect and nitro group.

The correlation between $\text{p}K_{\text{a}}[\text{IV}]$ and $\text{p}K_{\text{a}}[\text{V}]$ was poor, and the selection of the atom was important for predicting the $\text{p}K_{\text{a}}$ values. The correlations are:

For phenolic compounds:

$$\text{p}K_{\text{a}}[\text{V}] = 0.946 \times \text{p}K_{\text{a}}[\text{IV}] + 0.007,$$

$$r^2 = 0.435, (n = 64),$$

and for nitrogen-containing compounds:

$$\text{p}K_{\text{a}}[\text{V}] = 0.243 \times \text{p}K_{\text{a}}[\text{IV}] + 3.157,$$

$$r^2 = 0.180, (n = 22).$$

There is no single equation for predicting the $\text{p}K_{\text{a}}$ values of both phenolic and nitrogen-containing compounds at present. Therefore, further study is required for the development of a standard equation to predict $\text{p}K_{\text{a}}$ values of different types of compounds.

4. Conclusion

The prediction of dissociation constants, $\text{p}K_{\text{a}}$ values, is still difficult, especially for nitrogen-containing compounds. The reference $\text{p}K_{\text{a}}$ values can be used for the optimization of liquid chromatography after adjusting the $\text{p}K_{\text{a}}$ values for certain concentrations of organic modifiers. The computational chemical calculation improved the accuracy, however, the selection of the atom was important. Hammett's equations give the most practical values at present, if the constants are available, even though the selection of the correct optimal constant is not a simple or straightforward matter.

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