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# Quantitative structure–retention relationships of phenolic compounds without Hammett's equations

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## Abstract

Retention times of phenolic compounds in a given pH eluent in reversed-phase liquid chromatography were predicted from dissociation constants derived from atomic partial charges and log $P$-values calculated by a computational chemical method. The precision of the calculation of atomic partial charges by AM1 and PM3 methods of MOPAC™ was evaluated. The atomic partial charges obtained by AM1 were the more acceptable. The atomic partial charges obtained from the hydrogen of the hydroxyl group included an ortho-effect, therefore an ortho-effect was added to the predicted p$K_a$ values. The precision of predicted retention factors obtained using predicted p$K_a$ values was similar to that using reference p$K_a$ values.

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## 1. Introduction

Retention time in reversed-phase liquid chromatography can be predicted directly from octanol–water partition coefficient, log $P$, and dissociation constant, p$K_a$ values [1]. First, log $P$-values have been calculated by an empirical method, however, a calculation could not be made or the calculated error was large if the constants of the basic structure and/or substitutes are not known. A computational calculation simplified the log $P$ prediction. Improving the precision of the computational chemical calculation of molecular properties results in a more accurate predicted log $P$-value.

Dissociation constants, p$K_a$, have been predicted using Hammett's equations:

$$pK_a = A + B\Sigma\sigma \qquad (1)$$

where $A$ and $B$ are constants for individual groups of compounds, and $\sigma$ is Hammett's $\sigma$ constant measured by liquid chromatography or titration [2]. The simplification of Hammett's equations has been studied. Previously, a new approach was proposed for the prediction of aromatic acid p$K_a$ values using computational chemistry [3]

$$pK_a \text{ (predicted)} = pK_a \text{ (base compounds)}$$
$$+ \Delta pK_a \text{ (substitute effect)}$$

p$K_a$ (base compounds) was derived from the atomic partial charge of basic compounds, benzoic acid, phenylacetic acid, 3-phenylpropionic acid, mandelic acid, *trans*-cinnamic acid, indole-3-acetic acid, indole-3-butylic acid and phenol. The Δp$K_a$ (substitute effect) was derived from the difference in the atomic partial charge between derivatized and base

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compounds. In this study, these equations were further modified for the quantitative structure–retention relationships (QSRR) of acidic compounds including aromatic acids and phenolic compounds in reversed-phase liquid chromatography.

## 2. Experimental

The computers used for the calculations were an upgraded Macintosh 8100/250 and a Toshiba Dynabook 4000X. The software used was CAChe™ and Vlog P™ from Fujitsu (Tokyo). The chemical calculations were carried out without modification of the program [4]. A modified CAChe-log P™ calculation method was also used to study the performance in reversed-phase liquid chromatography. The Cricket-Graph™ program from Computer Associates (San Diego, CA, USA) was used for data handling. The retention factors of phenolic compounds and aromatic acids were measured previously by reversed-phase liquid chromatography using an octadecyl-bonded silica gel [5,6] and were used for the evaluation of computationally calculated values.

## 3. Results and discussion

The CAChe $pK_a$ calculation method was based on the correlation between the reference $pK_a$ values and the atomic partial charge calculated using MOPAC (molecular orbital package). First, atomic partial charge (apc) values for the hydroxyl group hydrogens and oxygens of phenolic compounds were correlated with measured $pK_a$ values and used for QSRR in reversed-phase liquid chromatography of phenolic compounds [5]. Later, two equations were derived from the atomic partial charge of the carboxyl group hydrogens of aromatic acids for the prediction of $pK_a$ values instead of using various Hammett's equations. The predicted $pK_a$ values were successfully used for QSRR of aromatic acids in reversed-phase liquid chromatography at various pH values of eluents [7,8].

AM1 and PM3 calculation methods in MOPAC have been used for a variety of applications. Therefore, atomic partial charge was calculated using AM1 and PM3 in the CAChe program, and a

suitable calculation method was evaluated for the prediction of $pK_a$ values. The calculated atomic partial charges of eight standard compounds are summarized in Table 1. The correlations between the partial charge of hydrogen (H), oxygen (O) of the hydroxyl group and carbon (C) connected to hydroxyl or carboxyl groups were obtained as the following equations:

From the partial charge calculated

$$(\text{O by PM3}) = 0.761 \times (\text{O by AM1}) - 0.065,$$
$$r^2 = 0.991, n = 8$$

$$(\text{H by PM3}) = 1.126 \times (\text{H by AM1}) - 0.048,$$
$$r^2 = 0.992, n = 8$$

$$(\text{C by PM3}) = 1.223 \times (\text{H by AM1}) + 0.003,$$
$$r^2 = 0.999, n = 8$$

The calculated atomic partial charges using PM3 are slightly larger except for the partial charge of oxygen. Such a difference is due to the precision of the atomic heat of formation according to Stewart [9] who developed the MOPAC™ program. therefore, these atomic partial charges were correlated with measured $pK_a$ values [10] in Table 1

$$pK_a = -209.611 \times (\text{H by AM1}) + 55.568,$$
$$r^2 = 0.993, n = 8 \tag{2}$$

$$pK_a = -183.885 \times (\text{H by PM3}) + 46.085,$$
$$r^2 = 0.976, n = 8$$

$$pK_a = 53.365 \times (\text{O by AM1}) + 21.412,$$
$$r^2 = 0.968, n = 8 \tag{3}$$

$$pK_a = 68.728 \times (\text{O by PM3}) + 25.558,$$
$$r^2 = 0.937, n = 8$$

$$pK_a = -21.982 \times (\text{C by AM1}) + 11.322,$$
$$r^2 = 0.862, n = 8$$

$$pK_a = -17.985 \times (\text{C by PM3}) + 11.388,$$
$$r^2 = 0.864, n = 8$$

Table 1
p$K_a$ and atomic partial charges of standard compounds

| Chemical | Atomic partial charge | | | | | |
|---|---|---|---|---|---|---|
| | Calculated using AM1 | | | Calculated using PM3 | | |
| | O | H | C | O | H | C |
| Benzoic acid | −0.3171 | 0.2455 | 0.3515 | −0.3069 | 0.2287 | 0.4316 |
| Phenylacetic acid | −0.3211 | 0.2447 | 0.3128 | −0.3059 | 0.2260 | 0.3813 |
| Mandelic acid | −0.3262 | 0.2476 | 0.2779 | −0.3099 | 0.2303 | 0.3448 |
| *trans*-Cinnamic acid | −0.3145 | 0.2436 | 0.3379 | −0.3053 | 0.2253 | 0.4201 |
| Phenylpropionic acid | −0.3209 | 0.2440 | 0.3047 | −0.3127 | 0.2274 | 0.3785 |
| Indoleacetic acid | −0.3180 | 0.2424 | 0.3131 | −0.3055 | 0.2241 | 0.3856 |
| Indolebutylic acid | −0.3215 | 0.2430 | 0.3064 | −0.3135 | 0.2271 | 0.3782 |
| Phenol | −0.2134 | 0.2172 | 0.0779 | −0.2273 | 0.1963 | 0.0985 |
| | Predicted p$K_a$ | | | | | |
| | p$K_a$[a] | O (AM1)[b] | H(AM1)[b] | O(PM3)[b] | H(PM3)[b] | |
| Benzoic acid | 4.200 | 4.4900 | 4.1085 | 4.4654 | 4.0305 | |
| Phenylacetic acid | 4.334 | 4.2765 | 4.2762 | 4.5341 | 4.5270 | |
| Mandelic acid | 3.420 | 4.0043 | 3.6683 | 4.2592 | 3.7363 | |
| *trans*-Cinnamic acid | 4.376 | 4.6287 | 4.5068 | 4.5753 | 4.6557 | |
| Phenylpropionic acid | 4.691 | 4.2872 | 4.4229 | 4.0668 | 4.2696 | |
| Indoleacetic acid | 4.590 | 4.4419 | 4.7583 | 4.5616 | 4.8764 | |
| Indolebutylic acid | 4.781 | 4.2552 | 4.6325 | 4.0118 | 4.3247 | |
| Phenol | 10.020 | 10.0239 | 10.0405 | 9.9361 | 9.9894 | |

[a] From Ref. [8].
[b] Calculation method in parentheses.

The above results indicated that partial charges of hydrogen and oxygen were suitable to predict p$K_a$ values of standard compounds. No significant difference was found between the AM1 and PM3 calculations. A term of Eq. (1) can be derived from the above results. Previously, the partial charge of hydrogen was shown to be suitable to predict the p$K_a$ value of aromatic acids [7], and that of oxygen was better than that of hydrogen for phenolic compounds. Which value derived atomic partial charge from hydrogen or oxygen is better for acidic compounds overall? The former calculation was achieved using version 3.7 of the CAChe system, while the recalculation was done using version 4.5 of the CAChe system. The partial charges of hydrogen and oxygen of 52 phenolic compounds were calculated using AM1 and PM3, and are listed in Table 2 with measured p$K_a$ values from Ref. [10].

The substitute effect ($\Delta$pc) on atomic partial charge was balanced between the atomic partial charge of the substituted phenol and phenol ($\Delta$pc = pc (substituted phenol) − pc (phenol)). The substitute effects of atomic partial charge were correlated with substitute effects of p$K_a$ values. The correlations between $\Delta$p$K_a$ (p$K_a$ of substituted phenol − p$K_a$ of phenol) and substitute effect $\Delta$pc were as follows, where p$K_a$ values were predicted using individual equations and atomic partial charges were calculated.

$$\Delta pK_a = -154.136 \times (\Delta pc \text{ O by AM1}) - 0.328,$$
$$r^2 = 0.900, n = 38 \tag{4}$$

$$\Delta pK_a = -204.529 \times (\Delta pc \text{ H by AM1}) + 0.216,$$
$$r^2 = 0.905, n = 38 \tag{5}$$

$$\Delta pK_a = -170.059 \times (\Delta pc \text{ O by PM3}) - 0.186,$$
$$r^2 = 0.892, n = 38$$

$$\Delta pK_a = -333.387 \times (\Delta pc \text{ H by PM3}) + 0.410,$$
$$r^2 = 0.758, n = 38$$

The atomic partial charge calculated by AM1

Table 2
Atomic partial charges calculated by computational chemical calculation and reference and predicted dissociation constants

| Chemical | $pK_a^a$ | pc | | | | $pK_a^b$ AM1 O | $pK_a^b$ AM1 H | $pK_a^c$ AM1[a] H |
|---|---|---|---|---|---|---|---|---|
| | | PM3 O | PM3 H | AM1 O | AM1 H | | | |
| Phenol | 10.02 | −0.2273 | 0.1963 | −0.2472 | 0.2184 | 10.0239 | 10.0405 | 10.0405 |
| 2-Methylphenol | 10.32 | −0.2300 | 0.1989 | −0.2490 | 0.2198 | 10.3013 | 9.7565 | 10.2025 |
| 3-Methylphenol | – | −0.2283 | 0.1962 | −0.2472 | 0.2183 | 10.0239 | 10.0608 | 10.0608 |
| 4-Methylphenol | 10.27 | −0.2274 | 0.1958 | −0.2464 | 0.2180 | 9.9006 | 10.1216 | 10.1216 |
| 2,3-Dimethylphenol | 10.54 | −0.2346 | 0.2013 | −0.2499 | 0.2196 | 10.4400 | 9.7971 | 10.2431 |
| 2,4-Dimethylphenol | 10.60 | −0.2299 | 0.1984 | −0.2488 | 0.2194 | 10.2705 | 9.8377 | 10.2837 |
| 2,5-Dimethylphenol | 10.41 | −0.2308 | 0.1989 | −0.2490 | 0.2198 | 10.3013 | 9.7565 | 10.2025 |
| 2,6-Dimethylphenol | 10.63 | −0.2292 | 0.1991 | −0.2498 | 0.2187 | 10.4246 | 9.9796 | 10.4256 |
| 3,4-Dimethylphenol | 10.36 | −0.2282 | 0.1957 | −0.2509 | 0.2170 | 10.5941 | 10.3245 | 10.3245 |
| 3,5-Dimethylphenol | 10.19 | −0.2288 | 0.1958 | −0.2499 | 0.2173 | 10.4400 | 10.2636 | 10.2636 |
| 2,3,4-Trimethylphenol | – | −0.2292 | 0.1963 | −0.2532 | 0.2164 | 10.9486 | 10.4462 | 10.8922 |
| 2,3,5-Trimethylphenol | – | −0.2295 | 0.1965 | −0.2516 | 0.2170 | 10.7020 | 10.3245 | 10.7705 |
| 2,3,6-Trimethylphenol | – | −0.2312 | 0.1993 | −0.2552 | 0.2187 | 11.2568 | 9.9796 | 10.4256 |
| 2,4,6-Trimethylphenol | 10.88 | −0.2276 | 0.1988 | −0.2520 | 0.2179 | 10.7636 | 10.1419 | 10.5879 |
| 2,3,4,5-Tetramethylphenol | – | −0.2356 | 0.2008 | −0.2521 | 0.2184 | 10.7790 | 10.0405 | 10.4865 |
| 2,3,5,6-Tetramethylphenol | – | −0.2373 | 0.2021 | −0.2536 | 0.2189 | 11.0102 | 9.9391 | 10.3851 |
| 2,3,4,5,6-Pentamethylphenol | – | −0.2378 | 0.2015 | −0.2560 | 0.2179 | 11.3801 | 10.1419 | 10.5879 |
| 2-Ethylphenol | 10.20 | −0.2338 | 0.2025 | −0.2555 | 0.2205 | 11.3030 | 9.6145 | 10.0605 |
| 3-Ethylphenol | 9.90 | −0.2282 | 0.1957 | −0.2534 | 0.2166 | 10.9794 | 10.4056 | 10.4056 |
| 4-Ethylphenol | 10.00 | −0.2275 | 0.1956 | −0.2529 | 0.2167 | 10.9023 | 10.3853 | 10.3853 |
| 4-tert-Butylphenol | – | −0.2267 | 0.1957 | −0.2506 | 0.2172 | 10.5479 | 10.2839 | 10.2839 |
| 2-Chlorophenol | 8.48 | −0.2197 | 0.2030 | −0.2416 | 0.2299 | 9.1609 | 7.7078 | 8.5998 |
| 3-Chlorophenol | 9.02 | −0.2244 | 0.1988 | −0.2426 | 0.2222 | 9.3150 | 9.2697 | 9.2697 |
| 4-Chlorophenol | 9.38 | −0.2237 | 0.1981 | −0.2438 | 0.2209 | 9.4999 | 9.5334 | 9.5334 |
| 2,3-Dichlorophenol | 7.45 | −0.2183 | 0.2040 | −0.2385 | 0.2323 | 8.6831 | 7.2210 | 8.1130 |
| 2,4-Dichlorophenol | 7.89 | −0.2166 | 0.2043 | −0.2379 | 0.2320 | 8.5907 | 7.2819 | 8.1739 |
| 2,5-Dichlorophenol | 7.50 | −0.2171 | 0.2045 | −0.2370 | 0.2326 | 8.4520 | 7.1602 | 8.0522 |
| 2,6-Dichlorophenol | 6.79 | −0.2085 | 0.2061 | −0.2278 | 0.2331 | 7.0342 | 7.0587 | 7.5047 |
| 3,4-Dichlorophenol | 8.39 | −0.2161 | 0.2005 | −0.2385 | 0.2244 | 8.6831 | 8.8235 | 8.8235 |
| 3,5-Dichlorophenol | 8.18 | −0.2214 | 0.2006 | −0.2377 | 0.2251 | 8.5599 | 8.6815 | 8.6815 |
| 2,3,4-Trichlorophenol | 7.59 | −0.2150 | 0.2050 | −0.2376 | 0.2336 | 8.5445 | 6.9573 | 7.8493 |
| 2,3,5-Trichlorophenol | 7.23 | −0.2153 | 0.2055 | −0.2334 | 0.2350 | 7.8972 | 6.6733 | 7.5653 |
| 2,3,6-Trichlorophenol | 6.12 | −0.2070 | 0.2071 | −0.2252 | 0.2354 | 6.6335 | 6.5922 | 7.0382 |
| 2,4,5-Trichlorophenol | 7.33 | −0.2142 | 0.2055 | −0.2242 | 0.2351 | 6.4794 | 6.6531 | 7.5451 |
| 2,4,6-Trichlorophenol | 6.42 | −0.2057 | 0.2073 | −0.2244 | 0.2351 | 6.5102 | 6.6531 | 7.0991 |
| 3,4,5-Trichlorophenol | 7.74 | −0.2189 | 0.2014 | −0.2341 | 0.2268 | 8.0051 | 8.3366 | 8.3366 |
| 2,3,4,5-Tetrachlorophenol | 6.96 | −0.2131 | 0.2061 | −0.2307 | 0.2364 | 7.4811 | 6.3894 | 7.2814 |
| 2,3,5,6-Tetrachlorophenol | 5.44 | −0.2063 | 0.2083 | −0.2221 | 0.2376 | 6.1558 | 6.1460 | 6.5920 |
| 2,3,4,5,6-Pentachlorophenol | 5.26 | −0.2044 | 0.2089 | −0.2193 | 0.2390 | 5.7243 | 5.8620 | 6.3080 |
| 2-Bromophenol | 8.44 | −0.2155 | 0.2068 | −0.2434 | 0.2309 | 9.4383 | 7.5050 | 8.3970 |
| 3-Bromophenol | 9.03 | −0.2242 | 0.1996 | −0.2454 | 0.2217 | 9.7465 | 9.3711 | 9.3711 |
| 4-Bromophenol | 9.36 | −0.2238 | 0.1989 | −0.2447 | 0.2217 | 9.6386 | 9.3711 | 9.3711 |
| 2,4-Dibromophenol | 7.80 | −0.2128 | 0.2078 | −0.2402 | 0.2335 | 8.9451 | 6.9776 | 7.8696 |
| 2,6-Dibromophenol | 6.60 | −0.1987 | 0.2047 | −0.2239 | 0.2363 | 6.4332 | 6.4096 | 6.8556 |
| 1,2-Dihydroxybenzene | – | −0.2064 | 0.1922 | −0.2295 | 0.2133 | 7.2962 | 11.0750 | 11.5210 |
| 1,3-Dihydroxybenzene | 9.81 | −0.2281 | 0.1989 | −0.2450 | 0.2219 | 9.6849 | 9.3306 | 9.3306 |
| 1,4-Dihydroxybenzene | 10.35 | −0.2270 | 0.1946 | −0.2500 | 0.2163 | 10.4554 | 10.4665 | 10.4665 |
| 1-Hydroxynaphthalene | – | −0.2272 | 0.1994 | −0.2525 | 0.2201 | 10.8407 | 9.6957 | 9.6957 |
| 2-Hydroxynaphthalene | – | −0.2271 | 0.1971 | −0.2514 | 0.2186 | 10.6712 | 9.9999 | 9.9999 |
| 2-Hydroxyacetophenone | – | −0.2291 | 0.2026 | −0.2487 | 0.2234 | 10.2551 | 9.0263 | 9.0263 |

Table 2. Continued

| Chemical | $pK_a$ [a] | pc | | | | $pK_a$ [b] AM1 O | $pK_a$ [b] AM1 H | $pK_a$ [c] AM1 [a] H |
|---|---|---|---|---|---|---|---|---|
| | | PM3 O | PM3 H | AM1 O | AM1 H | | | |
| 4-Hydroxybutylbenzoate | – | −0.2207 | 0.2004 | −0.2418 | 0.2239 | 9.1917 | 8.9249 | 8.9249 |
| 4-Hydroxypropylbenzoate | – | −0.2207 | 0.2004 | −0.2418 | 0.2239 | 9.1917 | 8.9249 | 8.9249 |
| Benzoic acid | 4.20 | −0.3069 | 0.2287 | −0.3170 | 0.2456 | – | – | – |
| 3-Methylbenzoic acid | 4.26 | −0.3072 | 0.2284 | −0.3172 | 0.2452 | – | – | – |
| 4-Methylbenzoic acid | 4.34 | −0.3076 | 0.2282 | −0.3177 | 0.2450 | – | – | – |
| 3,4-Dimethylbenzoic acid | 4.40 | −0.3073 | 0.2279 | −0.3175 | 0.2447 | – | – | – |
| 3,5-Dimethylbenzoic acid | 4.32 | −0.3070 | 0.2281 | −0.3171 | 0.2449 | – | – | – |
| 4-Ethylbenzoic acid | 4.35 | −0.3074 | 0.2282 | −0.3177 | 0.2450 | – | – | – |
| 3-Chlorobenzoic acid | 3.83 | −0.3048 | 0.2300 | −0.3144 | 0.2481 | – | – | – |
| 4-Chlorobenzoic acid | 3.96 | −0.3063 | 0.2298 | −0.3161 | 0.2476 | – | – | – |
| 3,4-Dichlorobenzoic acid | 3.50 | −0.3045 | 0.2308 | −0.3137 | 0.2497 | – | – | – |
| 3,5-Dichlorobenzoic acid | 3.46 | −0.3038 | 0.2312 | −0.3132 | 0.2501 | – | – | – |
| 3-Bromobenzoic acid | 3.86 | −0.3041 | 0.2302 | −0.3143 | 0.2484 | – | – | – |
| 4-Bromobenzoic acid | 3.98 | −0.3057 | 0.2303 | −0.3152 | 0.2481 | – | – | – |

[a] From Ref. [10] for phenolic compounds and Ref. [7] for benzoic acids.
[b] Predicted $pK_a$ values from atomic partial charges.
[c] Predicted $pK_a$ values from hydrogen partial charges with ortho-effect.

seemed better for the prediction of $pK_a$ values. The results suggested that the atomic partial charge of either the hydrogen or oxygen of a hydroxy group can be used for the prediction of $pK_a$. The recalculated data for 12 benzoic acid derivatives are listed in Table 2 with their properties. The correlation between $\Delta pK_a$ and $\Delta pc$ of benzoic acid derivatives are:

$$\Delta pK_a = -189.852 \times (\Delta pc\ O\ by\ AM1) + 0.042,$$
$$r^2 = 0.940, n = 12 \tag{6}$$

$$\Delta pK_a = -160.438 \times (\Delta pc\ H\ by\ AM1) + 0.042,$$
$$r^2 = 0.965, n = 12 \tag{7}$$

$$\Delta pK_a = -218.161 \times (\Delta pc\ O\ by\ PM3) + 0.024,$$
$$r^2 = 0.875, n = 12$$

$$\Delta pK_a = -267.958 \times (\Delta pc\ H\ by\ PM3) + 0.004,$$
$$r^2 = 0.935, n = 12$$

where atomic partial charges of benzoic acid, 3-methylbenzoic acid, 4-methylbenzoic acid, 3,4-dimethylbenzoic acid, 3,5-dimethylbenzoic acid, 4-ethylbenzoic acid, 3-chlorobenzoic acid, 4-chlorobenzoic acid, 3,4-dichlorobenzoic acid, 3,5-dichlorobenzoic acid, 3-bromobenzoic acid and 4-bromo-

benzoic acid were used for the calculation. These results indicated that the apc of hydrogen calculated using AM1 was more acceptable than the others, therefore, the term $B\Sigma\sigma$ of Eq. (1) was derived by AM1 from the relation between $\Delta pK_a$ and $\Delta pc$ H and $\Delta pc$ O of phenolic compounds and benzoic acid derivatives of Eqs. (4)–(7).

$$B\Sigma\sigma = (-7.260 \times pK_a - 129.947)$$
$$\times \Delta(partial\ charge\ of\ hydrogen) \tag{8}$$

$$B\Sigma\sigma = (6.137 \times pK_a - 215.626)$$
$$\times \Delta(partial\ charge\ of\ oxygen) \tag{9}$$

Finally, Eqs. (2), (3), (8) and (9) were used to predict the $pK_a$ values of phenolic compounds. The predicted $pK_a$ values are listed in Table 2. The correlation between the predicted and measured $pK_a$ values are:

$$pK_a\ (predicted\ from\ pc\ of\ H) = 0.904$$
$$\times (pK_a\ measured) + 0.676, r^2 = 0.904, n = 38$$

$$pK_a\ (predicted\ from\ pc\ of\ O) = 0.910$$
$$\times (pK_a\ measured) + 1.133, r^2 = 0.908, n = 38$$

Furthermore, these predicted $pK_a$ values were used for QSRR in reversed-phase liquid chromatography. The retention factors of ionizable compounds in a given pH solution were predicted in reversed-phase liquid chromatography using the following equation [11]:

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

where $k_m$ and $k_i$ are the retention factors of the molecular and ionized analytes, respectively, and $K_a$ is the dissociation constant of analytes. The experimental data measured previously [5] were used to evaluate this new approach. The retention factors both measured and predicted data are summarized in Table 3. The correlation between predicted and measured retention factors at pH 8.49 in reversed-phase liquid chromatography are: (1) predicted from the partial charge of oxygen calculated using the AM1 system:

$$k \text{ predicted} = 0.854 \times (k \text{ measured}) + 0.196,$$

$$r^2 = 0.598, n = 20 \text{ at } k_i = 0$$

$$k \text{ predicted} = 0.873 \times (k \text{ measured}) + 0.245,$$

$$r^2 = 0.641, n = 20 \text{ at } k_i \text{ measured}$$

and (2) predicted from the partial charge of hydrogen calculated using the AM1 system:

$$k \text{ predicted} = 0.928 \times (k \text{ measured}) - 0.119,$$

$$r^2 = 0.644, n = 20 \text{ at } k_i = 0$$

$$k \text{ predicted} = 1.001 \times (k \text{ measured}) - 0.058,$$

$$r^2 = 0.737, n = 20 \text{ at } k_i \text{ measured}$$

The correlation coefficients did not show high precision with this new approach. Therefore, the $pK_a$ values predicted using the partial charge of hydrogen were re-examined according to the ortho-effect. The ortho-effect for $pK_a$ values was 0.894. The addition of the ortho-effect improved the correlation coefficient between measured and predicted $pK_a$ values to 0.973 from 0.904 ($n = 38$), and the equation was $pK_a$ predicted $= 0.802 \times (pK_a \text{ measured}) + 1.940$.

Table 3
Retention factors measured and predicted at pH 8.49 in reversed-phase liquid chromatography

| Chemical | exp [a] | $k_i = \text{exp}$ [b] H | $k_i = 0$ H | $k_i = \text{exp}$ [b] O | $k_i = 0$ O | $k_i = \text{exp}$ [b] H [c] | $k_i = 0$ H [c] | $k_i = \text{exp}$ [b] [d] | $k_i = 0$ [d] |
|---|---|---|---|---|---|---|---|---|---|
| Phenol | 0.660 | 0.635 | 0.627 | 0.635 | 0.627 | 0.635 | 0.627 | 0.635 | 0.627 |
| 2-Chlorophenol | 0.700 | 0.477 | 0.125 | 0.799 | 0.727 | 0.676 | 0.496 | 0.643 | 0.436 |
| 3-Chlorophenol | 0.880 | 0.918 | 0.822 | 0.922 | 0.833 | 0.918 | 0.822 | 0.895 | 0.740 |
| 4-Chlorophenol | 0.890 | 0.907 | 0.880 | 0.898 | 0.831 | 0.899 | 0.836 | 0.895 | 0.808 |
| 2,3-Dichlorophenol | 0.310 | 0.145 | 0.062 | 0.774 | 0.740 | 0.420 | 0.359 | 0.181 | 0.102 |
| 2,4-Dichlorophenol | 0.466 | 0.121 | 0.074 | 0.732 | 0.709 | 0.448 | 0.414 | 0.295 | 0.255 |
| 2,5-Dichlorophenol | 0.390 | 0.109 | 0.059 | 0.658 | 0.631 | 0.391 | 0.353 | 0.170 | 0.123 |
| 2,6-Dichlorophenol | 0.091 | 0.124 | 0.045 | 0.121 | 0.043 | 0.193 | 0.119 | 0.104 | 0.025 |
| 3,4-Dichlorophenol | 0.920 | 1.057 | 0.910 | 0.993 | 0.812 | 1.057 | 0.910 | 0.849 | 0.590 |
| 3,5-Dichlorophenol | 0.680 | 1.089 | 0.999 | 0.993 | 0.887 | 1.089 | 0.999 | 0.694 | 0.540 |
| 2,3,4-Trichlorophenol | 0.140 | 0.128 | 0.051 | 0.988 | 0.951 | 0.397 | 0.333 | 0.270 | 0.200 |
| 2,3,5-Trichlorophenol | 0.095 | 0.071 | 0.032 | 0.459 | 0.427 | 0.259 | 0.223 | 0.147 | 0.109 |
| 2,3,6-Trichlorophenol | 0.042 | 0.064 | 0.023 | 0.066 | 0.025 | 0.102 | 0.062 | 0.050 | 0.008 |
| 2,4,5-Trichlorophenol | 0.110 | 0.137 | 0.029 | 0.128 | 0.019 | 0.303 | 0.205 | 0.233 | 0.130 |
| 2,4,6-Trichlorophenol | 0.051 | 0.081 | 0.031 | 0.073 | 0.022 | 0.133 | 0.084 | 0.069 | 0.018 |
| 2,3,4,5,6-Tetrachlorophenol | 0.084 | 0.093 | 0.010 | 0.091 | 0.007 | 0.110 | 0.027 | 0.086 | 0.002 |
| 2-Bromophenol | 0.750 | 0.448 | 0.090 | 0.901 | 0.861 | 0.646 | 0.428 | 0.660 | 0.451 |
| 3-Bromophenol | 0.940 | 1.001 | 0.922 | 1.024 | 0.988 | 1.001 | 0.922 | 0.962 | 0.810 |
| 4-Bromophenol | 0.970 | 0.985 | 0.894 | 0.996 | 0.944 | 0.985 | 0.894 | 0.985 | 0.891 |
| 2,4-Dibromophenol | 0.650 | 0.074 | 0.049 | 1.231 | 1.225 | 0.340 | 0.320 | 0.301 | 0.280 |

[a] $k$ from Ref. [5].
[b] $k_i$ = experimental data from Ref. [5].
[c] Used $pK_a$ with ortho-effect.
[d] Used $pK_a$ calculated using Hammett's equations from Ref. [10].

The $k$-values recalculated using p$K_a$ values with an ortho-effect were related to the measured $k$-values in the pH 8.49 eluent:

$k$ predicted $= 0.833 \times (k$ measured$) + 0.063,$

$r^2 = 0.812, n = 20$ at $k_i = 0$

$k$ predicted $= 0.888 \times (k$ measured$) + 0.114,$

$r^2 = 0.834, n = 20$ at $k_i$ measured

Furthermore, $k$-values were predicted using reference p$K_a$ values in Table 2. The correlation between predicted and measured $k$-values is:

$k$ predicted $= 0.817 \times (k$ measured$) - 0.044,$

$r^2 = 0.877, n = 20$ at $k_i = 0$

$k$ predicted $= 0.923 \times (k$ measured$) + 0.003,$

$r^2 = 0.895, n = 20$ at $k_i$ measured

These results indicated that the precision of predicted retention factors using predicted p$K_a$ values from atomic partial charges was not high, but that using reference p$K_a$ values was not significantly high, too. This means that the new method can be used to create a separation condition in reversed-phase liquid chromatography. The atomic partial charges of hydrogen are affected by the ortho-effect compared to those of oxygen, and differ with the version of the calculation system used. Improving the precision of the atomic heat of formation will improve the precision of atomic partial charges.

## 4. Conclusion

Retention times of phenolic compounds in a given pH eluent in reversed-phase liquid chromatography were predicted from dissociation constants derived from atomic partial charges and log $P$-values calculated by a computational chemical method. The precision of the calculation of atomic partial charges by AM1 of MOPAC were acceptable to the predicted p$K_a$ values of phenolic compounds and aromatic acids. The precision of predicted retention factors obtained using predicted p$K_a$ values was similar to that using reference p$K_a$ values.

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