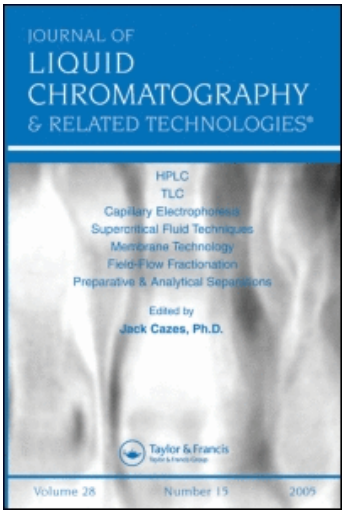

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Chromatography *In Silico* for Basic Drugs

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Chromatography *In Silico* for Basic Drugs

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Abstract: The retention factors in liquid chromatography can be quantitatively predicted from the molecular interaction energy calculated by molecular mechanics, using a model phase and nitrogen-containing compounds including basic drugs. The new system can also predict retention factors of ionized compounds. However, an old system using log *P* could not predict the retention of ionized compounds. The correlation coefficient between the molecular interaction energy and retention factors of both molecular and ionized forms was better than that between log *P* and retention factors. The addition of p*K*a to molecular interaction energy could enable one to predict retention factors of partially ionized compounds.

Keywords: Chromatography *in silico*, Basic drugs, Reversed-phase liquid chromatography, Computational chemistry, log *P*, p*K*a

INTRODUCTION

The optimization of separation conditions is fundamental in chromatography.[1–6] The trial and error system has been automated, and some computer control methods have been commercialized. DryLab, one marketed computer-assisted method, has been used for computer simulations of pharmaceuticals with Plackett-Burman experimental designs[7] and explosives and related compounds.[8] However, direct optimization from molecular properties has been studied, and an octanol-water partition coefficient, log *P*, and dissociation constant, p*K*a, were used for a variety of compounds.[9] A similar system was commercialized by the ACD.[10] The precision of this method depended on the selection of log *P* prediction methods.[11]

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However, log *P* is a property of molecular forms of analytes, not ionized forms. Therefore, the precision of predicted retention factors of partially ionized compounds is not satisfactory. The quantitative structure retention relationship, QSRR, based on log *P* values, would have limitations when applied to various chromatographic conditions. The computational chemical analysis of molecular interaction was used to study retention time difference in liquid chromatography. Direct calculations of molecular interaction energy values have been made for the optimization of chromatography. The molecular interaction energy was calculated with a docking method of computational chemistry that is used for drug design with a protein molecule. The design of the model phase is important. A large polycyclic aromatic hydrocarbon was used to study retention mechanisms of polar and nonpolar compounds. The ionic interaction between the model phase and an ion was explained by chemical computation.[12]

Carbohydrates are retained on a model graphitic carbon phase by hydrogen bonding at the edge of the model phase. Hydrocarbons are retained at the center of the model phase by van der Waals force.[13] The selective interaction was quantitatively analyzed with energy values calculated using molecular mechanics, MM2, with the CAChe^{TM} program from CAChe Scientific, Fujitsu.[14] Model bonded phases were constructed to study the molecular interactions in reversed-phase liquid chromatography.[12,15] A simulation of reversed-phase liquid chromatography for phenolic compounds was proposed using a molecular mechanics calculation (MM2) of the CAChe^{TM} program.

The interaction energy between a molecular or an ionized form compound and a model butyl-phase were calculated to analyze the quantitative structure retention relationship, QSRR, of phenolic compounds. The correlation between molecular interaction energy values (Δ energy) and retention factors obtained for the molecular forms was used to predict the maximum retention factors of these compounds, and that for the ionized forms was used to predict the minimum retention factors. Furthermore, these interaction energy values were used to predict retention factors in given pH eluents. The retention factors at different pH were well correlated with Δ values of the final structure or van der Waals, $r^2 > 0.85-0.99$ (pH 3–9) for phenolic compounds.[16] This new approach was used for nitrogen-containing compounds, including basic drugs whose structure is more complex than that of phenolic compounds.

EXPERIMENTAL

Liquid Chromatograph

An automated liquid chromatograph controlled by a host computer Model Vectra XM series 3 16/90 was obtained from Yokogawa Analytical

Systems (Tokyo, Japan). Three Model G1310A IsoPumps, and a Model G1313A ALS autosampler were purchased from Yokogawa Analytical Systems. A Jasco Model UV970 UV detector was obtained from Jasco (Tokyo, Japan), and the selected wavelength was 220 nm due to lack of an automated wavelength control system. A Model 860-CO column oven was purchased from Jasco.

Standard chemicals were obtained from Sigma Chemical Co. (St. Louis, MO, USA) and Wako Pure Chemical Industries (Osaka, Japan). Their properties are summarized in Table 1. Sodium dihydrogenphosphate dihydrate and disodiumhydrogenphosphate $12H_2O$ were purchased from Wako Pure Chemical Industries. HPLC-grade methanol was obtained from Kanto-Kagaku (Tokyo, Japan). The water used was of Milli-Q grade.

A 5 μm pentyl-bonded silica gel from Phenomenex, CA, USA was packed into a 50×2.1 mm I.D. column in house and was used for reversed-phase liquid chromatography at various pHs from 2.20 to 11.0. The eluent was a two-to-one mixture of 50 mM sodium phosphate solution and methanol. The flow rate was 0.2 mL/min. The column temperature was 37°C. The void volume marker was fructose. The chromatography was used for measurement of a protein-drug binding affinity.[17]

Computational Chemical Analysis

The computers used were a Power Macintosh G3 equipped with a 450 MHz processor and 512 MB memory and a Dell model Latitude C840 equipped with a 2 GHz processor and 1024 MB memory. The molecular properties of analytes and model phases and molecular interactions were calculated using molecular mechanics (MM2) from version 5 of the CAChe™ program from Fujitsu, Tokyo, Japan. The standard parameters used were bond stretch, bond angle, dihedral angle, improper torsion, van der Waals, hydrogen bond, and electrostatic energy (MM2 bond dipoles). The van der Waals cut-off distance was 9 Å. The energy unit was kcal/mol (1 kJ/mol = 4.18 kcal/mol). The Cricket-Graph™ program from Computer Associates (San Diego, CA, USA) and Project Reader of CAChe™ program were used for data handling.

RESULTS AND DISCUSSION

A model butyl-bonded phase was the phase previously used for phenolic compounds.[18] The surface is flat, and a docking on the surface is simple. The pentyl-bonded silica gel used in this experiment did not show silanol group activity.[19] The adsorption form of imipramine on the butyl-phase is shown in Figure 1. Butyl groups of the model butyl-bonded phase are highly dense and not pushed down by an analyte that lies on the top of the butyl-group brush.

Table 1. Molecular properties of basic drugs and nitrogen containing compounds

Chemicals	log n*K*	Vlog *P*	Clog *P*	Mlog *P*	p*K*a1	p*K*a2
Ajmaline	3.120	1.593	1.26	—	8.2	—
Allopurinol	2.373	−2.927	−0.92	−0.55	9.4	—
Amoxicillin	—	—	0.33	—	2.4/9.6	—
Aniline	—	—	—	—	4.63	—
Atropine	3.509	—	1.32	1.83	9.8	7.40
Benzylamine	—	—	—	—	9.33	—
Caffeine	2.748	−0.716	0.07	−0.07	0.6/14.0	—
Carbamazepine	3.356	2.524	1.98	2.45	1.98	6.47
Chloramphenicol	—	—	—	1.14	—	—
Dextromethorphan	4.053	2.801	3.99	—	8.3	8.54
Diazepam	—	—	3.18	2.80	3.3	—
Ethambutol	2.589	−1.993	0.12	—	6.3/9.5	—
Homatropine	3.421	1.213	1.45	—	9.9	—
Imipramine	4.202	4.654	4.41	4.80	9.5	—
Isoproterenol	—	—	0.08	—	8.6/10.1/12.0	—
Lidocaine	3.677	2.558	1.98	2.26	7.9	6.79
p-Methoxyaniline	—	—	—	—	5.34	—
Prazosin	3.200	1.315	2.16	—	6.5	5.65
Procaine	3.365	1.397	2.24	1.87	8.11/8.80	6.63
Pyridine	—	—	—	—	5.19	—
Quinine	3.843	−0.214	3.20	3.44	4.1/8.5	—
Rifampicin	3.857	5.961	2.99	—	1.7/7.9	—
Phenethylamine	—	—	—	—	9.84	—
Scoporamine	3.177	2.280	−0.20	1.20	7.75	—
Terbutaline	—	—	0.48	—	8.8/10.1/11.2	—
Tetracycline	—	—	−2.56	—	3.3/7.7/9.7	—
Theobromine	2.515	−1.175	−1.01	−0.78	0.12/10.05	—
Theophylline	2.675	−0.218	−0.25	−0.02	3.5/8.6	—
Triamterene	—	—	1.99	1.11	6.2	—

log n*K*: albumin-drug binding affinity;[17] Vlog *P*: calculated log *P* using Vlog *P* program (Fujitsu); Clog *P*: predicted log *P*;[21] Mlog *P*: measured octanol-water partition coefficient;[21] p*K*a1: from references [21]; p*K*a2: measured by reversed-phase liquid chromatography.

The energy values of nitrogen containing-compounds calculated using MM2 are listed in Table 2. The calculated energy values are final structure (FS), hydrogen bonding (HB), electrostatic (ES), and van der Waals (VW) energy. The energy values of individual complexes with a model butyl-phase and a nitrogen-containing compound are listed in Table 2 as FS1 and VW1 where hydrogen bonding and electrostatic energy values are not

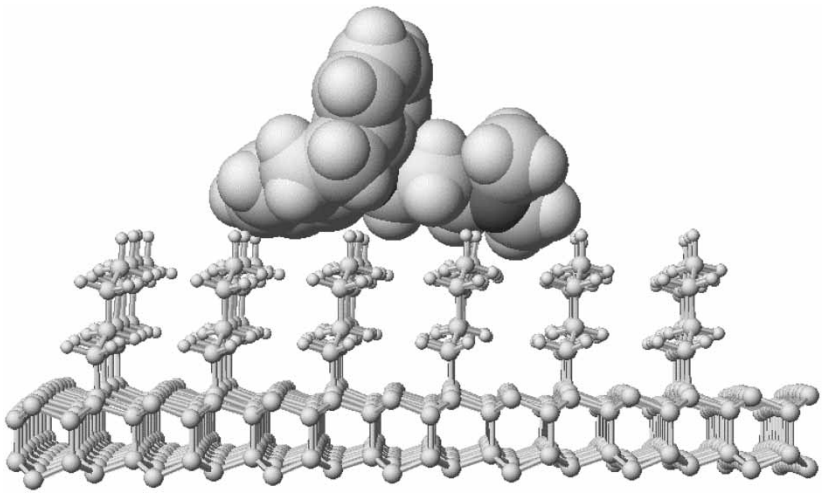

Figure 1. Imipuramine on butyl-phase. White small ball: hydrogen; white large ball: carbon; dark gray ball: nitrogen. The atomic size of imipuramine is five times of that of the model phase.

given, because these energy values did not show any meaningful relation with their retention. Hydrogen bonding and electrostatic energy values are important in ion-exchange liquid chromatography.[20] The interaction energy between a molecular form compound and the model butyl-phase was calculated using MM2 to analyze the retention of molecular form analytes quantitatively: Interaction energy values (Δ value) = energy value of individual molecule + energy value of a model phase-energy value of a complex. The relation between Δ FS1 or Δ VW1 calculated using the model butyl-phase and measured log k values of molecular form nitrogen containing-compounds (log k_m) are:

$$\Delta\text{FS1} = 4.792\ (\log k_m) + 11.101, \quad r = 0.610, \quad n = 13, \tag{1}$$

$$\Delta\text{VW1} = 2.910\ (\log k_m) + 11.797, \quad r = 0.609, \quad n = 13. \tag{2}$$

This model phase worked fine for simple phenolic compounds. The correlation, r, between measured and predicted molecular interaction energy values was more than 0.92 (n = 6) at pH 3–9.[16] However, the molecular interaction energy values of larger compounds were smaller than expected. The reason for this would be the poor contact between these two molecules.

Improved lap-top computer hardware permitted the construction of a better model bonded-phase. A model phase was constructed to increase the contact surface area. A model support consisted of 365 carbons, 248 hydrogens, 848 bonds and 3684 connectors. The molecular weight was 4,579. The 7 center hydrogens were replaced by methyl groups, and

Table 2. Final structure (FS) and van der Waals (VW) energy values of complexes

	Phase 1		Phase 2		Phase 3	
Chemicals	FS1	VW1	FS2	VW2	FS3	VW3
Ajmaliline	3449.2940	419.012	3702.4403	928.626	3683.1781	802.938
Aniline	—	—	—	—	—	—
Atropine	3373.5110	416.630	3630.5949	932.968	3613.4250	799.359
Carbamazepine	3326.5340	425.659	3584.6978	936.349	3571.7635	820.432
Dextromethorphan	3388.3076	420.233	3642.3606	934.649	3626.1670	811.153
Homatropine	3398.1179	415.366	3646.4543	924.010	3632.1829	803.156
Imipramine	3361.9492	418.889	3612.4900	929.130	3603.4149	809.565
Isoproterenol	—	—	3611.9596	929.881	3589.9364	800.608
Lidocaine	3351.7982	419.903	3601.6674	930.212	3588.7415	804.765
Prazosin	3378.7577	412.230	3635.4741	919.998	3625.9502	800.423
Procaine	3368.0581	416.316	3620.2030	926.001	3608.9217	802.734
Pyridine	3370.5447	414.878	3629.5056	934.842	3627.8096	821.228
Quinine	3371.5502	417.277	3629.5188	930.133	3618.3498	811.841
Theobromine	3319.4073	412.363	3575.4821	328.801	3564.9648	807.361
Triamterene	3340.0077	415.322	3600.4204	931.428	3581.2900	804.556
Benzylamine	—	—	—	—	—	—
Phenethylamine	—	—	—	—	—	—
N,N-Dimethylaniline	—	—	—	—	—	—
Model phase	3375.0355	419.967	3641.5884	947.116	3636.3325	831.618

	Phase 4				Phase 5	
	FS4m	VW4m	FS4i	VW4i	FS5	VW5
Ajmaliline	−586.2171	−412.489	−581.7239	−412.489	−444.492	−518.634
Aniline	−674.3700	−413.358	−670.4133	−414.091	−537.755	−525.313
Atropine	−663.7506	−416.743	−656.3950	−410.884	−526.630	−531.144
Carbamazepine	−711.1683	−405.831	−705.5730	−405.985	−574.687	−519.519
Dextromethorphan	−653.2251	−416.983	−652.8863	−415.706	−512.783	−528.443
Homatropine	−638.1184	−415.704	−638.0416	−416.332	−498.251	−528.148
Imipramine	−675.7248	−417.048	−676.9917	−418.246	−530.219	−519.314
Isoproterenol	−678.6589	−412.981	−687.9121	−421.162	−550.222	−532.496
Lidocaine	−689.7850	−417.076	−696.1161	−418.638	−551.447	−529.421
Prazosin	−650.7574	−415.567	−649.4318	−415.973	−518.306	−532.441
Procaine	−668.3104	−414.595	−661.7555	−414.490	−527.348	−522.378
Pyridine	−661.1491	−414.360	−662.5748	−413.368	−526.203	−526.468
Quinine	−668.7683	−417.033	−666.9434	−414.794	−521.414	−524.619
Theobromine	−713.9513	−417.599	−713.9513	−417.599	−581.891	−532.259
Triamterene	−691.7278	−411.881	−692.9782	−414.864	−561.068	−531.486
Triamterene	−681.0857	−416.515	−678.4571	−416.494	—	—
Benzylamine	−679.6221	−417.988	−679.5879	−418.284	—	—
Phenethylamine	−667.2389	−412.871	−671.2089	−415.362	—	—
N,N-Dimethylaniline	−648.6239	−400.533	−648.6239	−400.533	−518.739	−515.856

Unit: kcal/mol.

12 hydrogens of 2nd and 18 hydrogens of 3rd circles were replaced with octyl groups. The retention of lidocaine on the octyl-phase is shown in Figure 2. The relation between Δ FS2 or Δ VW2 calculated using the model phase and measured log k values of molecular form nitrogen-containing compounds are:

$$\Delta\mathrm{FS2} = 5.526\ (\log k_\mathrm{m}) + 22.232, \quad \mathrm{r} = 0.743, \quad \mathrm{n} = 14, \tag{3}$$

$$\Delta\mathrm{VW2} = 4.980\ (\log k_\mathrm{m}) + 24.126, \quad \mathrm{r} = 0.586, \quad \mathrm{n} = 14. \tag{4}$$

The correlation coefficient did not demonstrate the improvement even when analytes were varied in the octyl brushes. Furthermore, these octyl groups were replaced by dodecyl groups to increase the contact surface area. As an example, homatropine was buried in the dodecyl groups as shown in Figure 3.

$$\Delta\mathrm{FS3} = 6.032\ (\log k_\mathrm{m}) + 30.206, \quad \mathrm{r} = 0.562, \quad \mathrm{n} = 14, \tag{5}$$

$$\Delta\mathrm{VW3} = 5.380\ (\log k_\mathrm{m}) + 31.128, \quad \mathrm{r} = 0.466, \quad \mathrm{n} = 14. \tag{6}$$

There was no meaningful correlation between their molecular interaction energy values and their retention factors. This result indicated that the above two models did not reflect the chromatographic behavior of nitrogen-containing compounds. Therefore, a silica gel-based bonded phase was constructed. The new phase was constructed based on the dimethoxypentylsilane-bonded polysilicone dioxide phase, and consisted of 991 atoms, 1051

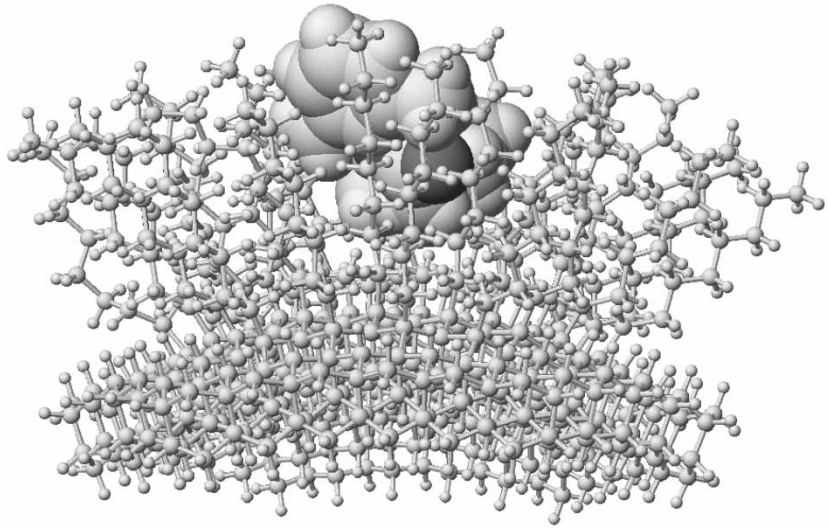

Figure 2. Lidocaine on octyl-phase. White small ball: hydrogen; white large ball: carbon; dark gray ball: nitrogen; black ball: oxygen. The atomic size of lidocaine is five times of that of the model phase.

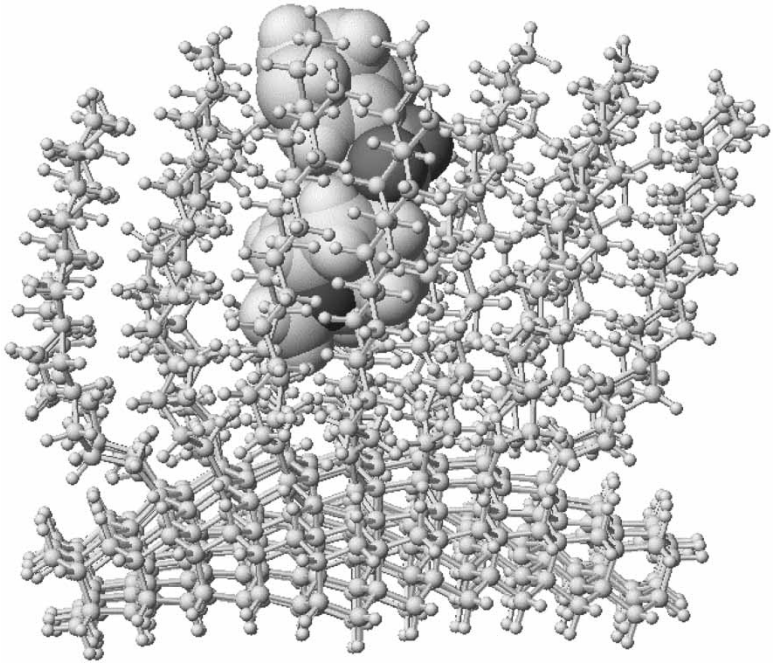

Figure 3. Homatropine on dodecyl-phase. White small ball: hydrogen; white large ball: carbon; dark gray ball: nitrogen; black ball: oxygen. The atomic size of homatropine is five times of that of the model phase.

bonds, and 15,193 connectors, containing 171 silicones, 328 oxygens, 143 carbons, and 349 hydrogens. Twenty dimethoxypentylsilanes and one trimethylsilane were bonded within 900 $Å^2$ on the polysilicone dioxide phase. The trimethylsilane was considered as an end-capped molecule. A pocket caused by a small molecule, trimethylsilane, was designed to follow the V-shape model of a porous silica gel. The optimized structure of a complex formed between this model phase and quinine is shown in Figure 4. Dimethoxypentyl groups stand close due to their steric hindrance. Some of them lie in free space after optimization of the molecular interaction. On this new bonded-phase, dimethoxypentyl groups surrounded one trimethyl group. Dimethoxypentyl groups of the 2nd circle should support dimethoxypentyl groups of the 1st circle. The interaction energy between a nitrogen-containing compound and the new model phase was calculated and values are listed as FS4m and VW4m in Table 2. The r between Δ FSm and log k_m was improved.

$$\Delta\text{FS4m} = 7.619\ (\log k_m) + 20.924, \quad r = 0.941, \quad n = 17, \qquad (7)$$

$$\Delta\text{VW4m} = 6.700\ (log k_m) + 18.600, \quad r = 0.919, \quad n = 17. \qquad (8)$$

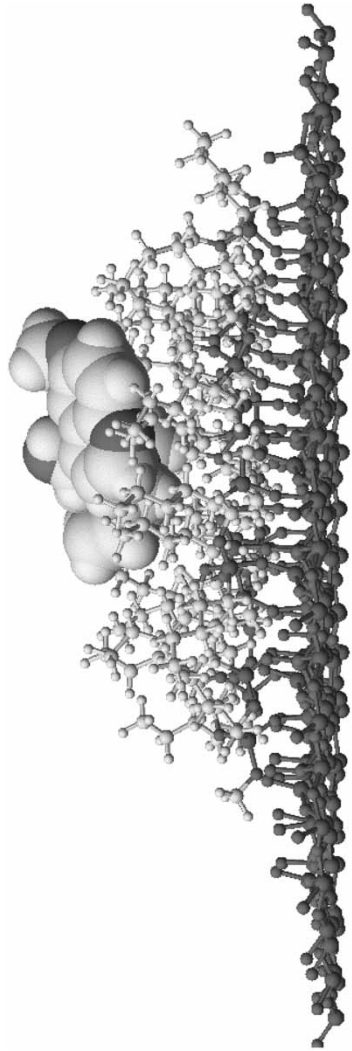

Figure 4. Quinine on dimethoxyoctylsilicone-phase. White small ball: hydrogen; white large ball: carbon; gray ball: nitrogen; dark gray ball: silicone; black ball: oxygen; The atomic size of quinine is five times of that of the model phase.

Furthermore, the above results were examined using log P values measured (log P_m) and calculated (log P_c) from a reference.[21]

$$\log P_m = 1.395\ (\log k_m) + 0.491, \quad r = 0.897, \quad n = 14, \tag{9}$$

$$\log P_c = 1.275\ (\log k_m) + 0.541, \quad r = 0.842, \quad n = 16. \tag{10}$$

These results are better than those of three previous models. This r value is not significantly high compared to the results for phenolic compounds.[18] The r between log P and log k_m was smaller than that obtained using Δ FS and Δ VW. This comparison indicated this new approach using molecular interaction energy values should work for the quantitative analysis of retention in chromatography, but further development is necessary for the development of simulation chromatography for drugs. The mass of a drug is quite large and the structure is complicated compared to that of phenolic compounds. Phase 4, the dimethoxypentyl-bonded silica gel, was further modified using dimethoxyoctyl groups. It consisted of 2021 atoms, 2081 bonds, and 21,450 connectors, containing 171 silicones, 328 oxygens, 143 carbons, and 349 hydrogens. It bonded 47 dimethoxyoctylsilanes and one trimethylsilane. The retention of triamterene on the dimethoxyoctyl-bonded silica gel is shown in Figure 5.

$$\Delta FS5 = 3.034\ (\log k_m) + 18.054, \quad r = 0.514, \quad n = 15, \tag{11}$$

$$\Delta VW5 = 4.278\ (\log k_m) + 18.744, \quad r = 0.602, \quad n = 15. \tag{12}$$

The longer alkyl chain did not improve the correlation coefficient. Therefore, such a correlation was studied for ionized nitrogen-containing compounds using phase 4, dimethoxypentyl-bonded silica gel. The final and van der Waals energy values are listed as FS4i and VW4i in Table 2. The relations are:

$$\Delta FS4i = 4.325\ (\log k_i) + 29.751, \quad r = 0.799, \quad n = 15, \tag{13}$$

$$\Delta VW4i = 4.414\ (\log k_i) + 26.636, \quad r = 0.781, \quad n = 15. \tag{14}$$

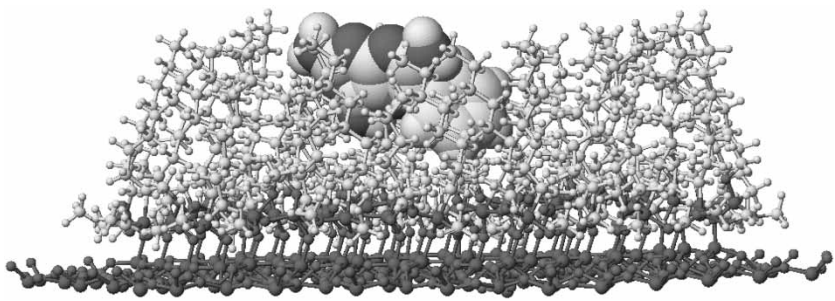

Figure 5. Triamterene on newSi-phase. White small ball: hydrogen; white large ball: carbon; gray ball: nitrogen; dark gray ball: silicone; black ball: oxygen. The atomic size of triamterene is five times of that of the model phase.

The retention time of ionized compounds was very short, and should include the experimental error, especially size- and ion-exclusion effects. When the log of retention factors of less than minus one was eliminated, the correlation coefficient improved from 0.799 (n = 15) to 0.807 (n = 11) and from 0.781 (n = 15) to 0.804 (n = 11). This new system using molecular interaction energy demonstrated it was possibile to predict retention factors of ionized compounds, but an old system using log *P* values cannot do this. Furthermore, the retention factors of partially ionized compounds were predicted using equation (15).[22]

$$k = \{k_m + k_i(Ka/[H^+])\}/\{1 + (Ka/[H^+])\} \quad (15)$$

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. H^+ is the hydrogen ion concentration in the eluent.

The p*K*a values measured in the above experiment were compared with reference p*K*a values to predict the retention factors of partly ionized compounds.

$$\begin{aligned} &\text{p}Ka\ (\text{reference}) = 1.010\ (\text{p}Ka\ \text{measured}) + 0.770, \\ &\quad r = 0.919,\ \ n = 18. \end{aligned} \quad (16)$$

The correlation coefficient was improved to 0.952 when the value of theobromine was excluded. The difference in the p*K*a value, 0.770, may be due to the solvent effect. The pH of eluents was measured before mixing with methanol. However, the difference was similar to that reported previously. The pH value of the buffer solution was influenced by the addition of methanol or acetonitrile as an organic modifier.[23] How to obtain pH value is still unclear for a practical purpose.

The correlation between the retention factors measured and predicted with this new method using molecular interaction energy, Δ FS4m, Δ VW4m, Δ FS4i, and ΔVW4i, was obtained from equations (7), (8), (13)–(15).

From Δ FS4m, ΔFS4i, and experimental p*K*a [calculated using eq. (16)]:

$$k_{pred}\ (\text{pH } 6.00) = 0.526\ (k_{mes}) + 0.428, \quad r = 0.863, \quad n = 16, \quad (17)$$

$$k_{pred}\ (\text{pH } 7.00) = 0.711\ (k_{mes}) + 0.444, \quad r = 0.933, \quad n = 16, \quad (18)$$

$$k_{pred}\ (\text{pH } 8.00) = 0.726\ (k_{mes}) + 1.487, \quad r = 0.858, \quad n = 16. \quad (19)$$

From Δ VW4m, Δ VW4i, and experimental p*K*a [calculated using equation (16)]:

$$k_{pred}\ (\text{pH } 6.00) = 0.487\ (k_{mes}) + 0.741, \quad r = 0.645, \quad n = 16, \quad (20)$$

$$k_{pred}\ (\text{pH } 7.00) = 0.735\ (k_{mes}) + 0.866, \quad r = 0.799, \quad n = 16, \quad (21)$$

$$k_{pred}\ (\text{pH } 8.00) = 0.645\ (k_{mes}) + 2.561, \quad r = 0.871, \quad n = 16. \quad (22)$$

Furthermore, the pH effect was calculated using reference p*K*a values. The p*K*a values used for the calculations were additive with the organic modifier concentration effect, Δ p*K*a = 0.022 × (% of methanol). The constant 0.022 was experimentally obtained.[23]

From Δ FS4m, Δ FS4i and modified reference p*K*a [calculated using equation (16)]:

$$k_{\text{pred}}\ (\text{pH } 6.00) = 0.587\ (k_{\text{mes}}) + 0.659, \quad \text{r} = 0.788, \quad \text{n} = 16, \quad (23)$$

$$k_{\text{pred}}\ (\text{pH } 7.00) = 0.719\ (k_{\text{mes}}) + 1013, \quad \text{r} = 0.932, \quad \text{n} = 16, \quad (24)$$

$$k_{\text{pred}}\ (\text{pH } 8.00) = 0.860\ (k_{\text{mes}}) + 0.870, \quad \text{r} = 0.967, \quad \text{n} = 16. \quad (25)$$

The above results indicated that the retention time of basic drugs can be predicted from molecular interaction energy values calculated using MM2. However, the molecular interaction energy of dextromethorphan was smaller than the expected value from the longest retention time. The interaction energy was small, even the longer alkyl-chain phases like phases 2 and 3 in Table 2 were used. Further development of a model phase is required to analyze a variety of compounds. With the addition of p*K*a values one can predict the retention time of partially ionized compounds. At present, the p*K*a values can be predicted without Hammett's equations from the atomic partial charge calculated by MOPAC for phenolic compounds and aromatic acids. However, no such simple calculation method has been established for nitrogen-containing compounds because of a lack of standard p*K*a values.

CONCLUSIONS

The retention time of nitrogen-containing compounds, including basic drugs in reversed-phase liquid chromatography was quantitatively analyzed from molecular interaction energy calculated using MM2 of the CAChe™ program. The precision of the retention factors predicted with this new method was better than that for a former method in which the retention time was predicted from log *P*. Furthermore, the prediction of retention factors of these compounds in reversed-phase liquid chromatography in a given pH eluent was performed using their dissociation constant (p*K*a). Computational chemical calculation demonstrated the possibility of simulation chromatography of the retention of basic drugs on a pentyl-phase. The addition of a solvent effect and the construction of a better model phase should improve the precision of qualitative analysis of retention factors in liquid chromatography. However, this MM2 calculation method cannot handle multi-solvent molecules at present.

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