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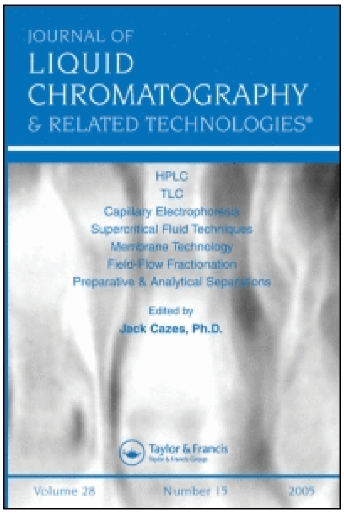

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QSRR in Liquid Chromatography Aided by Computational Chemistry

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QSRR IN LIQUID CHROMATOGRAPHY AIDED BY COMPUTATIONAL CHEMISTRY

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SUMMARY

A quantitative structure-retention relation in reversed-phase liquid chromatography was studied with values calculated by computational chemistry. These values were Van der Waals volume and surface area, calculated by MOPAC-BlogP, total energy calculated by Molecular Mechanics (MM2), kinetic, potential and total energies calculated by Molecular Dynamics (MD), and total energy and dipole moment calculated by Extended Huckel theory (EH). The precision of predicted retention time of non-ionic compounds is improved by using these values instead of Van der Waals volume calculated by Bondi's method and delocalization energy from literature.

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INTRODUCTION

In reversed-phase liquid chromatography, it is recognized that the retention time can be related to the solubility of solute in the eluent. The octanol-water partition coefficient was first used to make a prediction of the retention time in reversed-phase liquid chromatography [1,2]. The system worked well within a group of similar compounds but the equation to non-ionic compounds could not be applied for ionic compounds even in their molecular form. Van der Waals volume was therefore selected as the basic value to make a quantitative structure-retention relationship. Bondi's method was first used to calculate Van der Waals volume, and delocalization energy was used to fill the difference of retention time between n-alkanes and polyaromatic hydrocarbons[3]. The difference of capacity ratios between n-alkanes and others was related to delocalization energy of polyaromatic hydrocarbons, and defined as their selectivity (R*) [4]. This method lacked the precision of Van der Waals volume and delocalization energy, therefore these values have to be recalculated by an accurate method or replaced with other suitable values. In this study, physico-chemical properties of molecules were calculated by CAChe™ which can handle Molecular Mechanic, Molecular Dynamic, Extended Huckel and MOPAC (Molecular Orbital Package) calculations. The capacity ratio of non-ionic compounds in reversed-phase liquid chromatography was examined with newly obtained values.

EXPERIMENTAL

The computer program, CAChe™, was obtained from Sony-Tektronix (Tokyo, Japan) and the calculation was performed by Macintosh IIfx. The calculated values and chemicals used were summarised in Tables I and II. Chromatographic retention data were obtained from a previous study [5].

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Table I Physico-chemical properties and predicted capacity ratios

chemicals	VWV	SA	MM	Selectivity	log k'	
	Å^3	Å^2	Kcal/mole	R	pred.	meas.*1
pentane	95.970	136.624	2.834	0	-	0.721
hexane	112.787	158.710	3.474	0	-	0.895
heptane	129.552	180.088	4.117	0	-	1.070
octane	146.408	202.118	4.758	0	-	1.254
benzene	83.789	110.083	-8.235	4.486	0.208	0.212
naphthalene	127.598	157.293	-18.886	7.115	0.465	0.453
biphenyl	154.500	185.519	-17.281	9.583	0.569	0.586
fluorene	161.639	195.355	-12.514	9.478	0.652	0.651
phenanthrene	171.286	201.501	-24.769	10.017	0.716	0.710
anthracene	171.486	204.659	-17.170	9.590	0.748	0.751
pyrene	187.603	216.636	-32.358	9.820	0.902	0.881
chrysene	214.558	245.078	-30.012	12.483	1.007	1.002
tetracene	215.352	252.222	-39.242	12.499	1.015	1.017
benzopyrene	231.048	260.884	-38.184	11.573	1.241	1.201
toluene	100.337	131.748	-8.723	4.784	0.360	0.357
ethylbenzene	116.898	151.275	-6.850	5.283	0.496	0.489
isopropylbenzene	133.855	173.014	-6.671	6.003	0.618	0.606
propylbenzene	133.764	173.080	-6.150	5.401	0.664	0.648
butylbenzene	150.528	194.621	-5.525	5.813	0.809	0.811
hexylbenzene	184.133	238.200	-4.247	5.977	1.151	1.142
heptylbenzene	201.171	260.872	5.964	5.964	1.330	1.310
chlorobenzene	97.300	126.324	-7.928	4.544	0.346	0.353
1,2-dichlorobenzene	110.741	141.424	-4.131	4.378	0.501	0.479
1,3-dichlorobenzene	110.911	142.563	-10.188	3.574	0.569	0.541
1,4-dichlorobenzene	110.844	142.467	-7.020	4.086	0.526	0.509
1,2,4-trichlorobenzene	124.307	157.575	-5.779	3.424	0.723	0.688
1,3,5-trichlorobenzene	124.505	159.242	-15.017	2.498	0.802	0.774
1,2,3,4-tetrachlorobenzene	137.542	170.991	-0.408	3.298	0.873	0.826
1,2,3,5-tetrachlorobenzene	137.770	172.248	-6.825	2.659	0.929	0.888
1,2,4,5-tetrachlorobenzene	137.730	172.114	-3.922	2.879	0.910	0.869
pentachlorobenzene	150.870	185.123	-0.735	2.601	1.072	1.032
hexachlorobenzene	164.037	198.096	3.324	2.359	1.231	1.187
butylalcohol	87.308	125.440	2.129	12.306	-1.324	-0.308
pentylalcohol	104.057	147.579	2.784	12.792	-0.178	-0.172
hexylalcohol	120.924	169.096	3.424	13.291	-0.032	-0.028
heptylalchol	137.801	191.246	4.068	13.537	0.131	0.127
octylalcohol	154.646	212.952	4.707	13.830	0.290	0.283
decylalcohol	188.268	256.547	5.990	14.185	0.623	0.608
dodecylalcohol	221.851	300.653	7.272	14.335	0.968	0.946

*1 measured in 70% aq. ACN on end-capped ODS silica gel

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Table II Physico-chemical properties of polyaromatic hydrocarbons

PAH	VWV*1	DLE*2	MM	MD			EH		MOPAC-BlogP	
			TE*3	KE*4	PE *5	TE	TE	dipole	VWV	SA*6
	cm^3/ mole		Kcal/ mole	Kcal/ mole	Kcal/ mole	Kcal/ mole	a.u.	Debye	Å^3	Å^2
benzene	48.36	2.000	-8.235	4.469	-3.641	0.829	-17.896	0.000	83.789	110.083
naphtharene	73.96	3.683	-18.886	7.158	-11.562	-0.404	-28.433	0.000	127.598	157.293
biphenyl	90.08	4.383	-17.281	9.589	-8.785	0.805	-34.407	0.000	154.500	185.519
fluorene	93.22	4.750	-12.514	9.374	-2.912	6.461	-36.649	1.283	161.639	195.355
phenanthrene	99.56	5.448	-24.769	9.823	-14.736	-4.913	-38.971	0.228	171.286	201.501
anthracene	99.56	5.314	-17.170	9.822	-7.096	2.725	-38.858	0.575	171.486	204.659
pyrene	109.04	6.506	-32.358	10.751	-21.405	-10.654	-43.557	0.006	187.603	216.636
chrysene	125.16	7.190	-30.012	12.501	-17.246	-4.745	-49.508	0.001	214.558	245.078
tetracene	125.16	-	-39.242	12.515	-26.493	-13.979	-49.491	0.003	215.352	252.222
benzopyrene	134.64	-	-38.184	13.451	-24.328	-10.877	-54.090	0.216	231.048	260.884

*1 Van der Waal's volume calculated by Bondi's method, *2 Delocalization energy from ref.7, *3 Total energy, *4 Kinetic energy, *5 Potential energy, *6 Surface area.

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RESULTS AND DISCUSSION

The correlation coefficients (r^2) between Van der Waals volumes calculated by Bondi's method and MOPAC-BlogP is 0.992 (n=47). There is a slight difference between polyaromatic hydrocarbons (PAH) and chlorinated benzenes (Cl-Ph) as seen in Fig. 1 where the unit of Bondi's (cm^3/mole) was converted to Å^3.

This result indicated that Van der Waals volume calculated by MOPAC-BlogP may improve the precision of predicted retention time than that calculated by Bondi's method in reversed-phase liquid chromatography if alkylbenzenes (Al-Ph) are considered as the standard where alkanes are indicated as Al-Al.

The difference of log k' values (Δlog k') between n-alkanes and hypothetical n-alkanes having the same Van der Waals volume

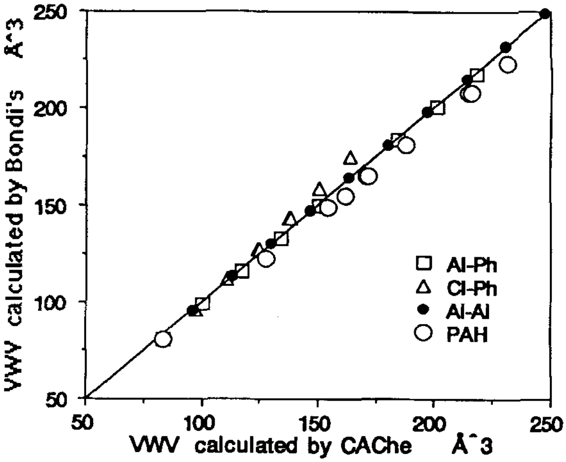

Fig. 1 Comparison of VWVs calculated by Bondi's and CAChe™

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(VWV) of polyaromatic hydrocarbons was previously correlated with their delocalization energy (DLE). The delocalization energy was first correlated with several values such as total energy (TE) calculated by Molecular Mechanics (MM), kinetic energy (KE), potential energy (PE) and total energy (TE) calculated by Molecular Dynamics (MD), total energy (TE) and dipole moment calculated by Extended Huckel theory (EH), and Van der Waals volume (VWV) and surface area (SA) calculated by Molecular Orbital Package (MOPAC-BlogP).

The correlation (r^2) between delocalization energy and kinetic energy by MD and total energy by EH was quite good if biphenyl and pyrene were removed from the calculation.

KE = 1.7621 + 1.5159*(DLE) r^2=0.989 n=6
KE = 2.3073 + 1.4119*(DLE) r^2=0.942 n=8
EH = -7.1372 - 5.9638*(DLE) r^2=0.992 n=6
EH = -8.1029 -5.7355*(DLE) r^2=0.984 n=8

The correlation between kinetic energy and the total energy rose from 0.987 (n=10) to 0.998 (n=9) if only biphenyl was removed from the calculation.

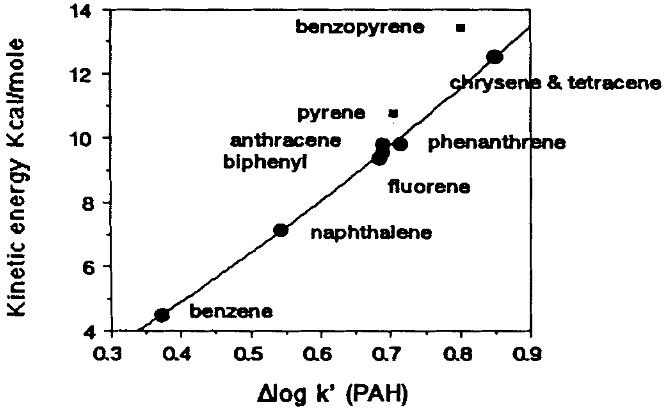

Fig. 2 Relation between kinetic energy and Δlogk' of PAH

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EH = 0.19515 - 3.9973*(KE) r^2=0.998 n=9

EH = 0.77338 - 4.0179*(KE) r^2=0.987 n=10

Δlog k' is the difference of maximum log k' (log k'_{max}) and measured log k' (log k'_{mes}) of polyaromatic hydrocarbons, and the result in 80% aq. acetonitrile is:

$$\Delta \log k' = \log k'_{max} - \log k'_{mes} \quad (1)$$

$$\log k'_{max} = -0.40285 + 0.9016e{-}2*(VWV) \quad (2)$$

where log k'_{max} was obtained from a relation between log k's of alkanes and Van der Waals volumes calculated by MOPAC-BlogP. The correlation between Δlog k' and the kinetic energy rose from 0.945 (n=10) to 0.996 (n=8) if pyrene and benzopyrene were removed from the calculation as shown in Fig. 2. This correlation was better than that between Δlog k' and EH.

KE = -1.9388 + 16.836*(Δlog k') r^2=0.996 n=8

KE = -2.4895 + 18.036*(Δlog k') r^2=0.945 n=10

EH = 7.5983 - 65.850*(Δlog k') r^2=0.977 n=8

EH = 10.139 - 71.543*(Δlog k') r^2=0.908 n=10

The correlation was much better than that where delocalization energy was used as the standard value.

DLE = -2.1566 + 10.778*(Δlog k') r^2=0.878 n=8

The kinetic energy was therefore selected to correlate with the Δlog k' of polyaromatic hydrocarbons instead of delocalization energy, and the correlated values were defined as the selectivity R* that was previously obtained from the correlation between delocalization energy and Δlogk' of polyaromatic hydrocarbons obtained from Van der Waals volume calculated by Bondi's method.
The best relation is given as an equation 3:

$$KE = -0.28708 + 11.131{*}(\Delta logk') + 4.6098{*}(\Delta logk')\hat{}2$$

$$r\hat{}2 = 0.998\ (n=8) \qquad (3)$$

The selectivity R* of other compounds was calculated from the modified equation (3):

$$R^* = -0.28708 + 11.131{*}(\Delta logk') + 4.6098{*}(\Delta logk')\hat{}2 \qquad (4)$$

The selectivity R* was previously applied to the result obtained on a different manufacturer's octadecyl bonded silica gel column, and it was successfully used as the standard value to predict the retention time in reversed-phase liquid chromatography [6]. The R* obtained by this system had good correlation with the selectivity obtained on Hypersil ODS and Develosil ODS [5]. The correlation was 0.994 (n=34) and 0.991 (n=34), respectively.

The prediction of capacity ratios in 70% aq. acetonitrile was performed by following equations.
First, log k' of alkanes and polyaromatic hydrocarbons was measured to obtain constants of equation 2 and 3, then log k'_{max} was calculated by equation 5 and Δlog k'_{pred} was calculated by equation 6:

$$\log k'_{max} = -0.29318 + 1.0549e\text{-}2{*}(VWV) \qquad (5)$$

$$\Delta \log k'_{pred} = -1.8712e\text{-}3 + 9.0454e\text{-}2{*}(R^*) - 1.0610e\text{-}3{*}(R^*)\hat{}2 \qquad (6).$$

The predicted capacity ratio (log k'_{pred}) was obtained from equations 5 and 6:

$$\log k'_{pred} = \log k'_{max} - \Delta \log k'_{pred}$$

$$= -0.29131 + 1.0549e\text{-}2{*}(VWV) - 9.0454e\text{-}2{*}(R^*)$$

$$+ 1.0610e\text{-}3{*}(R^*)\hat{}2 \qquad (7)$$

The correlation coefficient was 0.997 (n=35) between predicted capacity ratios from log k' values of n-alkanes, the new R* and

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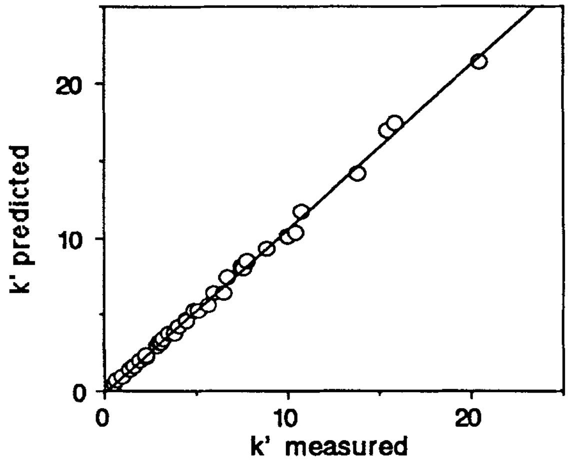

Fig. 3 Relation between predicted and measured k' in 70% aq. ACN

measured capacity ratios in 70% aqueous acetonitrile on a well bonded octadecyl bonded silica gel [5].

$k'_{pred} = -9.12776 + 1.0699*(k'_{mes})$ r^2=0.997 n=35

The relation between predicted and measured capacity ratios is shown in Fig. 3.

Compounds having more than 5% of error were benzopyrene and polychlorinated benzenes. This result demonstrated that there is a fair possibility of devising a prediction method for the retention time in reversed-phase liquid chromatography. The large error for chlorinated benzenes was however not significantly less than in the previous method [5].

The surface area of molecules is expected to be related to the solubility. The calculated surface area was therefore examined instead of Van der Waals volume to obtain the predicted retention times. The error was larger than that calculated from Van der Waals volumes. Chlorinated benzenes had more than 10% error, and even alkylalcohols had minus 10% error. One reason may be due to the calculation of kinetic energy which includes Van der Waals volume but not surface area.

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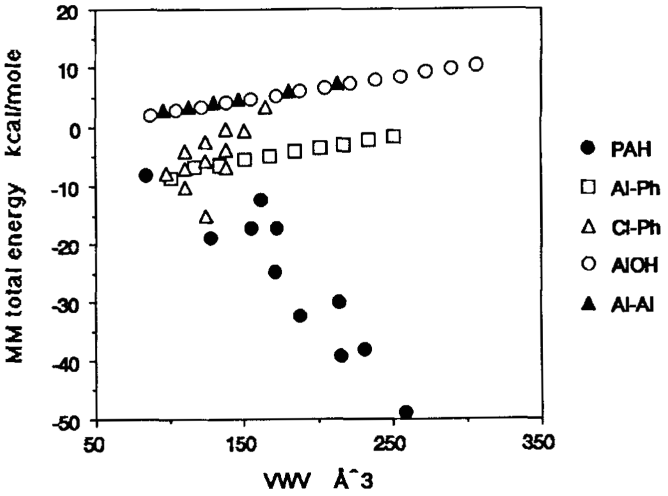

Fig. 4 Relation between MM total energy and Van der Waals volume
PAH: polyaromatic hydrocarbons, Al-Ph: alkylbenzenes, Cl-Ph: chlorobenzenes, Al-OH: alkylalcohols, Al-Al: alkanes

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In general, retention in reversed-phase liquid chromatography may be related to hydrophobicity of solutes. The total energy calculated by Molecular Mechanics includes Van der Waals volume, hydrogen bonding and electrostatic energies, therefore the calculated total energy was expected to have a good correlation with log k' in reversed-phase liquid chromatography. The correlation was however quite good only for homologous series of alkyl compounds, but not for chlorinated benzenes and polyaromatic hydrocarbons as shown in Fig. 4.

A combination of Van der Waals volume and kinetic energy of polyaromatic hydrocarbons is the most precise method to predict retention time in reversed-phase liquid chromatography. Further study is required to obtain an accurate relation between capacity ratios and the values calculated by computational chemistry based on quantum mechanics.

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