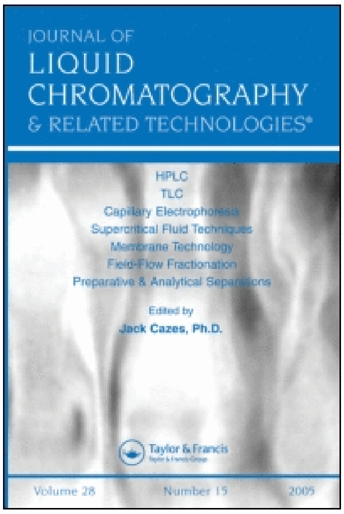

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PREDICTION OF LOG K_W USING MCIS AND LSER METHODS FOR HETEROCYCLIC NITROGEN COMPOUNDS

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ABSTRACT

The HPLC capacity factors(k') measured on a C_{18} column, using methanol-water mobile phase of different compositions, were determined for 15 heterocyclic nitrogen compounds. The linear relationship between the log k' values and the percentage of the methanol in the eluent was studied for each compound. The log k_w' values of these compounds were obtained by extrapolating the retention data in binary solvent system to pure water eluent.

Various MCI's (molecular connectivity indices) were calculated and LSER(linear solvation energy relationship) parameters were observed for these compounds. Good correlations were established between MCI's and log k_w', and between LSER parameters and log k_w'. The present correlation can be used to predict log k_w' values for other derivatives.

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Table 1

The Selected Heterocyclic Nitrogen Compounds

No.	Compounds
1	2,6-Dichloro-4-morpholino-1,3,5-triazine
2	2,6-Dichloro-4-diethylamino-1,3,5-triazine
3	2,6-Dichloro-4-N-phenylamino-1,3,5-triazine
4	2,6-Dichloro-4-N-methyl-phenylamino-1,3,5-triazine
5	3,6-Dichloro-pyridazine
6	2,6-Dichloro-3-nitro-pyridine
7	3-Amino-2-chloro-pyridine
8	2-Methyl-pyridine
9	2,6-Dimethyl-pyridine
10	2-Phenylvinyl-pyridine
11	2-Amino-3-methyl-pyridine
12	2-Amino-5-methyl-pyridine
13	2-Chloro-5-chloromethyl-pyridine
14	Diethyl-2,6-pyridinedicarbonyl ester
15	2-Amino-pyridine

INTRODUCTION

Application of chromatographic retention in quantitative structure-property /activity relationship(QSPR/QSAR) studies is an active research field which attracts many analytical chemistry, environmental chemistry, and pharmaceutical chemistry researchers. For substituted benzenes or aliphalics, researches concerning quantitative structure retention relationship (QSRR) have been vastly reported.[1-4]

Heterocyclic nitrogen compounds are important in both agriculture and industry. Pyridine derivatives are massively used as adhesives for textiles and as solvents, catalysts and precursors of other compounds, and they, as well as triazine, are also used as herbicides and pesticides due to their high bioactivity.[5-7] However, for heterocyclic nitrogen compounds, little information is available for their QSRR study.

Th.Braumann[8] observed that log k_w' was a better hydrophobic parameter than other hydrophobic parameters, and has its superiority in predicting the biological activity of compounds, which implies that log k_w' is a very important parameter in QSRR. In our recent work, we obtained capacity factors (log k') for 15 heterocyclic nitrogen compounds, using ODS as stationary phase, and different ratios of methanol-water as mobile phase.

Investigation on the relationship between log k' vs methanol percentage was made for each compound, and linear relationship was observed for each chemical. Then log k_w' values were obtained.

Molecular connectivity indices (MCIs) and linear solvation energy relationship (LSER) have been widely used to develop QSRRs. In this paper, we presented the statistical results of the two methods to show which is more satisfactory for the prediction of log k_w' for a group of heterocyclic nitrogen compounds.

EXPERIMENTAL

Instruments

A complete HPLC system of HP 1050 series modules consisted of a system monitor, a pump, an integrator, and an ultraviolet variable wavelength detector. A C_{18} reverse phase Kromasil (Tianjing Turner Scientific Instrument Company) (150 × 4.6mm) column was used.

Materials

The compounds which were studied are shown in Table 1. These compounds, which are triazines, pyridazines and pyridines derivatives, were synthesized by Department of Chemistry, Nanjing University. Their purities were monitored by HPLC to ensure their high purity. The water used as a mobile phase component was double stilled. Methanol was analytical grade and was redistilled before use. Sodium nitrate was also analytical grade.

Methods

The log k' values were determined for each compound. Mobile phases were made by mixing methanol with water in the proportions 90:10, 85:15, 80:20, 70:30, 60:40, 50:50(v/v). The flow rate was 0.8mL/min. Aqueous solution of sodium nitrate was used for the measurement of dead time.[9] All measurements were made at least triplite. The average reproductivity of each determination was better than 1.0% relative. The capacity factors were determined using $k'=(t_r-t_0)/t_0$, where t_r is the retention time of the compound, and t_0 is the dead time. The log k_w' values were obtained by extrapolating the retention data in binary system to pure water eluent. The capacity factors obtained at different mobile phase composition are shown in Table 2.

Table 2

Log k' Values in Different Ratio of Mobile Phase

No.*	logk' ϕ=90%	logk' ϕ=85%	logk' ϕ=80%	logk' ϕ=70%	logk' ϕ=60%	logk' ϕ=50%	logk' ϕ=0%
1	0.018	0.082	0.206	0.438	0.773	1.224	2.618
2	0.216	0.321	0.465	0.779	1.158	1.597	3.016
3	-0.053	0.032	0.142	0.404	0.819	1.344	2.947
4	0.043	0.153	0.279	0.584	0.992	1.526	3.247
5	-0.330	-0.321	-0.305	-0.246	-0.154	-0.030	0.310
6	-0.024	0.049	0.149	0.396	0.707	1.067	2.379
7	-0.341	-0.318	-0.258	-0218	-0.130	0.065	0.482
8	-0.193	-0.171	-0.100	0.002	0.166	0.437	1.133
9	-0.139	-0.092	0.007	0.141	0.350	0.620	1.503
10	0.067	0.179	0.346	0.675	1.089	1.330	3.113
11	-0.056	0.002	0.086	0.212	0.361	0.541	1.260
12	-0.086	-0.024	0.049	0.176	0.354	0.542	1.298
13	-0.148	-0.085	0.028	0.211	0.457	0.830	1.947
14	-0.317	-0.261	-0.221	-0.131	0.014	0.297	0.934
15	-0.174	-0.120	-0.063	0.027	0.171	0.334	0.929

---

* The No. represents the same compound as in Table 1.

The LSER parameters were estimated by Hichey's "Rule of Thumb."[10] The LSER values of triazine ring were calculated by the benzene ring substituted by three aromatic nitrogen. The estimated values are shown in Table 3. The molecular connectivity indices (MCI's) were calculated according to the method outlined by Kier and Hall.[11] The non-dispersive force factor, $\Delta^0\chi^v$ and $\Delta^1\chi^v$ were obtained by using the method described in reference.[11] All the calculations were performed on an 80586 personal computer. Some of the calculated values are shown in Table 4. All the regression analysis were performed using the "statgraphics" program (STSC, Inc; 1987).

RESULTS AND DISCUSSIONS

LSER Methods

The linear solvation energy relationship(LSER) was initially developed by Kamlet and co-workers. They demonstrated that many types of chemical

Table 3

Some LSER Parameters of Studied Compounds

No.*	**$V_i/100$**	**π^***	**β**	**α**
1	1.119	1.750	1.790	0.000
2	1.080	1.710	1.820	0.000
3	1.179	2.300	1.530	0.170
4	1.277	2.300	1.960	0.000
5	0.667	0.430	0.620	0.000
6	0.792	1.440	0.560	0.160
7	0.642	1.100	0.780	0.260
8	0.570	0.830	0.440	0.000
9	0.570	0.790	0.450	0.000
10	0.937	1.560	0.670	0.050
11	0.650	0.960	0.720	0.260
12	0.650	0.960	0.720	0260
13	0.848	1.530	0.750	0.120
14	1.142	1.210	1.010	0.240
15	0.552	1.000	0.810	0.260

---

* The No. represents the same compound as in Table 1.

properties (designated as XYZ) such as aqueous solubility,[13] octanol-water partition coefficient,[14] HPLC capacity factors using a number of mobile and stationary phases,[15-17] and toxicity to a variety of species,[18] depended on solute-solvent interactions. The model can be expressed by an equation containing three simple and conceptually explicit types of terms:

$$\text{XYZ(property)} = \text{cavity term} + \text{dipolar term} + \text{hydrogen-bonding terms} \tag{1}$$

In the LSER model, chemical properties (as XYZ) are related to molecular structure through the energy required to surround a solute with solvent molecules and the energy gained or lost through formation of electrostatic and hydrogen bonds between the chemical and the medium to stabilize this solvent molecule cavity and keep the compound inside it. Chemical properties dependent on this solute-solvent interaction are the result of the contribution from the component groups that form the molecule. The energy terms for component groups then make up the four energy terms for the molecule used in predictive equation:

Table 4

Some Calculated MCIs Values of Studied Compounds

No.*	$^0\chi^v$	$^1\chi^v$	$^2\chi^v$	$^3\chi^v$	$^4\chi_{pc}^v$	$\Delta^0\chi^v$	$\Delta^1\chi^v$
1	8.790	4.907	3.448	2.200	0.592	0.819	1.063
2	8.968	4.744	3.020	1.953	0.658	0.520	0.448
3	8.993	4.885	3.363	1.948	0.439	0.661	0.177
4	9.940	5.279	3.743	2.350	0.765	0.521	0.640
5	5.314	1.831	0.912	0.219	0.073	0.260	0.597
6	6.591	3.278	2.401	1.440	0.557	0.767	0.651
7	4.889	2.417	1.399	0.801	0.219	0.553	0.351
8	4.257	2.270	1.471	0.813	0.149	0.130	0.141
9	5.179	2.579	1.688	0.814	0.074	0.130	0.098
10	7.798	4.592	2.999	1.934	0.296	0.130	0.140
11	4.757	2.476	1.706	1.050	0.370	0.552	0.351
12	4.757	2.470	1.760	0.934	0.257	0.552	0.351
13	6.151	3.401	2.276	1.474	0.423	0.130	0.141
14	9.226	4.999	2.849	1.718	0.389	2.066	1.785
15	3.834	2.059	1.255	0.688	0.086	0.553	1.352

---

* The No. represents the same compound as Table 1.

$$XYZ = XYZ_0 + mVi/100 + s\pi^* + b\beta + a\alpha \qquad (2)$$

The endoergic energy term mVi/100 represents the free energy required to separate the solvent molecules and provide a suitably configured cavity for the contaminant molecule. Vi/100 is the intrinsic (van der Waals) molecular volume scaled by a factor of 100 for magnitudes that are comparable to the other three variables. The dipolar-polarizability term, π^*, represents the exoergic effects of solute-solvent dipole-dipole and dipole-induced dipole interaction and π^* is a measure of the molecule's ability to stabilize a neighboring charge or dipole through nonspecific dielectric interaction.

The hydrogen-bonding terms β and α represent the exoergic effects of hydrogen bonding involving the solvent as hydrogen bond donor acid (HBD) and the solute as hydrogen bond acceptor base β(HBA), and the solute as hydrogen bond donor acid α and the solvent as hydrogen bond acceptor base. And s, a, and b are regression coefficients. By stepwise regression, the obtained correlation between log k_w' and LSER parameters is as follows:

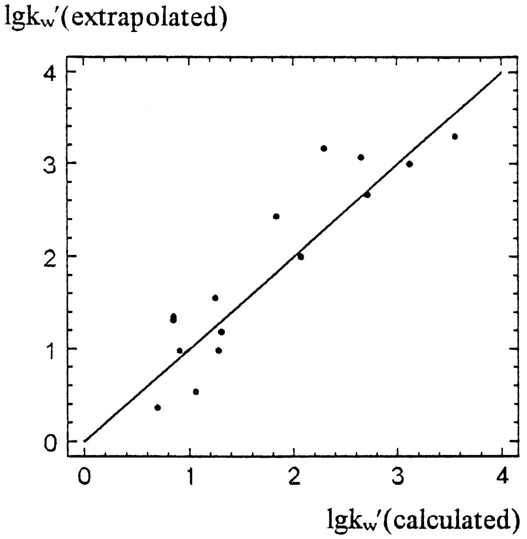

Figure 1. Plot of extrapolated and the calculated log k_w' values according to Eq. 3.

$$\log k_w' = 0.0848(0.349) + 1.528\ (0.218)\ \pi^* - 2.540(1.020)\alpha \qquad (3)$$

$$R=0.916;\ SE=0.437;\ n=15;\ F=31.14$$

In the above equation, R is the correlation coefficient, SE is the standard error, n is the sample number, and F is the F value in F test. The relationship described by Eq.3 is statistically significant at the confidential level better than 0.01: $F=31.14 > F(2,12,0.01)=6.93$. Figure 1 shows the extrapolated values of log k_w' and the calculated values by the equation. Only the dipole-polarizability term π^* and the hydrogen bonding term α are included in the equation, which suggest that the dipole-dipole (Keesom), dipole-induced dipole (Debye) interaction and hydrogen bonds interaction play an important role in the RP-HPLC process of these heterocyclic nitrogen compounds. In this case, the solute acts as hydrogen bond donor acid (HBD) and the solvent acts as hydrogen bond acceptor base (HBA).

MCI's Methods

Molecular connectivity is a method of deriving topological indices from the hydrogen suppressed skeleton of a molecule. A detailed calculation method is provided by Kier and Hall,[19] only a brief description of the procedure used to calculate MCI's will be presented here. To calculate simple MCI of a molecule, first, each non-hydrogen atom is assigned a delta value (δ) which is equal to the number of atoms to which it is bonded. Valence indices are obtained by assigning atom δ values based on the number of valence electrons not involved in bonds to hydrogen atoms. Simple and valence indices of different orders and types can be calculated for a given molecule. The order refers to the number of bonds in the skeletal substructure or fragment used in computing the index: zero order defines individual atoms, first order uses individual bond lengths, second order uses two adjacent bond combinations, and so on. The type refers to the structural fragment (path, cluster, path/cluster or chain) used in computing the index. Only path indices are possible for order less than 3. The symbol $^1\chi^v$ represent a first order valence index while $^2\chi$ represents a simple second order index. Each index is computed by an algorithm introduced by Randic[20] which sums the reciprocal square roots of the assigned δ values over all molecular fragments as illustrated below for zero, first, and second order indices:

$^0\chi = M(\delta_i)^{-1/2}$ for all atoms

$^1\chi = M(\delta_i\delta_j)^{-1/2}$ for bonded pairs of atoms

$^2\chi = M(\delta_i\delta_j\delta_k)^{-1/2}$ for bonded pairs of atoms

There have been many papers concerning the utility of molecular connectivity indices for describing HPLC retention parameters. Since the MCI's can be calculated quickly and accurately, only based on the structure of a chemical and with no experimental requirements, they are becoming more and more of interest.

The non-dispersive force factor, $\Delta\chi$ term is derived from molecular connectivity indices. Bahnich[12] initially developed the non-dispersive force $\Delta^1\chi^v$ in order to predict the soil sorption coefficient $\log k_{oc}$ values for a variety of organic chemical types using one regression equation. The definition and calculation method can be found in reference.[12]

Using the stepwise regression, we obtained the equation as follows:

$$\log k_w' = -0.0411(0.175) + 1.478(0.136)\,^3\chi^v - 1.068(0.198)\Delta^1\chi^v$$

$$R = 0.966;\ SE = 0.282;\ n = 15;\ F = 83.02 \qquad (4)$$

In the above equation, $^3\chi^v$ is the third order valence path index, $\Delta^1\chi^v$ is the first order nonspecific force, R is the correlation coefficient, SE is the standard error, n is the sample number, and F is the F value in F test. As what can be seen from the equation, the correlationship is significant at the confidential level

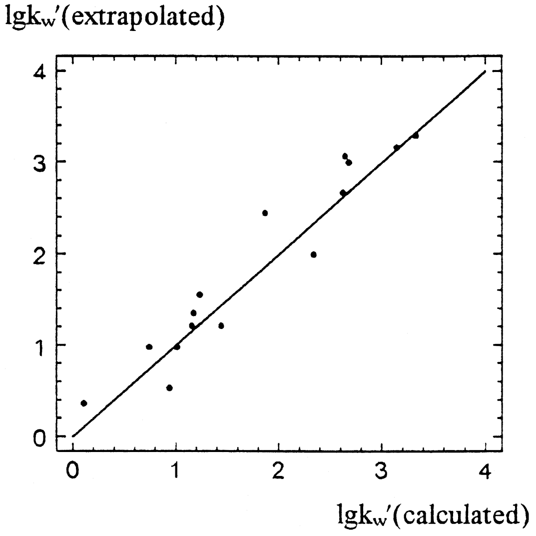

Figure 2 . Plot of extrapolated and calculated log k_w' values according to Eq.4.

better than 0.01: F = 83.02 > F (2,12,0.01) = 6.93, although the selected compounds contain three kinds of substituted central moiety (triazine, pyridazine, pyridine) and several kinds of substituent groups (chloro-, phenylamino-, N-methyl-phenylamino-, nitro-, methyl, amino-, chloromethyl-, phenylvinyl-). Figure 2 shows the extrapolated values and the calculated log k_w' values by the equation.

$\Delta^1\chi^v$ was deemed as useful by Kalisan[21] in estimating chromatographic retention time because of the importance of non-disperse interaction on the values of this partitioning parameter. Our results are in accord with their observations.

The inclusion of $^3\chi^v$ in the equation indicate that the RP-HPLC process correlates with the dimension of molecular. The results suggest that for these studied compounds, both non-specific interaction and polar interaction are important in the RP-HPLC process.

The better correlation between log k_w' and MCIs shows retention in RP-HPLC is sensitive to size and shape differences in the solute molecules, i.e., log k_w' includes additional information about topological solute properties, which agrees with the observation of Th. Braumann.[8]

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