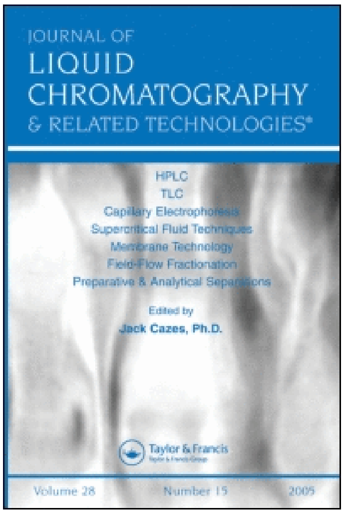

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Prediction of High-Performance Liquid Chromatographic Retention Data of Carboxamides and Oxadiazoles

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PREDICTION OF HIGH-PERFORMANCE LIQUID CHROMATOGRAPHIC RETENTION DATA OF CARBOXAMIDES AND OXADIAZOLES

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ABSTRACT

Regression models that predict the high-performance liquid chromatographic retention behavior of carboxamides and oxadiazoles were proposed. A new intermolecular interaction parameter was developed that combines dispersion interaction and total water solvation shell surface energy ratio of structural(*o*, *m*, *p*) isomers to form nonpolar bonding constant descriptor. Also resonance effect constant and field effect constant were used as electronic descriptor. A three-variable model indicated high multiple correlation(R>0.996) between the observed and the calculated values.

INTRODUCTION

Quantitative structure-retention relationships(QSRRs) are the methodology of relating chemical structure with chromatographic retention parameter(1). QSRRs have two main goals, the prediction of chromatographic retention and the explanation of the chromatographic mechanism. Through the use of statistical methods, retention data are characterized by various combinations of solute descriptors. Valuable QSRRs models obtained can be used to predict retention for new solutes, identify the most informative structural descriptors and suggest separation mechanism in a given chromatographic system.

In general, there are four available descriptors : topological, geometric, electronic, and physicochemical descriptors. Topological descriptors include molecular connectivity descriptors(2), κ indexes(3), path descriptors(4), and fragment descriptors. Fragment descriptors are evaluated from simple counts of atoms, bonds, rings, and substructures of the molecule. Geometric descriptors are evaluated from three-dimensional coordinates. They include principal moments of inertia, van der Waals molecular volumes(5), and length-to-breadth ratios(6). Physicochemical descriptors include molar refraction, polarizabilities(7), solubility parameters(8), Hammett constants, and boiling points. Electronic descriptors include σ electron density(9), dipole moments, orbital energies, and superdelocalizabilities. The QSRRs equations using these descriptors have been developed successfully for many compound classes and chromatographic systems(1).

Since the chromatographic retention is based on the intermolecular interactions such as solute-stationary phase, solute-mobile phase, and mobile phase-stationary phase interactions, the goal of this study is to find which of the available descriptors that describe the intermolecular interaction and discrimination of structural(*o,m,p*) isomers are related to the retention of the carboxamides and the oxadiazoles.

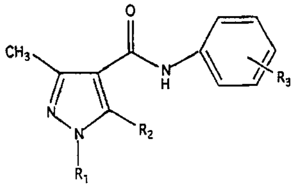
Multiple linear regression analysis was performed to find the regression model that correlates the retention data.

MATERIALS AND METHODS

Eight carboxamides and five oxadiazoles(10) were used for this study(Figure 1) and their retention data are listed in Table 1 and Table 2.

Methanol(HPLC grade) and acetonitrile(HPLC grade) were all from J.T. Baker (Phillipsburg, U.S.A.). Water was purified by using a Milli-Q water purification system(Millipore, Bedford, MA, U.S.A.).

A. Carboxamides



No.	R_1	R_2	R_3
1132	CH_3	Cl	*p*-Cl
1138	CH_3	Cl	*m*-OCH_3
1139	CH_3	Cl	*o*-OCH_3
1249	CH_3	CH_3	*m*-OCH_3
1250	CH_3	CH_3	*o*-OCH_3
1251	CH_3	CH_3	*o*-Cl
1253	CH_3	CH_3	*p*-Cl
1258	CH_3	CH_3	*p*-OCH_3

B. Oxadiazoles

No.	R_1	R_2	R_3	R_4
10392	*m*-Cl	*p*-CH_3	*i*-Pr	*m*-CH_3
10369	*m*-Cl	*p*-CH_3	*i*-Pr	*p*-CH_3
10397	*m*-Cl	*p*-CH_3	*i*-Pr	*p*-OCH_3
10380	*m*-Cl	*p*-CH_3	*i*-Pr	*o*-Cl
10378	*m*-Cl	*p*-CH_3	*i*-Pr	*m*-Cl

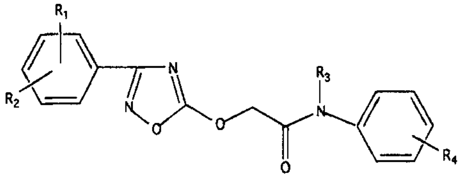


Figure 1. Compounds used in this study

TABLE 1
Observed and Calculated log k' of Carboxamides at 55% MeOH and 40% MeCN

	55% MeOH		40% MeCN	
No.	Obsd.	Calc.	Obsd.	Calc.
1258	0.129	0.128	0.045	0.061
1249	0.241	0.245	0.161	0.152
1138	0.454	0.463	0.431	0.431
1253	0.607	0.581	0.509	0.474
1250	0.677	0.668	0.487	0.483
1251	0.738	0.768	0.599	0.625
1132	0.800	0.795	0.751	0.754
1139	0.908	0.902	0.777	0.774

TABLE 2
Observed and Calculated log k' of Oxadiazoles at 75% MeOH and 65% MeCN

	75% MeOH		65% MeCN	
No.	Obsd.	Calc.	Obsd.	Calc.
10397	0.718	0.717	0.799	0.799
10380	0.790	0.788	0.934	0.932
10378	0.816	0.816	0.932	0.934
10392	0.835	0.837	0.952	0.957
10369	0.851	0.848	0.963	0.958

Apparatus

All chromatograms were obtained using a Shimadzu LC-10AD liquid chromatograph (Kyoto, Japan) equipped with a Shimadzu spectrophotometric detector SPD-10A at a wavelength 254nm. A Alltech NucleosilC18 column(250 × 4.6 mm i.d., Deerfield, Il, U.S.A.) was used. Isocratic elution was carried out with 55% and 75%(v/v) mixtures of methanol and water and 40% and 65%(v/v) mixtures of acetonitrile and water at 35°C. The flow rate was 1.0mL/min. The retention times for all solutes were measured three times and their average values were used for further analysis.

Descriptor Generation

Five descriptors were investigated : nonpolar bonding constant, polarizability, solubility parameter, resonance effect constant(11), and field effect constant(11). Nonpolar bonding constant descriptor is composed of two parts, the measure of the energy of dispersion forces acting between the solute and the stationary phase molecules(12) and the total water solvation shell surface energy ratio of structural(*o*,*m*,*p*) isomers. Calculation of the total water solvation shell surface energies were performed with a 33-MHz IBM compatible 486PC with the PCMODEL software. Polarizability descriptors were calculated using

Miller method(7) and solubility parameter descriptors were calculated using the group contribution additive method(8).

Regression Analysis

Multiple linear regression analysis(13) was used for descriptor selection and model construction. Preliminary information on the interrelationships among the descriptors was obtained from the correlation matrix. Also, multicollinearity was examined using tolerance. Multiple linear regression analysis was performed by a stepwise procedure, followed by model generation. The criteria for judging the best model were multiple correlation coefficient, standard error, and overall F-value for analysis of variance. Statistical calculations were performed with Macintosh Classic II using SYSTAT software.

RESULTS AND DISCUSSION

Since chromatogrpahic retention is basically dependent on the intermolecular interactions among solute, stationary phase, and mobile phase, it is necessary to develop the intermolecular interaction descriptor. The interaction acting between the solute and the stationary phase molecules has been calculated by dispersion interaction based on the group contributions(12). Structural(*o,m,p*) isomers had same values of dispersion interaction, because calculation method used is based on group contributions. The separation of the isomers could not be explained by dispersion interaction. The different retention behavior of the isomers in reverse-phase liquid chromatography is thought to occur through the interaction between the solute and the mobile phase rather than between the solute and the stationary phase.

The interaction between the solute and the mobile phase corresponds to the effect of solvation. However, since it was difficult to assess the extent of solvation of the solute in the mobile phase, the total water solvation shell surface energy of the isomers was calculated, followed by calculation of their relative ratio(Table 3), instead of determining the extent of the solvation of the solute in the mobile phase.

TABLE 3
Relative Isomer Ratios based on Total Water Solvation Shell Surface Energy

Sample	Position	Substituent		
		OCH_3	CH_3	Cl
Carboxamides	*o*-	1.565	1.037	1.187
	m-	1.123	1.038	1.051
	p-	1.000	1.000	1.000
Oxadiazoles	*o*-	1.213	1.236	1.013
	m-	0.979	1.014	0.980
	p-	1.000	1.000	1.000

TABLE 4
Resonance Effect Constants and Field Effect Constants for Substituents

Substituent	Resonance Effect Constant	Field Effect Constant
OCH3	-0.50	0.41
CH3	-0.14	-0.05
Cl	-0.16	0.69

Nonpolar bonding constant descriptor was determined by multiplying the value of dispersion interaction by the relative isomer ratio.

The solvation of solute may cause the change of the electronic environment of aromatic ring and the extent of the change is related to the electronic properties of substituents in the aromatic ring. The resonance effect constant and field effect constant describing the change separation were used as electronic descriptor(Table 4).

The best model selected for carboxamides and oxadiazoles is presented in Table 5 and Table 6, respectively. A plot of the observed vs. calculated retention data for carboxamides and oxadiazoles is presented in Figure 2 and Figure 3, respectively. They show the high degree of correlation.

TABLE 5
Regression Model Developed for the Carboxamides Separated at 55% MeOH

Coefficient	Std. Error	Tolerance	Descriptor
0.002	0.000	0.833	(Nonpolar bonding constant)/1000
-8.837	0.808	0.955	Resonance effect of pyrazole ring
1.184	0.050	0.869	Resonance effect of phenyl ring
-1.474	0.118		Constant
R=0.998	s=0.022	n=8	F=372.20

TABLE 6
Regression Model Developed for the Oxadiazoles Separated at 75% MeOH

Coefficient	Std. Error	Tolerance	Descriptor
1.862	0.322	0.574	(Nonpolar bonding constant)/1000
0.337	0.015	0.649	Resonance effect
-0.029	0.006	0.708	Field effect
1.691	0.140		Constant
R=0.999	s=0.004	n=5	F=268.11

In the correlation matrix of the descriptors used in the model, high correlation among nonpolar bonding constant, polarizability, and solubility parameter was observed. The evaluated model, keeping nonpolar bonding constant descriptor but eliminating polaizability and solubility parameters, gave a much better F-value.

In the model for carboxamides, resonance effect constant descriptors on phenyl ring and pyrazole ring are included, but field effect constant descriptors are excluded. It suggests that the polarization of charge density is influenced by both substituents of phenyl ring and pyrazole ring, because π electrons can transfer easily through amide bond.

In summary, each three-variable regression model for carboxamides and oxadiazoles showed a high degree of correlation between observed and

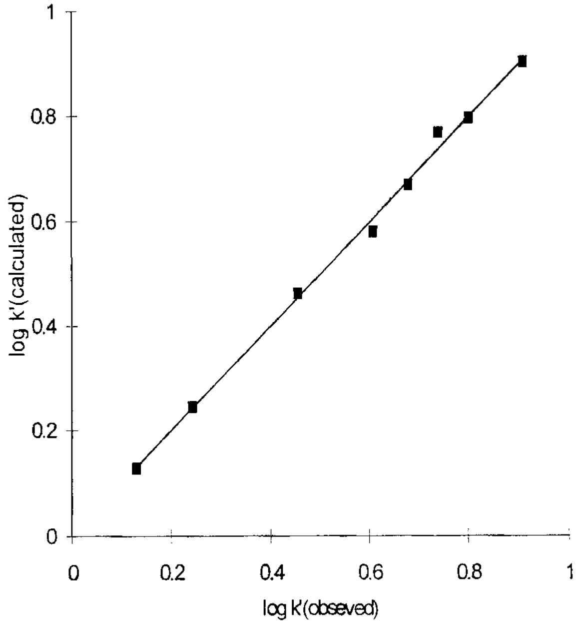


Figure 2. Plot of the Observed vs. Calculated Retention Data for the Carboxamides Separated at 55% MeOH

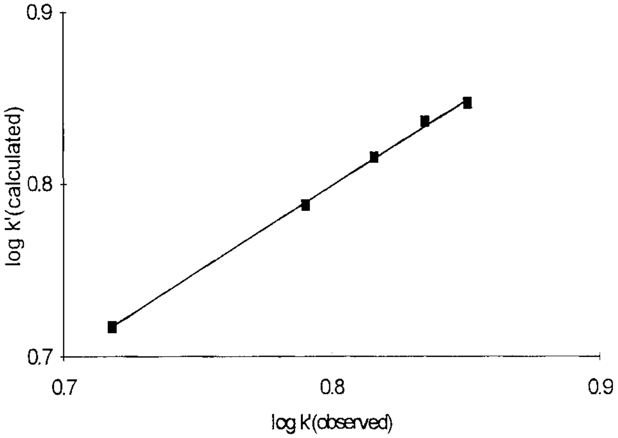


Figure 3. Plot of the Observed vs. Calculated Retention Data for the Oxadiazoles Separated at 75% MeOH

calculated values. This study showed that the models have a good predictive ability for application.

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