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Theoretical analysis of the retention behavior of alcohols in gas chromatography

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Abstract—Quantitative structure–retention relationship (QSRR) models for the chromatographic (GC) retention times of alcohols on Superox 20M-diglycerol polarity stationary phase have been developed. Semi-empirical quantum chemical method (AM1) in MOPAC and Hartree–Fock (HF) method in Gaussian 98 implemented were employed to calculate a set of molecular descriptors of alcohols and ethyl acetate. Using multiple linear regression (MLR), we obtained the empirical functions with high correlation coefficient between retention times and quantum-chemical descriptors. The retention mechanism of alcohols of separation operating in the gas chromatogram was discussed. The results indicated that the QSRR models proposed were satisfactory.

1. Introduction

The alcohols such as 1-pentanol, which are very deleterious to human beings, usually exist in wines. An effective method for determination of these alcohols is gas chromatography. However, similar chemical properties of such alcohols in wines make separation of the alcohols difficult using gas chromatography. Therefore, it is necessary to study the retention mechanism for the separation of alcohols operating in gas chromatography in order to choose a useful stationary phase and to predict the retention time of alcohols in wine.

The quantitative structure–retention relationship (QSRR) of solutes is a useful method of discussing the retention mechanism in gas chromatograph and an important topic in chromatographic thermodynamics. In the last two decades QSRR have often been applied to:[1] (1) predict retention for a new solute; (2) identify the most informative structural descriptors (regarding properties); (3) gain insight into the molecular mechanism of separation operating in a given chromatographic system; (4) evaluate complex physicochemical properties of analytes; and (5) predict relative biological activities.

Over the past several years, QSRR studies are widely investigated. Correlation between gas chromatographic retention indices and molecular parameters provided significant information: on the effect of the molecular structure on retention time and on the possible mechanisms of absorption and elution.[2] This could be achieved using quantitative structure with the retention phenomena.[3–7] Good correlation was obtained between Kováts indices (RI) and theoretically calculated data for molecules with different functional groups: alkanes,[8] dialkylhydrazones,[9] alkenes,[10] alkybenzenes and naphthalenes,[11] phenol derivatives,[12] azo compounds,[10] primary, secondary and tertiary amines,[13] etc. This interest in studies dealing with the retention behavior of solutes in different stationary phases has been increasing nowadays substantially.[14] In the literature several models have been described, from linear ones (MLR) to non-linear ones (artifical neural network) in order to calculate these values as accurately as possible.[15,16]

The goal of our present study is to develop QSRR models for the correlation of chromatographic retention times of a set of alcohols on polarity stationary phases with their molecular structures. The structures of these molecules are represented by quantum chemical descriptors.

Keywords: Quantitative structure–retention relationship; Multiple linear regression; Molecular descriptors; Retention mechanism.
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2. Theory

2.1. Descriptor generation

To obtain a QSRR model, the compounds must be represented by molecular descriptors and retain as much structure information as possible. Here quantum-chemical descriptors were used because they could be easily obtained using quantum chemistry program and also had specific chemical meaning. The calculation of quantum-chemical descriptors was described as follows: all molecules were drawn into MOPAC (ChemOffice, 2004) program and pre-optimized using AM1 method,[17] and then heat of formation was calculated (HOF). The final geometry was obtained with the Hartree–Fock (HF) method[18] at 6-31G(d)[19] level. The Gaussian 98[20] with HF method at 6-31G(d) level was used for calculation of the sum of Mülliken negative charges with hydrogens summed into heavy atoms in molecule (Q), dipole moments (D), molecular volumes (V), the lowest unoccupied molecular orbital (LUMO) and molecular radiuses (R).

2.2. Statistical analysis

In the present work, the linear model was used. The linear model uses multiple linear regression (MLR), which is a common method used in QSRR study. The QSRR equations were obtained by using forward stepwise multiple regression techniques following the multi-linear forms: $t = b_0 + b_1D_1 + b_2D_2 + \cdots + b_nD_n$, where t was the retention times, D_1, D_2 and D_n are the descriptors, the intercept (b_0) and the regression coefficients of the descriptors ($b_1, b_2, \ldots, b_n$) were determined by using the least squares method, and n is the number of the descriptors. In the MLR models, the molecular descriptors used included: HOF (kcal mol^{-1}), D (Debye), Q, LUMO (hartree), R (Å) and V (cm^3 mol^{-1}).

3. Experiment and methodology

3.1. Instrument

Retention times (t) of 10 standard samples were determined for alcohols and ethyl acetate (shown in Table 1). An SP-2305 gas chromatograph (China) coupled with a hydrogen flame temperature detector with a (polarity stationary phase of Superox 20M:diglycerol:101 white support (0.177–0.25 mm i.d.) = 20:2:100) stainless steel column (3 m × 4 mm i.d.) was used. Nitrogen gas was used as a carrier gas at a flow rate of 50.0 mL/min. A 1 μL volume of sample (0.3 μg/μL) every standard sample in mixture of ethanol and water (60:40, v/v) was injected into the vaporizer. Temperatures of the vaporizer, the column and the detector were set at 125, 79 and 110 °C, respectively.

3.2. Materials

The compounds included in the study were obtained from the Shanghai reagent Corp. (China). All reagents are chromatographically pure.

3.3. Data

The QSRR model developed in MLR was accomplished through the following statistical validation techniques. The t values of alcohols and ethyl acetate on stationary phases were versus some of the descriptors. The best regression model was selected on the basis of the highest correlation coefficient (r), F value (a statistic for assessing the overall significance) and the lowest standard error of estimation (SE).

In MLR analysis, the descriptors in the regression equation must be independent. So, in order to reduce the number of the descriptors and minimize the information overlap in the descriptors, the concept of non-redundant descriptors (NRD)[21,22] was used. The linear correlation coefficient value of the two descriptors should be less than 0.9. Table 2 shows the correlation matrix of the descriptors.

4. Results and discussion

4.1. Molecular geometry

The molecular geometries of alcohols and ethyl acetate optimized with (HF) method at 6-31G(d) level is shown in Figure 1. The calculated frequencies of alcohols and ethyl acetate with HF method have no imaginary vibrational frequency, indicating that the optimized geometries are reasonable and reliable.

Table 1. The descriptors of QSRR models

Compounds	t (min)	HOF (kcal mol^{-1})	V (cm^3 mol^{-1})	R (Å)	Q	D (Debye)	LUMO (hartree)
1-Pentanol	24.01	−83.249221	85.835	4.07	−0.305867	1.6246	0.22874
3-Methyl-1-pentanol	18.48	−80.299120	88.727	4.04	−0.312275	1.6553	0.21408
2-Butanol	12.80	−71.665900	70.542	3.84	−0.319479	1.6480	0.20733
2-Pentanol	10.46	−80.299050	71.573	3.86	−0.312275	1.6553	0.21408
1-Butanol	8.82	−75.849725	74.397	3.90	−0.300396	1.6732	0.22550
2-Methyl-1-propanol	7.18	−74.075560	56.009	3.59	−0.306073	1.5966	0.22491
1-Propanol	6.33	−69.583987	54.591	3.57	−0.304357	1.6490	0.22938
Ethanol	4.37	−62.702088	43.730	3.35	−0.297587	1.7381	0.22695
Methanol	3.48	−57.053769	39.221	3.25	−0.289069	1.8667	0.22681
Ethyl acetate	3.18	−69.799871	76.144	3.93	−0.526810	4.0199	0.19154

Table 2. The correlation matrix for the descriptors used in MLR

	HOF	*V*	*R*	*Q*	*D*	LUMO
HOF	1.0000					
V	−0.8672	1.0000				
R	−0.8792	0.9922	1.0000			
Q	−0.0331	−0.2857	−0.3145	1.0000		
D	0.1952	0.1451	0.1654	−0.9785	1.0000	
LUMO	0.0955	−0.4228	−0.4404	0.8407	−0.7695	1.0000

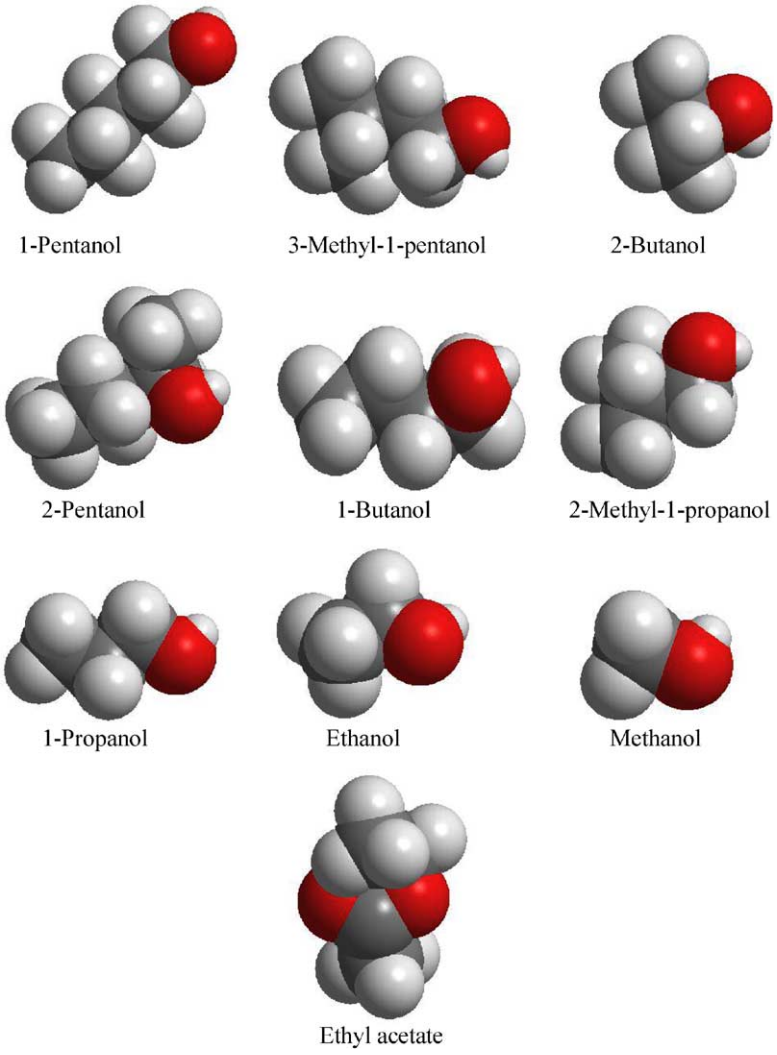

Figure 1. Molecular geometry.

From Figure 1 it can be seen that the shape and size of the compounds are different. Both factors may have important influence on retention times.

4.2. Retention times of standard samples

The chromatogram for the separation of 10 standard samples is shown in Figure 2. It shows that the peaks of methanol and ethyl acetate is difficult to separate, but other alcohols are separated better.

4.3. The molecular descriptors of QSRR models

The retention times and the molecular descriptors of QSRR models calculated using AM1 method and HF method are summarized in Table 1.

4.4. Results of the model with MLR

Three main types of QSRR have been employed in the previous work. The oldest type correlates logarithms of retention factors ($\log k$) with the logarithms of

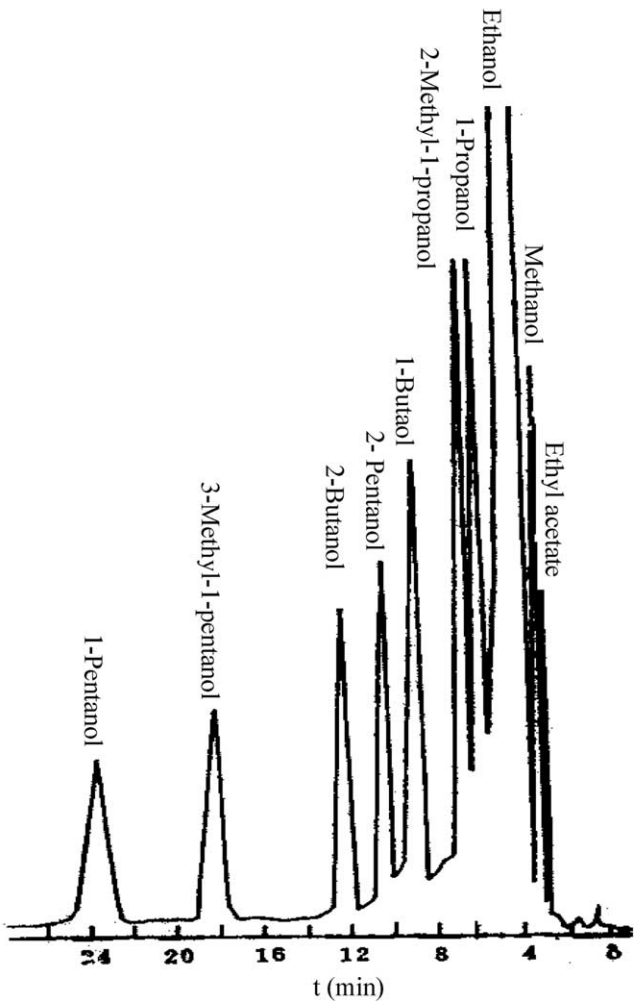

Figure 2. Chromatogram of standard samples.

n-octanol–water partition coefficients (log *P*).[23] The second type of QSRR is based on the solva-tochromic comparison method and the so-called linear solvation energy relationships (LSERs).[24–26] The third type of QSRR equation describes the chromatographic retention values in terms of quantum chemical indices and/or other structural descriptors from calculation chemistry,[27,28] which is very popular today. Previous results on the QSRR of alcohols from different authors using the novel semi-empirical topological index were reported,[29–31] although these models obtained good correlation coefficient, the descriptors on QSRR are difficult to describe in the retention mechanism.

In this paper, stepwise regression routine was used to develop QSRR models. Molecular descriptors included in the regression equation were non-redundant ($R < 0.9$) as deduced from Table 2, Q and D or V and R must be presented solely in models. The linear models from diverse combination of molecular descriptors of alcohols and ethyl acetate were obtained and the regression coefficients of the descriptors (included standard estimation errors and correlation coefficients) are listed in Table 3.

The regression equation obtained with selected molecular descriptors, which include Q, V, HOF and LUMO, is presented in Table 3. Analysis of variance showed that the highest correlation coefficient (r) for the regression equation was 0.915. Compared with the values of b_0, b_1HOF, b_2V, b_4Q, b_6LUMO in equation 1 in Table 3, for example, the values of b_0, b_1HOF, b_2V, b_4Q, b_6LUMO of 1-pentanol were −21.84, −10.69, 37.73, 12.55, 26.59, respectively. Therefore, V and LUMO have primary influence on the retention times.

By interpreting the regression coefficients of the model in Table 3, we found that the structural factors affect the retention behavior of these compounds. R or V represents the molecular shape and size, which affect rate of mass transfer. Retention times of alcohols increase with increasing of R or V. HOF is a quantum chemical index obtained by subtracting atomic heats of formation from the binding energy. It correlates with the measure of the energy demand of removing an electron from the molecule, and it is proportional to the ionization potential that is corrected with van der Waals forces. In gas chromatography (GC), as we know, the contribution of the molecules' of van der Waals forces to t decreases with the increasing polarity of the stationary phase molecules. So, from Table 3, HOF plays an important role in determining the retention times. Otherwise, D (dipole moment) is also important in the interaction of the molecules with apolar and polar stationary phases. As a directional force, the contribution of the dipole moment to t increases with the increasing polarity of the stationary phase and the polar interactions become more dominant in the interaction of the solute and stationary phase molecules. So, in the regression equations, the partial correlation coefficients of HOF decrease and the partial correlation coefficient of D increase with the increasing polarity of the stationary phase molecules. Q is the maximum of the net atomic charge on the atom, affecting formation of the hydrogen bond between the solute and stationary phase, at the same time, the hydrogen bond has a covalent or charged-transfer component; from the molecular orbital theory of chemical reactivity, LUMO, as an electron acceptor, represents the ability to obtain electron. From the molecular orbital theory of chemical reactivity, transition states are formed during interaction between

Table 3. The descriptors and regression equation of alcohols and ethyl acetate

Equation	b_0	b_1(HOF)	$b_2(V)$	$b_3(R)$	$b_4(Q)$	$b_5(D)$	b_6(LUMO)	r	F	SE
1	−21.8435	0.1284	0.4395		41.0189		116.2407	0.9150	6.4256	3.6973
2	−29.5734	0.2203	0.4624			−3.7628	146.5715	0.8454	6.6361	3.6476
3	−85.9418	0.1698		27.0203	47.2433		103.085	0.8955	5.0615	4.0773
4	−100.6382	0.2549		28.0636		−4.0971	145.6966	0.8944	5.0011	4.0969

LUMO (electron acceptor) and HOMO (electron donor) of the reacting species.[32] It becomes easier to obtain electron with the decreasing of LUMO, meanwhile it becomes easier to form hydrogen bond with the stationery phase. So a combination of Q and LUMO could be used to model hydrogen bond donor and acceptor ability.

5. Conclusion

In the study, based on the quantum chemical descriptors computed by AM1 and HF, good models for QSRR of alcohols were obtained. By using MLR analysis, retention mechanism of alcohols of separation operating in the gas chromatogram was discussed. The main influence factors of retention times are Q or V and LUMO. The good predictive ability of MLR model should allow us for estimation of retention times for similar compounds in cases where retention values are not readily available.

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