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Predicting Chromatographic Retention Time of C_{10}-Chlorinated Paraffins in Gas Chromatography-Mass Spectrometry Using Quantitative Structure Retention Relationship

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Abstract Chlorinated paraffins(CPs) are potential persistent organic pollutants(POPs), which threat the safety of environment and organisms. However, the analysis of CPs is a difficult task due to their complex composition containing thousands of congeners. In the present work, quantitative structure retention relationship(QSRR) of CPs was studied. A total of 470 molecular descriptors were generated, for describing the structures of 28 CPs and 12 descriptors relevant to retention time of the CPs were selected by stepwise regression. Then, QSRR models between retention time on the one hand and the selected descriptors on the other hand were established by multiple linear regression(MLR), partial least squares(PLS) and least square support vector regression(LS-SVR). The result shows that PLS model is better than MLR and LS-SVR, obtaining a squared correlation coefficient(r^2) of 0.9996 and a root mean squared error(RMSE) of 0.015. The PLS model was then used to predict the retention time of 49 C_{10}-CPs. Three of them were investigated by gas chromatography coupled with mass spectrometry(GC-MS). A well-defined correlation was found between the measured retention time and the predicted value.

Keywords Chlorinated paraffin; Multivariate calibration; Retention time; Quantitative structure retention relationship

1 Introduction

Chlorinated paraffins(CPs) have been extensively used as additives in cutting fluids and high-temperature lubricants in the metal working industry, as well as for plastics, paints and sealants due to their high chemical stability and viscosity, flame resistance, and low vapor pressure[1,2]. It is estimated that the annual production of CPs in USA is 68 kilotons, while the total production of CPs in 2007 in China was *ca*. 600 kilotons[3—5]. With their massive production and extensive application, CPs have been found in all the compartments of environment, aquatic and terrestrial food webs[2], as well as in human breast milk[6—8]. CPs are produced by chlorination of *n*-alkane feed stocks. According to the carbon chain length of CPs, they can be categorized into short(C_{10}—C_{13}), medium(C_{14}—C_{17}) and long(more than C_{17}) chains, and given the names of SCCPs, MCCPs and LCCPs, respectively. SCCPs are most worthy to be concerned because they have the chance to produce higher adverse effects on environment and human tissue than MCCPs and LCCPs, thus posing a significant threat to public health[9]. Furthermore, SCCPs have been under review in the Stockholm Convention as potential persistent organic pollutants(POPs) candidate since 2009[10]. Consequently, the analysis of SCCPs is an important and urgent task.

Currently, the most commonly used method for the analysis of CPs is gas chromatography coupled with mass spectrometry(GC-MS)[11—14]. For example, Zencak *et al.*[11] described a GC-MS method for the determination of total polychlorinated *n*-alkane concentration in biota. Coelhan *et al.*[12] developed a method for determinating total SCCPs in fish samples by GC-MS without clean-up procedures. Castells *et al.*[13] and Zencak *et al.*[14] proposed a quantification procedure for the analysis of CPs in paint samples by means of GC-MS. However, a major problem associated with the methods is the low resolution of the chromatograms, and thus only a total content of SCCPs can be determined. So it is still a very hard task to separate the thousands of congeners by chromatographic and mass spectrometric technique. Even only one chlorine atom binds to a carbon atom, there will be more than 7600 constitutional isomers of SCCPs[1]. Only humpy peaks caused by a large number of co-eluting components are observed in the measured GC-MS signals. It is almost impossible to analyze and quantify the congeners in CPs[15].

Quantitative structure-retention relationship(QSRR) is a technique for relating the variations in retention time to the changes of molecular structure described by descriptors with predictive or explanatory purpose. Numerous investigators have reported the high correlation between experimental retention time and molecular descriptor[16,17]. For instances, a QSRR study was performed for the retention behavior of

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environmentally important POPs polybrominated diphenyl ethers(PBDEs)[18], and the QSRR model developed with 46 PBDEs was used to deduce the retention of the remaining 163 congeners[19]. The QSRR method can predict the retention time of PBDE congeners for which the standards are not currently available. The application of neural networks to the prediction of chromatographic retention time of sports doping was presented by Miller *et al.*[20]. Creek *et al.*[21] proposed a retention time prediction model for improving metabolite identification, providing opportunities for the future studies of metabolism from a global system biology perspective. More examples of QSRR studies can be found in the comprehensive review by Heberger [22].

In view of the complexity of SCCPs and the difficulties in separation, the retention time of SCCP congeners has not been studied. The aim of this work is to explore a QSRR model for predicting the retention time of SCCP congeners. Descriptors relevant to the retention time of SCCP congeners were selected by stepwise regression, and QSRR models between the retention time on the one hand and the selected descriptors on the other hand were studied by multiple linear regression(MLR), partial least squares(PLS) and least square support vector regression(LS-SVR). Furthermore, the PLS model was used to predict the retention time of 49 C_{10}-CPs and three of them were validated with experimental results.

2 Data and Methodology

2.1 Data Set

The retention time data used in this study were obtained from ref.[23], in which chlorinated compounds with a chain length of C_{10}, C_{11} and C_{12} were synthesized and the retention time of each of 28 synthesized molecules was obtained on a DB-5 nonpolar GC capillary column. Table 1 summarizes the retention time of each of the 28 molecules. By Kennard-Stone(KS) method[24], 18 of the molecules were selected as the training sets and the other 10 molecules, marked with the asterisk in Table 1, were used as the test sets to test the practicability of the models.

Table 1 Experimental retention time for the training and test sets

No.	Compound	Rentention time/min	No.	Compound	Rentention time/min
1*	5,6-Dichloro-1,9-decadiene	9.90	15	1,2,5,6,9,10-Hexachloro-5-decene	29.18
2	5,6-Dichloro-1,9-decadiene	10.20	16*	9,11,11,11-Tetrachloro-1,5-decene	19.51
3	5,6,9,10-Tetrachloro-1-decene	21.05	17	9,11,11,11-Tetrachloro-1,5-decene	19.73
4*	5,6,9,10-Tetrachloro-1-decene	21.27	18*	1,1,1,3,10,12,12,12-Octachloro-6-dodecene	35.48
5	1,2,5,6,9,10-Hexachlorodecane	30.98	19	1,1,1,3,10,12,12,12-Octachloro-6-dodecene	35.74
6	1,2,5,6,9,10-Hexachlorodecane	31.10	20	1,1,1,3,6,7,10,11-Octachloroundecane	36.73
7*	2,5,6,9-Tetrachlorodecane	21.40	21	1,1,1,3,10,12,12,12-Octachlorododecane	36.45
8*	2,5,6,9-Tetrachlorodecane	21.53	22	1,1,1,3,6,7,10,12,12,12-Decachlorododecane	44.71
9	1,2,5,6,9-Pentachlorodecane	26.32	23	1,1,1,3,8,10,10,10-Octachlorodecane	32.47
10*	1,2,5,6,9-Pentachlorodecane	26.42	24*	8,10,10,10-Tetrachloro-1-decen	17.76
11*	1,2,5,6-Tetrachlorodecane	21.41	25	1,1,1,3,9,11,11,11-Octachloroundecane	34.51
12*	1,2,5,6-Tetrachlorodecane	21.60	26	1,1,1,3,9,10-Hexachlorodecane	28.33
13	1,2,5,9,10-Pentachloro-5-decene	26.75	27	9,11,11,11-Tetrachloro-1-undecene	20.30
14	1,2,9,10-Tetrachlorodecane	23.81	28	1,1,1,3,10,11-Hexachloroundecane	30.49

* Test sets.

2.2 Molecular Descriptors

A total of 470 molecular descriptors were generated for developing the QSRR model. ChemDraw Ultra 8.0 program[25] was used for generating the structures, and the optimization was performed by MM+ and AM1 method successively with the program of HYPERCHEM[26]. Then, the molecular descriptors were generated *via* software DRAGON 5.4. Description of the software and the meaning of the descriptors can be found in the literature of DRAGON package[27]. To only keep the statistically significant descriptors in QSRR models, stepwise regression[28] was used for variable selection. In order to eliminate the effect of numerical value difference between descriptors and make each descriptor have a comparable contribution to the classification, normalized data were used in the calculations.

2.3 Multivariate Calibration

QSRR models were built by multivariate calibration methods including MLR, PLS and LS-SVR from the selected molecular descriptors. MLR is the most frequently applied technique in building QSRR models. However, the method is limited when the number of the variables is less than the number of the samples. In this case, PLS is commonly used for building the model. After the establishment of the linear model by MLR and PLS, a nonlinear model was also studied by LS-SVR. These multivariate calibration methods were compared with each other to obtain a better performance in the prediction.

The performance of the built models is evaluated by leave-one-out cross-validation(LOOCV) approach. The procedure involves removing one sample from the training set, constructing the model based on the remaining samples, and then testing on the removed sample.

Then, the samples in training set are tested and model performance is evaluated by the parameters including squared correlation coefficient(r^2) and root mean squared error(RMSE). r^2 can be interpreted mathematically as the proportionate reduction of the total variation associated with the independent variable.

2.4 Experimental

Three CP standards were measured by GC-MS for validating the predicted retention time. The standards were 2,5,6,9-tetrachlorodecane(CP-1), 1,2,9,10-tetrachlorodecane (CP-2) and 1,2,5,6,9-pentachlorodecane(CP-3), which were purchased from Ehrenstorfer(Augsburg, Germany) as 10 ng/μL solutions in cyclohexane. A GC-MS-QP2010 Ultra system (Shimadzu, Japan) consisted of a GC-2010 Plus gas chromatograph and a twin line MS system with an electron impact ionization(EI) source was employed in the experiments. A 30-m Rxi-5 weak polarity capillary column(0.25 mm i.d. and 0.25 μm film thickness, Restek, Bellefonte, USA) was used, and the oven temperature was set at 100 °C for the first 2 min, increased to 250 °C at a rate of 20 °C/min, next increased to 280 °C at a rate of 3 °C/min, then held for 11 min. Helium was used as a carrier gas at a flow rate of 1.0 mL/min. Splitless injection was used and the temperature of the GC injector was controlled at 250 °C. The mass spectrometer was operated at a transfer line temperature of 250 °C and an ion source temperature of 200 °C. The electron impact ionization was tuned at 70 eV, the mass range for the MS detector was from 10 amu to 650 amu, and the scan event time was 0.20 s. The retention time values of CP-1, CP-2 and CP-3 are 8.78, 9.36 and 9.98 min, respectively.

3 Results and Discussion

3.1 Descriptor Selection

To select the descriptors which are most relevant to the retention time of the congener molecules, stepwise regression method was employed. The 470 descriptors were used as the input of the calculation. Forward selection was adopted, and in each step of the calculation, the descriptor is added or removed in accordance with the criterion of probability of P=0.05 for inclusion and P=0.1 for exclusion. The result shows that 12 descriptors, including TI1, S2K, PW4, EEig10r, RDF100u, RDF110m, RDF145m, RDF120v, R3V+, H-052, Q2 and Hy, were selected, and the meanings of them are listed in Table 2. It can be seen that the P values of all the selected descriptors are less than 0.05, indicating the rationality of the selected descriptors.

Table 2 Meanings of the molecular descriptors selected by stepwise regression

Descriptor	Meaning of descriptor	Regression coefficient	P value
TI1	First Mohar index from Laplace matrix	–0.23	6.8×10^{-9}
S2K	2-Path Kier alpha-modified shape index	0.25	1.7×10^{-16}
PW4	Path/walk 4-Randic shape index	0.01	2.0×10^{-2}
EEig10r	Eigenvalue n. 10 from edge adjacency matrix	0.09	1.6×10^{-6}
RDF100u	Radial distribution function-100/unweighted	0.02	4.1×10^{-4}
RDF110m	Radial distribution function-110/weighted by mass	0.04	3.6×10^{-8}
RDF145m	Radial distribution dunction-145/weighted by mass	–0.11	1.0×10^{-14}
RDF120v	Radial distribution function-120/weighted by van der Waals volume	0.05	2.6×10^{-7}
R3V+	R maximal autocorrelation of lag 3/weighted by van der Waals volume	0.02	2.9×10^{-5}
H-052	H attached to C0(sp3) with 1X attached to next C	0.07	9.6×10^{-7}
Q2	Total squared charge	0.05	2.9×10^{-6}
Hy	Hydrophilic factor	0.51	1.2×10^{-16}

The rationality can also be explained by the structural information described by the selected descriptors. Molecular 2D and 3D information, topology information, distance information between atoms, molar volume, charge distribution and hydrophilic feature are included in the 12 descriptors. For examples, TI1 and R3V+, belonging to the 2D matrix-based descriptor and Getaway descriptor, respectively, characterize the 2D(the number, location and adjacency information of carbon and chlorine atoms) and 3D information of SCCP congeners. S2K and PW4 belong to topological indices to describe the topology of SCCP congeners. RDF100u, RDF110m, RDF145m and RDF120v, belonging to radial distribution function(RDF) descriptors, are reflections of the distance information between the atoms in SCCP congeners. H-052, EEig10r, Q2 and Hy belong to atom-centred fragment descriptor, edge adjacency indices descriptor, charge descriptor and molecular properties descriptor, respectively, which give descriptions of the neighboring atom, molar volume, charge distribution and hydrophilic properties. The information or properties obviously have an influence on the retention nature of SCCP congeners.

The relative importance of the descriptors can be reflected by the coefficients in the model optimized by the stepwise regression. P-Level associated to a descriptor measures its significance. On the other hand, from the coefficients listed in Table 2, it can be seen that the molecular hydrophilic factor(Hy) is the most important descriptor and plays a leading role in affecting the retention time of SCCP congeners. The result may be explained by the fact that the retention time of SCCP congeners in a nonpolar separation column depends on their dispersion force. The topological index S2K, representing 2-path Kier alpha-modified shape index, is the secondly important descriptor. The result may be demonstrated by the fact that SCCP congeners take more time to be eluted with the increase of chlorine atoms and the S2K value is correlated with the chlorine atoms. Thus the retention time of SCCP congeners may increase with the S2K value. EEig10r, H-052, Q2, RDF120v, RDF110m, R3V+, RDF100u and PW4 also play positive effects on the retention time but the importance of them is in a descending order with the decrease of the coefficients. Contrarily, TI1 and RDF145m perform negative effect on the retention time. The result can be accounted for by the fact that TI1 and RDF145m provide the information about the

number of graph vertices, bond distances, planar and non-planar systems and atom types, which play a negative influence on retention time of the congeners. Thus the retention time of congeners decrease with the increased values.

3.2 QSRR Models

QSRR models between retention time on the one hand and the selected descriptors on the other hand were established by MLR, PLS and LS-SVR, respectively. The models were evaluated by LOOCV approach with the results summarized in Table 3. From r^2 of the training set, it can be seen that all the models are acceptable with r^2>0.999. The result of the RMSE obtained by LOOCV also shows the rationality of the models.

Table 3 Statistical parameters for QSRR models built by MLR, PLS and LS-SVR, respectively

Parameter	Training set		Test set	
	r^2	RMSE	r^2	RMSE
MLR	0.9994	0.024	0.9991	0.023
PLS	0.9992	0.028	0.9996	0.015
LS-SVR	0.9994	0.024	0.9989	0.025

In order to test the practicability of the models, external validation was done with the test set. The models of MLR, PLS and LS-SVR were used for the prediction with the results also summarized in Table 3. From the values of r^2 and RMSE of the test set, it can be found that all the models are acceptable, and PLS can produce a slightly better prediction than MLR and LS-SVM. The result may be explained by the fact that PLS reduces the disturbance of randomness in data.

Fig.1(A) shows the relationship between the predicted retention time by PLS model and experimental value in the training and test sets, respectively. It can be seen that the line obtained by least squares fitting is very close to the diagonal and all the points are reasonably distributed along the straight line. The slope and intercept are 1.008 and –0.28 for the training set and the slope and intercept are 1.008 and –0.28 for the test set. It is obviously indicated that the predicted retention time and the experimental retention time are in a good linearity. Fig.1(B) shows the deviations between the predicted retention time and experimental retention time in the training and test sets. It can be found that the deviations are randomly distributed around 0, and generally fa- lling within ±0.4, and the deviations are less than the most differences in retention time among the SCCP congeners.

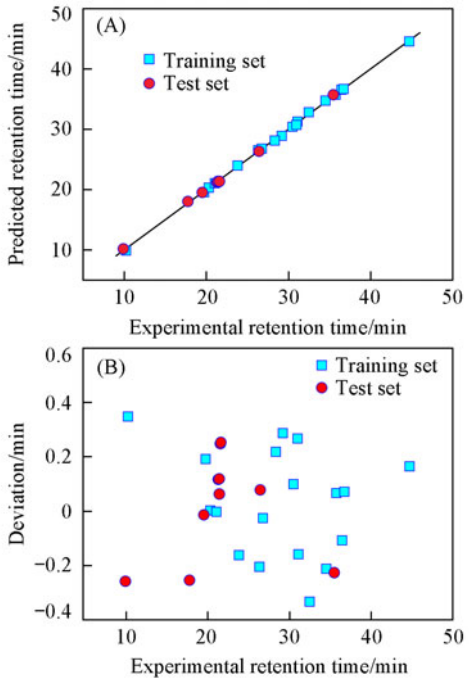

Fig.1 Plots of predicted retention time(A) and deviation between the predicted and experimental retention time(B) *vs.* experimental retention time for training and test sets

3.3 Prediction

QSRR model was then used to predict the retention time of 49 C_{10}-CPs congeners. The 49 C_{10}-CPs congeners included ten molecular formulas with different chlorine atom numbers and a carbon atom bound one chlorine atom at the most. For each formula, one to six positional isomers were selected to cover diverse molecular structures. Table 4 lists the names and the predicted retention time of each of the C_{10}-CPs congeners. It is found that the retention time of C_{10}-congeners shows an increase with the increasing of chlorine atom number. For example, C_{10}-CPs congeners with one chlorine atom are eluted faster than C_{10}-CPs congeners with two chlorine atoms. For the congeners with the same chlorine atom number, it can be seen that the retention time of C_{10}-CPs congeners is correlated with the location of chlorine atom. For example, the retention time of 5,6-dichlorodecane is shorter than that of 1,10-dichlorodecane.

To visually show the relative retention time of 49 C_{10}-CPs, a series of Gaussian functions was used to simulate the chromatogram, as shown in Fig.2. The peak centers are the predicted retention time, the intensity of each peak is generated randomly, and the standard deviation of peaks is 0.03. From Fig.2, it can be found that the most congeners have a good separation and the most variances in retention time among congeners are more than deviations.

To further validate predicted results, three C_{10}-CPs congeners(CP-1, CP-2 and CP-3) were measured with GC-MS. Experiment retention time values were 8.78, 9.36 and 9.98 min, respectively, and the predicted retention time values were 24.57, 25.99 and 28.86 min, respectively. By comparison, the experimental retention time values are shorter than the predicted ones. The difference in retention time may be caused by different chromatographic conditions. Experiment data were measured on a weak polarity column with a quick temperature program introduced in Section 2.4, but predicted data were measured on a nonpolar column with a slow temperature program. By calculation of correlation between the experimental retention time and predicted retention time, however, there is a good relativity with r of 0.992. Therefore, the predicted retention time values of the C_{10}-CPs congeners are rational by the mean of QSRR model proposed in the work. QSRR model may be useful for

Table 4 Retention time of C_{10} SCCP congeners predicted by PLS

No.	Compound	Rentention time/min	No.	Compound	Rentention time/min
1	2-Chlordecane	11.74	26	2,3,4,5,6,7,8-Heptachlorodecane	27.64
2	5-Chlorodecane	11.92	27	1,3,5,7,9-Pentachlorodecane	27.88
3	3-Chlorodecane	11.94	28[c]	1,2,5,6,9-Pentachlorodecane	28.86
4	4-Chlorodecane	11.94	29	1,2,3,4,5,6,7-Heptachlorodecane	28.92
5	1-Chlorodecane	14.54	30	1,2,7,8,10-Pentachlorodecane	29.81
6	5,6-Dichlorodecane	15.22	31	1,2,3,4,9,10-Hexachlorodecane	30.63
7	1,10-Dichlorodecane	15.34	32	1,2,3,4,5,6,7,8-Octachlorodecane	31.48
8	4,5-Dichlorodecane	15.49	33	1,2,4,6,8,10-Hexachlorodecane	31.54
9	1,5-Dichlorodecane	16.86	34	2,3,4,5,6,7,8,9-Octachlorodecane	31.88
10	4,5,6-Trichlorodecane	17.44	35	1,2,5,9,10-Pentachlorodecane	32.44
11	1,3-Dichlorodecane	17.55	36	1,2,3,4,5,9,10-Heptachlorodecane	32.76
12	1,2-Dichlorodecane	17.77	37	1,3,4,5,6,7,10-Heptachlorodecane	32.83
13	3,5,7-Trichlorodecane	17.78	38	1,2,5,5,6,9,10-Heptachlorodecane	33.44
14	1,3,5-Trichlorodecane	19.86	39	1,2,4,5,6,9,10-Heptachlorodecane	33.45
15	4,5,6,7-Tetrachlorodecane	20.19	40	1,2,5,6,9,10-Hexachlorodecane	33.92
16	3,4,5,6-Tetrachlorodecane	20.46	41	1,2,3,4,5,6,9,10-Octachlorodecane	34.69
17	1,5,6-Trichlorodecane	21.23	42	1,2,3,4,5,6,7,8,9-Nonachlorodecane	34.91
18	1,2,3,4-Tetrachlorodecane	22.09	43	1,2,3,4,7,8,9,10-Octachlorodecane	35.05
19	3,4,5,6,7-Pentachlorodecane	22.25	44	1,2,3,6,7,9,10-Heptachlorodecane	35.06
20[a]	2,5,6,9-Tetrachlorodecane	24.57	45	1,2,3,4,6,7,9,10-Octachlorodecane	35.11
21	1,2,5,6-Tetrachlorodecane	24.63	46	1,2,3,4,5,6,8,9,10-Nonachlorodecane	36.52
22	1,2,3,4,5-Pentachlorodecane	24.64	47	1,2,3,4,5,7,8,9,10-Nonachlorodecane	36.63
23	3,4,5,6,7,8-Hexachlorodecane	25.36	48	1,2,3,4,5,6,7,8,10-Nonachlorodecane	37.54
24[b]	1,2,9,10-Tetrachlorodecane	25.99	49	1,2,3,4,5,6,7,8,9,10-Decachlorodecane	38.81
25	1,2,3,4,5,6-Hexachlorodecane	26.39			

a—*c*. CP-1, CP-2 and CP-3, respectively.

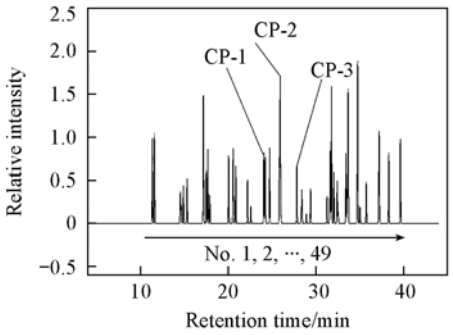

Fig.2 Simulated chromatogram of C_{10}-CPs congeners according to the retention time predicted by PLS

the qualitative analysis of CP congeners while their separation is difficult by experimental methods.

4 Conclusions

The relationship between retention time of SCCP congeners on the one hand and molecular descriptors on the other hand was quantitatively studied. Twelve descriptors relevant to the retention time of congener molecules were selected by stepwise regression method. QSRR models were built by multivariate calibration methods including PLS, MLR and LS-SVR. And PLS can produce a slightly better result. QSRR models can be applied to the prediction of retention time of the abundant SCCP congeners. Reasonable results were obtained, and a well-defined correlation was found between the measured retention time and the predicted retention time of three CP congeners, although the values were significantly different due to the different experimental conditions. Therefore, the proposed method has a great potential in the identification of CP congeners when experimental data were unavailable. Because only 28 retention time data are used to develop the QSRR model, further validation of the results is still needed to obtain more retention time data of CPs.

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