Reversed-phase thin-layer chromatography behavior of aldopentose derivatives

Dragana J. Livaja-Popović[1], Eva S. Lončar[2], Lidija R. Jevrić[2], Radomir V. Malbaša[2]

[1]*CRM Consulting, Rodenbacher Chaussee 6 – Gebäude 801, D-63457 Hanau-Wolfgang, Germany*
[2]*University of Novi Sad, Faculty of Technology, Novi Sad, Serbia*

Abstract

Quantitative structure–retention relationships (QSRR) have been used to study the chromatographic behavior of some aldopentose. The behavior of aldopentose derivatives was investigated by means of reversed-phase thin-layer chromatography (RP TLC) on silica gel impregnated with paraffin oil stationary phases. Binary mixtures of methanol–water, acetone–water and dioxane–water were used as mobile phases. Retention factors, R_M^0, corresponding to zero percent organic modifier in the aqueous mobile phase was determined. Lipophilicity, C_0, was calculated as the ratio of the intercept and slope values. There was satisfactory correlation between them and log *P* values calculated using different theoretical procedures. Some of these correlations offer very good predicting models, which are important for a better understanding of the relationships between chemical structure and retention. The study showed that the hydrophobic parameters R_M^0 and C_0 can be used as a measures of lipophilicity of investigated compounds.

Keywords: aldopentose derivatives, QSRR-analysis, lipophilicity, RP-TLC, impregnated silica gel.

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The majority of biologically active compounds are chiral molecules. Monosaccharides are frequently used as starting materials in the synthesis of simpler or more complex biomolecules [1], owing to their availability and to their stereochemical, conformational and functional properties. Monosaccharide molecules contain a high density of functional groups; this enables various transformations from acyclic and/or cyclic forms. Because of their variety of functional groups these derivatives are also of chromatographic interest [2,3]. It is well known that the chromatographic mechanism is basically dependent on the solute size and its hydrogen bonding capability. The solute size depends on the molecular structure of the parent molecule and of the substituents existing in the molecule.

Selected derivatives of aldopentoses have conveniently been used as starting compounds and key intermediates in the synthesis of several biologically active compounds.

Lipophilicity of an investigated compound is one of the parameters, which influences its biological activity. It is a term mainly employed by medicinal chemists to describe the transport process of compounds in biological systems and is the most frequently used parameter in QSAR analysis. It is predominant descriptor of pharmacodynamic, pharmacokinetic and toxic aspects of drug activity. The lipophilic character of compounds has been defined in many ways. The hydrophobicity parameter introduced by Fujita *et al.* [4] has been widely accepted and defined as the logarithm of the ratio of the concentrations of an analyte in a saturated two-phase system formed by 1-octanol/water (log *P*). A number of methods for the calculation of log *P* have been developed [5–7], but experimental determination still remains the most reliable. Experimental measurement of log *P* values by the conventional „shake flask" method is often faced with problems; besides being time consuming, the method is not applicable to very hydrophilic or very hydrophobic compounds.

Chromatographic techniques have frequently been applied in the determination of relative partition coefficients for use in quantitative relationships between chemical structure and biological activity (QSAR) [8––10]. Reverse phase thin layer chromatography and high performance liquid chromatography are used to evaluate the lipophilicity of a series of organic compounds. Chromatography is a unique method which can yield a great amount of quantitatively comparable, precise, and reproducible retention data for large sets of structurally diversified compounds. Therefore, quantitative structure–(chromatographic) retention relationships (QSRR) have been considered a model approach to establish strategy and methods of property predictions [11,12]. QSRR analysis appears especially attractive from the general chemometric point of view because provide the best testing of the applicability of

Correspondence: L.R. Jevrić, Department of Applied and Engineering Chemistry, Faculty of Technology, University of Novi Sad, Bulevar Cara Lazara 1, 21000 Novi Sad, Serbia.
E-mail: lydija@uns.ac.rs
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individual structural parameters for property description. Currently, QSRR studies can be applied to: identify the most useful structural descriptors; predict retention for a new analyte and to identify unknown analytes; gain insight into molecular mechanism of separation operating in a given chromatographic system; quantitatively compare separation properties of individual types of chromatographic layers; evaluate properties, other than chromatographic physicochemical properties of analytes, such as lipophilicity [13,14].

The aim of this methodology is to derive a model to describe the chromatographic retention on a given chromatographic system, which then can be used for future retention prediction of new solutes. Thus, when a meaningful and statistical significant model is found, no additional experiments are needed to predict the retention for new solutes.

RP-TLC provides a variety of indices (descriptors) that can be used as lipophilicity estimators. The most popular lipophilicity indices estimated by RP-TLC are derived by the R_F according to the following formula [15]:

$$R_M = \log(\frac{1}{R_F} - 1) \quad (1)$$

where R_F is the retention factor calculated on the basis of migration distance of compound/migration distance of solvent front. Because R_M generally depends linearly on the concentration of the organic modifier in the mobile phase, the value has been frequently extrapolated to zero concentration of organic modifier (R_M^0):

$$R_M = R_M^0 + S\varphi \quad (2)$$

where φ is the volume fraction of organic solvent in the mobile phase, R_M^0 (intercept) is the extrapolated value obtained at φ = 0% modifier, and S is the slope of the linear plot. The R_M^0 value is a widely used chromatographic hydrophobicity parameter. Equations (1) and (2) are the best for deriving data for the QSRR studies.

Based on the obtained intercept and slope values of Eq. (2), another hydrophobic parameter, C_0, can be calculated:

$$C_0 = \frac{R_M^0}{S} \quad (3)$$

This hydrophobicity parameter corresponds to the parameter φ_0, previously defined for the HPLC method as the concentration of the organic component in the mobile phase for which the distribution of the analyzed substance between the mobile and stationary phase is equal (1:1) [16–18].

Hence, we have studied the relationship between log *P* and chromatographic parameters in order to examine whether RP-TLC can be utilized for log *P* determination of aldopentose derivatives under such circumstances.

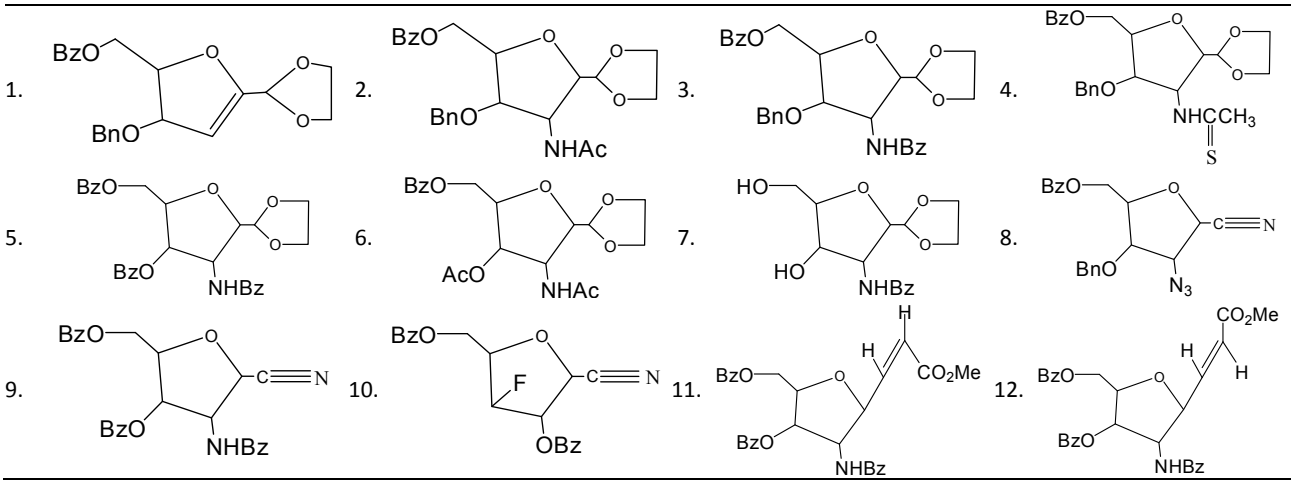
The aim was to develop a statistical model in order to predict lipophilicity for a new solute in a satisfactory way. This would help in better understanding the separation mechanisms through the QSRR studies.

EXPERIMENTAL

Twelve derivatives of aldopentose (Table 1) were investigated. The compounds were synthesized in the laboratory of the Department of Organic Chemistry, Faculty of Sciences, University of Novi Sad [19].

The compounds were dissolved in chloroform (2 mg cm^{-3}) and 1 µl volumes of the solutions were spotted on the plates. TLC was performed on 20×20 cm glass plates precoated with impregnated silica gel. The thin-layer of impregnated silica gel was prepared by suspending 25 g silica gel 60 GF_{254} (Merck) in 100 ml diethyl ether containing 2.5 % paraffin oil. To ease the visualization, fluorescent indicator F_{254} (Merck) was incorporated into the layers. Impregnated silica gel layer

Table 1. Structural formulas of the examined compounds (Ac = (CH_3CO–), Bn = ($C_6H_5CH_2$–), Bz = (C_6H_5CO–), Me = (CH_3–), N_3 = azid)



was developed using the following mobile phases: acetone–water (φ = 0.5–0.7 v/v), dioxane–water (φ = 0.5––0.7 v/v) and methanol–water (φ = 0.5–0.7 v/v) (5% increments) to investigate the retention parameter of the various derivatives of aldopentose.

The plates were developed to a distance of 15 cm by the ascending technique at room temperature with prior saturation of the chamber for 20 min with mobile phase. Dark spots were observed under UV light (λ = = 254 nm).

Ten values of log *P* for each solute: *A*log P_s, *AC*log *P*, *A*log *P*, *M*log *P*, log P_{Kow}, *X*log P_2, *X*log P_3, log P_{Chem} and *C*log *P* and *ACD*log *P* were calculated using a commercially available computer program [20–23] and are presented in Table 2.

RESULTS AND DISCUSSION

Determination of R_M^0 values and TLC equations

Separation process in chromatography could be explained by a complex combination of the various interaction between the solute–mobile phase and solute––stationary phase. Although no satisfactory explanation exists, quite simple intermolecular interactions make the understanding of the retention mechanism possible.

A linear relationship has been obtained between retention and concentration of organic modifier in the eluent for reversed phase chromatography, characterized by high correlation coefficients, *r* (Eq. (2), Table 3). An increase in the concentration of the organic modifier led to a decrease in R_M values, *i.e*., the greater migration of the compounds. Constants *S* and R_M^0 could not be determined for compounds with very low (**5** and **9**, in eluents with methanol) or very high (**7**, in eluents with doxane) R_F values.

The statistics obtained (Table 3) illustrate that the R_M^0 values obtained depend on the modifier used. Higher R_M^0 values were obtained for methanol (average value 3.575), than for acetone (average value 2.105) and for dioxane (average value 1.976). The higher R_M^0 values indicate greater lipophilicity.

Table 2. Partition coefficients calculated by different programs

Com.	*A*log P_s	*AC*log *P*	*A*log *P*	*M*log *P*	log P_{Kow}	*X*log P_2	*X*log P_3	log P_{Chem}	*C*log *P*	*ACD*log *P*
1	3.04	2.65	2.74	2.13	2.34	3.56	2.75	2.57	3.64	3.59
2	2.29	1.70	1.89	1.46	1.42	2.31	1.97	1.87	3.04	3.18
3	3.27	3.18	3.55	2.51	3.32	4.03	3.63	3.77	4.54	5.09
4	2.67	1.67	2.79	1.80	1.75	2.56	2.57	2.72	3.41	3.77
5	3.41	3.32	3.61	2.78	3.37	4.25	3.83	3.81	4.38	5.11
6	1.07	0.37	0.28	0.60	0.02	0.82	0.51	0.011	1.39	1.18
7	–0.29	–0.61	–0.48	–0.34	–0.68	–0.02	–0.08	–0.45	0.06	–0.28
8	3.32	2.34	1.78	1.25	2.97	1.85	3.64	–	2.93	–
9	3.43	3.81	3.79	2.65	3.12	4.66	4.49	3.83	3.99	4.34
10	3.36	3.04	3.34	2.40	2.09	3.48	3.31	3.09	3.45	3.54
11	4.01	3.93	4.24	3.24	4.40	5.04	4.30	4.14	5.24	5.32
12	4.01	3.93	4.24	3.24	4.40	5.04	4.30	4.14	5.24	5.32

Table 3. Regression data for linear relationships R_M–φ according to Eq. (2) and C_0 values of aldopentose derivatives

Com.	Acetone–water				Dioxane–water				Methanol–water			
	R_M^0	*S*	*r*	C_0	R_M^0	*S*	*r*	C_0	R_M^0	*S*	*r*	C_0
1	2.597	–4.680	0.997	0.554	2.379	–3.880	0.995	0.613	4.312	–6.198	0.999	0.695
2	1.756	–3.020	0.997	0.582	1.521	–3.034	0.974	0.501	3.064	–4.902	0.994	0.625
3	2.389	–3.890	0.999	0.614	2.129	–3.640	0.991	0.585	4.298	–6.308	0.997	0.681
4	2.148	–3.590	0.997	0.598	1.945	–3.516	0.969	0.553	3.872	–5.840	0.998	0.663
5	2.089	–3.382	0.996	0.617	1.674	–3.046	0.995	0.549	–	–	–	–
6	0.892	–2.388	0.992	0.373	0.659	–2.004	0.989	0.329	1.233	–2.610	0.997	0.472
7	–0.030	–1.422	0.986	0.211	–	–	–	–	–0.054	–0.986	0.971	0.054
8	2.699	–3.970	0.997	0.679	2.433	–3.910	0.989	0.622	4.683	–6.746	0.999	0.694
9	2.576	–4.112	0.998	0.626	2.067	–3.718	0.977	0.556	–	–	–	–
10	2.756	–4.256	0.997	0.647	2.231	–3.746	0.982	0.595	4.347	–6.482	0.998	0.670
11	2.745	–4.196	0.999	0.654	2.552	–4.164	0.990	0.613	5.222	–7.462	0.998	0.699
12	2.584	–4.102	0.998	0.629	2.152	–3.816	0.982	0.564	4.670	–6.930	0.999	0.673

The extrapolated R_M^0 values from TLC systems with different organic modifiers were correlated. The equations of these linear relationships and statistical data (correlation coefficient, *r* and standard deviation, *SD*) are listed in Table 4. These differences are most probably a consequence of the different chemical natures of the three organic modifiers and indicates that the values basicaly reflect the same molecular properties of the solute in the mobile phases used, but that these properties contribute differently to retention.

Table 4. Correlations between R_M^0 values determined with different mobile phases; Ac = acetone, Dx = dioxane, MeOH = methanol

Equation	*r*	*SD*
$R_{M\ Ac}^0 = 0.108 + 0.546 R_{M\ MeOH}^0$	0.988	0.150
$R_{M\ Dx}^0 = 0.069 + 0.486 R_{M\ MeOH}^0$	0.982	0.117
$R_{M\ Dx}^0 = -0.151 + 0.927 R_{M\ Ac}^0$	0.974	0.126

High correlation was obtained between the intercept R_M^0 and the slopes, *S*, values (Eq. (2)). The regression data for relationships expressed by Eq. (2), with the corresponding correlation coefficients, are listed in the Table 5. High correlation coefficients indicate that the substances investigated could be regarded as a homologous series [24].

Table 5. Equations of the relationship between R_M^0 and slope S; Ac = acetone, Dx = dioxane, MeOH = methanol

Equation	r	SD	N
$R_{M\ Ac}^0 = -1.162 - 0.910S$	0.974	0.205	12
$R_{M\ Dx}^0 = -1.098 - 0.879S$	0.991	0.075	11
$R_{M\ MeOH}^0 = -0.877 - 0.815S$	0.999	0.072	10

Results of log *P* calculations

The main purpose of this study was to use chromatographic data (R_M^0) as descriptor of the lipophilic character of aldopentose derivatives studied. The correlation between R_M^0 values and different calculated values of log *P* was examined.

Ideally, regardless of a method used for calculation, all values of the calculated log *P* should be the same and correlation between them full (*r* = 1). A correlations check for the lipophilicity descriptors, log *P*, was performed and the correlation matrix for variables is shown in Table 6. The method used was row-wise deletion.

The lipophilicity parameters obtained from the reversed-phase experiments, R_M^0, were compared with the calculated log *P* values.The correlation coefficients between R_M^0 obtained with different modifiers and log *P* are given in Table 7.

By comparing the calculated values for defining the lipophilicity of the investigated molecules it is evident that methanol as a modifier gives the highest degree of correlation (calculated mean value of correlation coefficient is 0.931).

Since the correlation between R_M^0 and log *P* gives different correlations, an additional retention related parameter, C_0, was used. The relationship between C_0 and log *P* may be expressed by polynomial function. The correlation coefficients between C_0 obtained with different modifiers and log*P* are given in Table 8.

QSRR Analysis of the investigated newly synthesized aldopentose derivatives

In defining a QSRR model which would best explain the correlation between the retention behavior of in-

Table 6. The correlation matrix for calculated log P values

r	*A*log P_s	*AC*log *P*	*A*log *P*	*M*log *P*	log P_{Kow}	*X*log P_2	*X*log P_3	log P_{Chem}	*C*log *P*	*ACD*log *P*
*A*log P_s	1	0.963	0.937	0.932	0.948	0.901	0.964	0.969	0.949	0.966
*AC*log *P*		1	0.967	0.968	0.954	0.969	0.973	0.973	0.953	0.945
*A*log *P*			1	0.988	0.919	0.979	0.933	0.995	0.972	0.972
*M*log *P*				1	0.923	0.988	0.913	0.979	0.978	0.972
logP_{Kow}					1	0.916	0.960	0.964	0.955	0.964
*X*log P_2						1	0.901	0.978	0.960	0.956
*X*log P_3							1	0.988	0.918	0.951
log P_{Chem}								1	0.971	0.978
*C*log *P*									1	0.991
*ACD*log *P*										1

Table 7. Correlation coefficients (r) between R_M^0 and log P

R_M^0	*A*log P_s	*AC*log *P*	*A*log *P*	*M*log *P*	log P_{Kow}	*X*log P_2	*X*log P_3	*log* P_{Chem}	*C*log *P*	*ACD*log *P*
Acetone	0.963	0.896	0.862	0.839	0.854	0.806	0.908	0.913	0.858	0.892
Dioxane	0.861	0.727	0.682	0.611	0.739	0.607	0.782	0.813	0.672	0.744
Methanol	0.986	0.940	0.908	0.887	0.919	0.860	0.967	0.968	0.915	0.960

Table 8. Correlation coefficients (r) between C_0 i logP

C_0	*A*log P_s	*AC*log *P*	*A*log *P*	*M*log *P*	log P_{Kow}	*X*log P_2	*X*log P_3	*log* P_{Chem}	*C*log *P*	*ACD*log *P*
Acetone	0.989	0.975	0.948	0.952	0.957	0.925	0.961	0.949	0.972	0.988
Dioxane	0.948	0.936	0.869	0.799	0.925	0.805	0.952	0.944	0.870	0.925
Methanol	0.997	0.981	0.956	0.978	0.956	0.946	0.952	0.930	0.987	0.989

vestigated aldopentose derivatives and their structure, it was necessary to start from the simplest linear relationships. The reliability of the obtained mathematical models was estimated on the basis of the values of statistical parameters: correlation coefficient (*r*) and standard deviation (*SD*).

By comparing the calculated values for defining the lipophilicity of the investigated molecules it is evident that only *A*log P_s and *X*log P_3 theoretical methods, gives the acceptable value correlation coefficient.

The equations expressing the relationships between lipophilicity R_M^0–*A*log P_s and between C_0–*A*log P_s and *X*log P_3, with corresponding statistical parameters, are listed in Table 9.

These results lead to four conclusions. Good linear correlation was found between chromatographically determined, R_M^0, and computer calculated *A*log P_s lipophilicity. The lowest values were obtained for the dioxane–water as mobile phase. Good polynominal correlation was found between C_0 and computer calculated *A*log P_s (for acetone and methanol as modifiers of mobile phase) and *X*log P_3 for dioxane as modifier. Results show that another retention-related measure of lipophilicity, C_0, beside R_M^0, can be used as a measure of the lipophilicity of compounds investigated.

In order to check the validity of the shown mathematical models, the calculations of the retention parameter values R_M^0 and C_0 were performed, using these equations, and their comparison with experimentally obtained data was made (Table 3).

To illustrate the prediction capabillities of the QSRR specified by Eqs. (4) and (6) the respective experimental R_M^0 data, and Eqs. (7)–(9) the respective experimental C_0 values were plotted against the calculated ones in Figures 1 and 2, respectively. The statistics obtained (Table 10) illustrate that linear equations fits satisfactorily to the experimental data.

As the slope is not different from unity, the method does not show proportional error. In addition, the value of an intercept which almost equals zero indicates the absence of systematic error and method bias.

This leads us to the conclusion that the chosen mathematical models can predict the retentive behaviour of the investigated group of newly synthesized aldopentose derivatives in a reversed-phase chromatography.

Good knowledge of quantitative correlations between a chemical structure and retention constant of newly synthesized aldopentose derivatives enables more quality conditions for their further investigation and contributes to better understanding of their structural, biological and physicochemical properties.

CONCLUSION

Twelve aldopentose derivatives were investigated by reversed-phase thin-layer chromatography on paraffin oil-impregnated silica gel plates, with acetone–water, dioxane–water and methanol–water as mobile phases. A linear relationship between R_M^0 and *S* values was found for all mobile phases; this is a characteristic of closely related compounds. Very good correlation is found between R_M^0 of different organic modifiers. Correlations of different quality were obtaines between R_M^0 values and log *P* values calculated using different theoretical procedures. Very good linear correlations observed between R_M^0 values calculated by the numerical method and *A*log P_s parameters, confirm that these chromatographic indices are good descriptors of hydrophobicity of test aldopentose derivatives. On the basis of this correlations, methanol–water was the best RP TLC system for determination of log *P*. Next to R_M^0 we show that another retention related parameter C_0 can be used as alternative descriptor. The correlation between C_0 and *A*log P_s (for acetone and methanol as

Table 9. Relationships between retention constants R_M^0, C_0 and calculated values of Alog P_s and Xlog P_3

Mobile phase	Equation	*r*	*SD*	*N*	Eq.
Acetone–water	$R_M^0 = 0.258 + 0.658A\log P_s$	0.963	0.243	12	3
Dioxane–water	$R_M^0 = 0.277 + 0.552A\log P_s$	0.861	0.287	11	4
Methanol–water	$R_M^0 = 0.262 + 1.235A\log P_s$	0.986	0.298	10	5
Acetone–water	$C_0 = 0.109 + 0.281A\log P_s - 0.037(A\log P_s)^2$	0.989	0.030	12	6
Dioxane–water	$C_0 = 0.226 + 0.208X\mathrm{LOG}P_3 - 0.029(X\log P_3)^2$	0.952	0.028	11	7
Methanol–water	$C_0 = 0.161 + 0.313A\log P_s - 0.046(A\log P_s)^2$	0.997	0.018	10	8

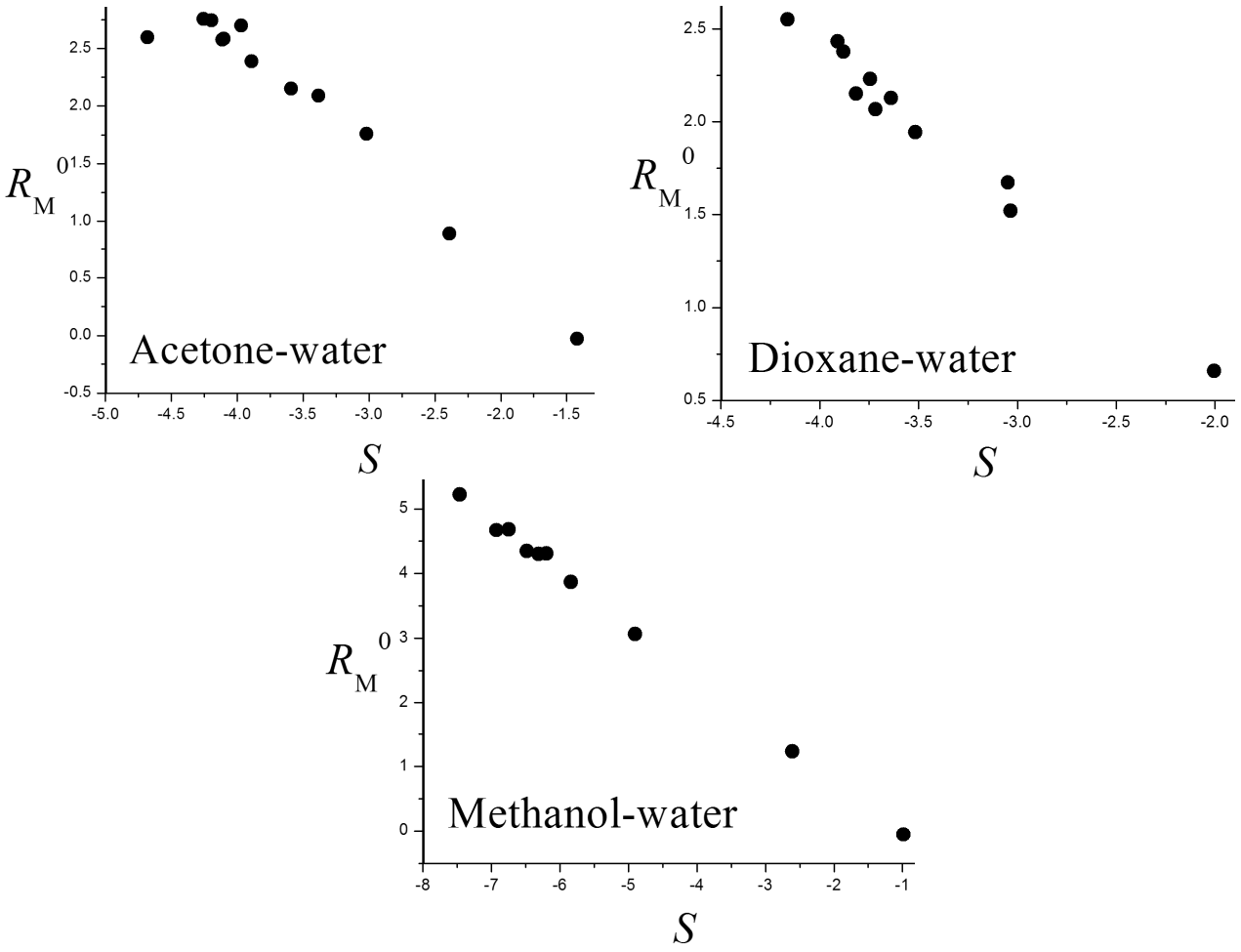


Figure 1. Correlation between experimentally obtained values and calculated values R_M^0 on different modifiers.

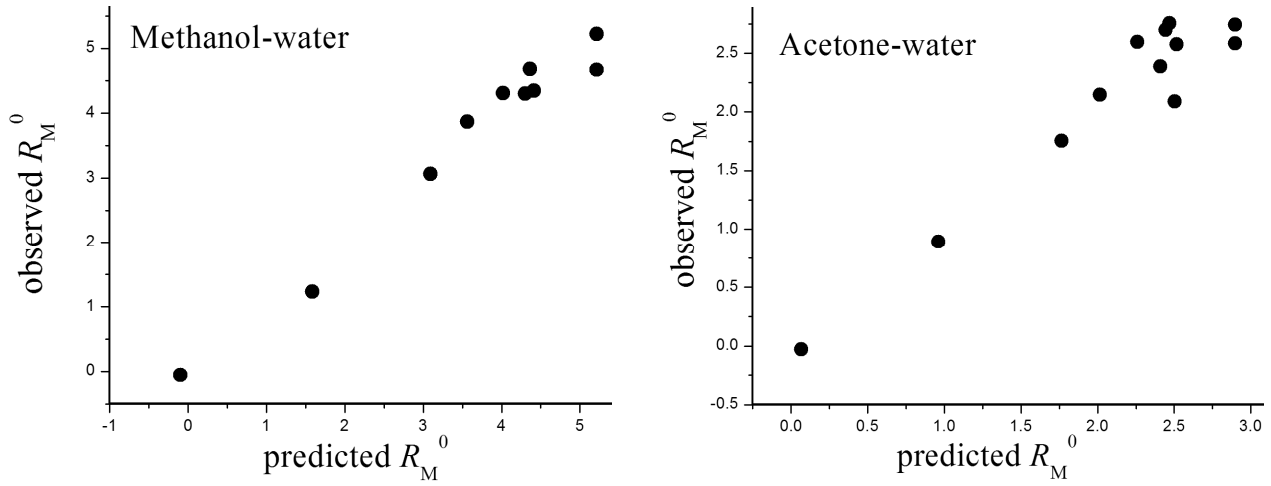


Figure 2. Correlation between experimentally obtained values and calculated values C_0 on different modifiers.

modifiers of mobile phase) and C_0 and *X*log P_3 (for dioxane as modifier of mobile phase) was a polynomial function, in contrast to the linear correlation between R_M^0 and *A*logP_s. These results show that for the aldopentose derivatives investigated C_0 is a better mean of expressing lipophilicitty than the retention constant R_M^0.

Table 10. Statitistical parameters derived from the linear regression observed vs. predicted lipophilicity parameters

Modifier	Intercept	Slope	*R*	R^2	*SD*	*P*
			R_M^0 observed *vs*. R_M^0 predicted			
Acetone	3.36E–04	0.999	0.963	0.927	0.243	0.0000
Methanol	–6.81E–04	0.999	0.986	0.972	0.298	0.0000
			C_0 observed *vs*. C_0 predicted			
Acetone	1.99E–03	0.993	0.988	0.994	0.003	0.0000
Methanol	3.00E–04	0.999	0.997	0.998	0.017	0.0000
Dioxane	8.06E–03	0.977	0.952	0.976	0.026	0.0000

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IZVOD

HROMATOGRAFSKO PONAŠANJE NEKIH DERIVATA ALDOPENTOZA PRIMENOM REVERSNO-FAZNE HROMATOGRAFIJE NA TANKOM SLOJU

Dragana J. Livaja-Popović[1], Eva S. Lončar[2], Lidija R. Jevrić[2], Radomir V. Malbaša[2]

[1]*CRM Consulting, Rodenbacher Chaussee 6 – Gebäude 801, D-63457 Hanau-Wolfgang, Germany*
[2]*Univerzitet u Novom Sadu, Katedra za primenjene i inženjerske hemije, Tehnološki fakultet, Novi Sad, Srbija*

(Naučni rad)

Savremeni pristup dizajniranju novih lekova i drugih biološki aktivnih supstanci zasniva se na utvrđivanju veze između hemijske strukture jedinjenja (kvantifikovanja efekta strukturne promene) i njihove biološke aktivnosti postavljanjem preciznih matematičkih modela. Pošto je poznato da su različito supstituisani derivati aldopentoza fiziološki aktivna jedinjenja zbog izraženog antivirusnog, antibakterijskog i antitumorskog delovanja, u radu su analizirani uslovi za kvantitativna ispitivanja strukturno različito supstituisanih derivata aldopentoza i njihovog retencionog ponašanja. Retencioni mehanizam određen je upotrebom mobilnih faza aceton–voda, dioksan–voda i metanol–voda variranjem zapreminskog udela modifikatora u pokretnoj fazi. Kao nepokretna faza koristio se silika gel impregniran parafinskim uljem. Takođe je ispitan i kvalitativni kvantitativni uticaj sastava pokretne faze na retenciju. Dobre korelacije postignute su između retencione konstante, R_M^0 (retencija rastvorka u čistoj vodi) i nagiba, S, hromatografske jednačine. Ispitana je i primena hromatografskih retencionih parametara kao mera lipofilnosti molekula primenom QSRR analize. Za sve derivate aldopentoza definisani su deskriptori lipofilnosti izračunati primenom različitih programskih paketa: *A*log P_s, *AC*log *P*, *A*log *P*, *M*log *P*, log P_{Kowin}, *X*log P_2, *X*log P_3, log P_{Chem} i *C*log *P*. Na osnovu dobijenih rezultata, razvijeni su matematički modeli koji omogućavaju procenu hromatografskog ponašanja ispitivanih molekula na osnovu njihove hemijske strukture. Definisale su se statistički značajne korelacije, koje povezuju retenciju ispitivanog molekula, R_M^0 i C_0 sa vrednostima parametara lipofilnosti. Kompletno poznavanje kvantitativnih zavisnosti između strukture i retencionih konstanti ispitivane serije derivata aldopentoza, ukazuju da hromatografski retencioni parametri realno oslikavaju složene fizičko–hemijske karakteristike molekula.

Ključne reči: Derivati aldopentoza • Hromatografija na tankom sloju • Retencioni parametar • Parametar lipofilnosti • Kvantitativna zavisnost retencija–struktura