Romanian Biotechnological Letters *Vol. 17, No. 1, 2012*

ORIGINAL PAPER

Prediction of s-triazine components lipophilicity of total herbicides

Received for publication, June 17, 2011
Accepted, July 20, 2011

LIDIJA R. JEVRIĆ[*], SONJA D. VELIMIROVIĆ, GORDANA B. KOPRIVICA, NEVENA M. MIŠLJENOVIĆ, TATJANA A. KULJANIN, ALEKSANDRA N. TEPIĆ
Faculty of Technology, University of Novi Sad, Bulevar Cara Lazara 1, 21000 Novi Sad, Serbia
[*]L.R. Jevrić, Department of Apllied and Engineering Chemistry, Faculty of Technology, University of Novi Sad, Bulevar Cara Lazara 1, 21000 Novi Sad, Serbia, +381 21 485 3648, lydija@uns.ac.rs

Abstract

A liquid chromatography method has been developed and validated for the determination of mathematical models for prediction of the lipophilicity of s-triazine compounds. Correlation between retention factors, R_M^0, of several s-triazine derivatives and their physico-chemical and structural properties has been studied by TLC on silica gel impregnated with paraffin oil. The research in this paper is focused on testing the influence of chemical structure on the retentive behavior newly synthesized derivatives of triazine. Retention mechanism has been determined using the following mobile phases: water-acetone, water-acetonitrile, water-dioxane, water-tetrahydrofuran, water-methanol and water-ethanol, by changing the volume fraction of modifier in the mobile phase. The reversed-phase chromatographic process has been carried out on impregnated silica gel. Then, the relationship between lipophilic character of molecules, logP, and chromatographic retention parameters has been determine. Relationships between these molecular descriptors and retention factors have been established, and their predictive and interpretive ability has been evaluated. Relationships equation between the retention factors and various lipophilicity descriptors of s-triazine derivatives hase been suggested as linear and multiple linear forms, QSRR models, and the obtained correlation coefficients estimated are relatively higher than 0,90.

Keywords: Quantitative structure-retention relationships (QSRR), impregnated silica gel, multiple linear regression analysis.

Introduction

Modern agricultural activities, industrial waste disposal, and landfills, provide potential sources for pesticides and other organics which, once released into the subsurface environment, may contaminate soil and groundwater systems, as well as surface water bodies. Mitigation of these pollution problems over the past several decades has been made easier because of an improved conceptual understanding of soil-solute interactions.

1,3,5-triazine (s-triazine) derivatives are widely employed in agriculture as effective components of herbicides. They have been extensively used worldwide as a germination controller of the broad-leaved weeds in corn, soybean, peanuts, potato, garlic, orchard and mulberry fields.

In addition to advantages, their use is accompanied by negative aspects linked with enviromental protection. For example, it has been shown that s-triazines have mutagenic and sometimes pathogenic effect on living organisms, as a consequence of proven carcinogenic action. Triazines are subjected to various abiotic and biotic degradation processes, and consequently, quantification of the metabolic products provides an additional analytical index to check their residues in water, air, and foods.

s-Triazine is the chemical species of six-membered heterocyclic ring compound with three nitrogens replacing carbon-hydrogen units in the benzene ring structure. Triazines are

weak base. In addition, s-triazine ring has an excellent potential for the formation of non-covalent bonds which involve either its nitrogen ione-pairs (coordination and H-bonds). It must be highlighted that non-covalent bonds have a very important role in exhibition of biological activity of compounds in general. This has a huge importance, primarily for further synthesis of bio-active compounds, and understanding of the degradation process, methabolism and s-triazine elimination as well, either from living organisms or from the nature, when generally speaking.

Quantitative structure-(chromatographic) retention relationships (QSRR) have been considered a model approach to establish strategy and methods of property predictions. QSRR analysis appears especially attractive from the general chemometric point of view because it provides the best testing of the applicability of individual structural parameters for property description. Currently, QSRR studies can be used 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 columns, evaluate properties, other than chromatographic physicochemical properties of analytes, such as lipophilicity, estimate relative bioactivities within sets of drugs and other xenobiotics [1]. In QSRR studies, a relation between molecular descriptors and retention has been searched [2]. 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 statistically significant model is found, no additional experiments are needed to predict the retention for new solutes [3].

In QSRR studies, molecular descriptors have either been determined from experiments or computed by molecular mechanics or even semi-empirical quantum chemical techniques [4]. Chromatographic retention is a physical phenomenon that is primarily dependent on the interactions between the solute and the stationary phase. With the aid of QSRR the interactions associated with chromatographic retention can be related to the constitutional, molecular graph (topological), geometrical, electrostatic, and quantum descriptors of the molecules. The compatibility of experimental and theoretical approaches for the determination of organic compound lipophilicity remains also a focus of scientific interest [5, 6]. Determination of partition coefficient using classical "shake-flask" technique has a series of disadvantages and has been successfully replaced by reverse-phase high-performance thin-layer chromatography (RP-HPTLC). RP-HPTLC technique has significant advantages: dynamic process and the consumption of the investigated compounds is minimal [7, 8].

Multiple linear regression (MLR) is utilized to construct the linear QSRR model. The applied MLR is based on a variety of theoretical molecular descriptors selected by the stepwise variable subset selection procedure. Modeling of retention parameter, R_M^0, of these compounds as a function of the theoretically derived descriptors was established by MLR. The results indicate that a strong correlation exists between the R_M^0 and the previously mentioned descriptors for investigated compounds. The prediction results are in good agreement with the experimental values [9-12].

The aim of this work was to determine the lipophilicity parameters for fourteen s-triazine derivatives (using reversed-phase liquid chromatography and different computational methods). The purpose of the work described in this paper was, therefore, to select the log*P* data and TLC system that best characterize octanol/water partitioning, and thus the lipophilicity of the investigated molecules studied by TLC on silica gel impregnated with paraffin oil.

Experimental

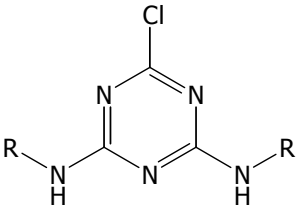
Fourteen derivatives of s-triazine (**Table 1**) were investigated. The compounds were synthesized in the laboratory of the Department of Organic Chemistry, Faculty of Technology and Metallurgy, University of Belgrade [13, 14].

Standard solutions (1 mg cm^{-3}) were prepared in methanol, acetone, or chloroform. Samples were spotted on the plates by means of a micro-pipette. 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 was developed using the following mobile phases:

Aprotic solvents : Acetonitrile-water (φ = 0.2-0.6; *v/v*), Acetone-water (φ = 0.5-0.8; *v/v*), Tetrahydrofuran-water (φ= 0.45-0.7; *v/v*), Dioxane-water (φ = 0.5-0.8; *v/v*).***Protic solvents***: Methanol-water (φ = 0.5-0.8; *v/v*), Ethanol-water (φ = 0.5-0.8; *v/v*).

The plates were developed to a distance of 15 cm by the ascending technique at room temperature without previous saturation of the chamber with mobile phase. Dark spots were observed under UV light (λ = 254 nm). The partition coefficients: *A*logP_s, *AC*log*P*, *mi*log*P*, *AB*/log*P*, *A*log*P*, *M*log*P*, logP_{Kowin}, *X*logP_2, *X*logP_3, i *C*log*P* were calculated for the compounds by applying different theoretical procedures [15, 16] and *ACD*log*P* was calculated using commercial software and the other partition coefficients were obtained from the Internet [17].

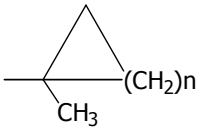
Table 1. Chemical structures of the studied s-triazines

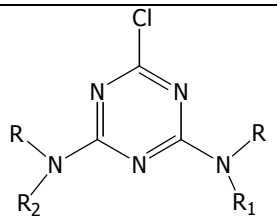


Series I

Compound	R
I.1	-CH(CH_3)-C_6H_5
I.2	-CH(CH_3)-C_6H_4-4-CH_3
I.3	-CH(CH_3)-C_6H_4-4-Cl
I.4	-CH(CH_3)-C_6H_4-4-Br

Series II

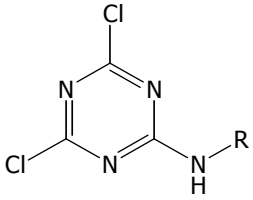
Compound	R	n
II.1		3
II.2		4
II.3		5



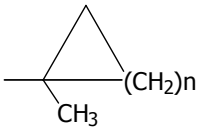
Series III

Compound	R	R_1	R_2
III.1	C_6H_{11}	H	H
III.2	C_6H_{11}	CH_3	CH_3

	III.3	C_6H_{11}	C_6H_5	H
	III.4	C_6H_{11}	C_6H_5	C_6H_5



Series VI

Compound	R	n
II.1		3
II.2		4
II.3		5

Molecular Modeling

Molecular modeling studies were performed by using CS Chem-Office Software version 7.0 (Cambridge software) running on a P-III processor [18]. All molecules were constructed using Chem Draw Ultra 7.0 and saved as the template structure [19]. For every compound, the template structure was suitably changed considering its structural features, copied to Chem 3D 7.0 to create a 3-D model and, finally, the model was cleaned up and subjected to energy minimization using molecular mechanics (MM2). The minimization was executed until the root mean square (RMS) gradient value reached a value smaller than 0.1 kcal/mol·A. The lowest energy structure was used for each molecule to calculate lipophilicity parameters.

Statistical Methods

All calculations and the complete regression analysis were carried out by Data Analysis and Graphing Software Origin, Version 8.1. [20].

Results and Discussion

Lipophilicity determination by Reversed-phase Thin-Layer Chromatography

Lipophilicity is a molecular property which expresses the relative affinity of a solute for aqueous and organic phases, respectively. Accordingly, lipophilicity encodes most between a solute and a solvent. 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:

$$\log\left(\frac{1}{R_f}-1\right)=R_M \qquad (1)$$

where R_f is the retention factor calculated on the basis of migration distance of compound/migration distance of solvent front. Because R_M value 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) [21, 22]:

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

where φ is the volume fraction of the organic solvent in the mobile phase. The slope *S*, indicating the role of which the solubility of solute increases in mobile phase, has been associated with the specific hydrophobic surface area and is considered an alternative measure of lipophilicity. Many studies suggested that the biological activity cannot be associated only with R_M^0 values, especially when polar interactions may take place. The specific hydrophobic surface area of the compounds plays an important role, fact confirmed by the R_M^0 and *S* correlation.

The obtained slopes, *S*, and intercept values, R_M^0, of TLC equation for each solute are presented in Table 2. The correlation coefficients of the TLC equations were satisfactory.

Table 2. Correlation data for the partition RP TLC equation $R_M = R_M^0 + S\varphi$

compound	Acetone-water			Acetonitrile-water			Tetrahydrofuran-water		
	R_M^0	*S*	*r*	R_M^0	*S*	*r*	R_M^0	*S*	*r*
I.1	1.892	-2.753	0.997	2.905	-5.405	0.985	1.972	-2.436	0.997
I.2	2.352	-3.240	0.999	3.850	-6.97	0.993	2.576	-3.332	0.990
I.3	2.589	-3.526	0.999	4.578	-8.307	0.985	2.854	-3.753	0.988
I.4	2.418	-3.267	0.996	5.169	-9.324	0.984	2.857	-3.721	0.992
II.1	2.878	-3.976	0.999	3.246	-5.953	0.946	2.652	-3.385	0.994
II.2	3.218	-4.274	0.999	4.793	-8.495	0.969	3.257	-4.14	0.992
II.3	3.750	-4.914	0.998	5.320	-9.222	0.976	3.408	-4.311	0.996
III.1	2.626	-3.501	0.998	5.072	-7.764	0.993	3.031	-3.948	0.998
III.2	3.364	-4.187	0.999	5.497	-8.370	0.987	3.601	-4.682	0.995
III.3	3.154	-4.022	0.998	5.718	-8.650	0.983	3.495	-4.549	0.997
III.4	3.946	-4.889	0.999	5.880	-8.393	0.987	4.142	-5.425	0.990
IV.1	1.867	-2.601	0.999	2.334	-4.304	0.996	2.367	-3.424	0.995
IV.2	2.013	-2.740	0.998	2.465	-4.415	0.996	2.653	-4.821	0.998
IV.3	1.364	-2.102	0.999	2.257	-4.163	0.996	3.500	-5.593	0.998
compound	Ethanol-water			Methanol-water			Dioxane-water		
	R_M^0	*S*	*r*	R_M^0	*S*	*r*	R_M^0	*S*	*r*
I.1	2.933	-4.648	0.997	2.143	-3.119	0.993	2.888	-4.616	0.996
I.2	2.921	-4.224	0.997	2.602	-3.506	0.998	2.729	-4.955	0.993
I.3	3.847	-5.652	0.993	2.704	-3.700	0.996	2.491	-5.340	0.995
I.4	3.580	-5.252	0.992	3.056	-4.085	0.994	3.658	-5.598	0.997
II.1	2.929	-4.116	0.998	2.930	-3.878	0.997	3.624	-5.257	0.989
II.2	2.323	-3.226	0.995	3.185	-4.038	0.996	3.840	-5.423	0.995
II.3	3.215	-4.277	0.991	3.672	-4.538	0.994	4.363	-5.993	0.994
III.1	2.650	-3.768	0.997	3.391	-4.485	0.997	3.454	-5.078	0.991
III.2	3.798	-4.637	0.995	3.888	-4.956	0.998	4.368	-6.003	0.997
III.3	3.677	-4.973	0.991	3.978	-4.924	0.998	4.219	-5.942	0.998
III.4	4.436	-5.725	0.995	4.454	-5.280	0.993	5.268	-7.200	0.997
IV.1	1.635	-2.694	0.996	2.250	-3.424	0.996	2.342	-3.763	0.994
IV.2	1.809	-2.851	0.996	2.625	-3.832	0.995	2.392	-3.856	0.998
IV.3	2.091	-3.155	0.995	2.258	-3.42	0.997	2.751	-4.219	0.994

Correlation of Retention Constants, R_M^0 and logP

The main purpose of this study was to use chromatographic data (R_M^0) as descriptor of the lipophilic character of s-triazine studied. The correlation between R_M^0 values and different calculated values of log*P* was examined. It is a quantitative descriptor of lipophilicity, one of the key determinants of pharmacokinetic properties. The lipophilicity modifies the penetration of bioactive molecules through the non-polar cell membranes. This property is usually characterized by the partition coefficient, which is essentially determined from distribution studies of the compound between an immiscible polar and non-polar solvent pair. By knowing exact values for this parameter, it is possible to predict the inhibitory activity of a drug. The calculated partition coefficients obtained by use of different programs are listed in Table 3. Different calculated values of log*P* give various correlation coefficients with R_M^0 in Table 4.

Because the retention of a compound in reversed-phase chromatography is governed by hydrophobic interactions, ***linear relationships*** between the retention constant, R_M^0, and log*P* could be expected.

Table 3. Partition coefficients calculated by different theoretical methods

Comp.	**A**logP_s	***AC*log*P***	***AB*/log*P***	***mi*log*P***	**ALOG*P***	***M*LOG*P***	logP_{Kowwin}	***X*LOGP_2**	***X*LOGP_3**	***ACD*log*P***	**C**log*P*
I.1	5.25	4.86	5.91	5.41	5.38	4.96	5.07	4.83	5.36	3.87	4.85
I.2	5.66	5.49	6.73	6.26	6.36	5.40	6.16	5.70	6.09	4.79	5.85
I.3	6.00	6.09	7.07	6.72	6.71	5.66	6.36	6.07	6.62	5.06	6.28
I.4	6.18	6.26	7.49	6.99	6.88	5.88	6.85	6.43	6.74	5.42	6.58
II.1	4.95	4.42	4.89	5.19	4.68	4.51	5.88	3.71	4.48	3.70	5.32
II.2	5.78	5.05	5.67	6.20	5.59	4.99	6.86	4.85	5.56	4.82	6.44
II.3	6.56	5.69	6.45	7.21	6.50	5.45	7.85	5.99	6.64	5.95	7.55
III.1	4.91	4.38	4.97	5.31	5.18	4.51	5.96	4.01	5.07	3.74	5.40
III.2	5.78	5.05	5.67	6.20	5.59	4.99	6.86	4.85	5.56	4.82	5.48
III.3	6.07	5.61	5.05	6.83	7.13	5.90	8.17	6.14	6.89	5.36	7.21
III.4	6.97	6.85	6.40	8.30	9.07	6.90	10.39	8.27	8.58	7.07	9.02
IV.1	3.82	3.67	4.88	3.74	3.59	3.57	3.81	2.37	3.67	2.85	3.12
IV.2	4.21	3.99	5.27	4.25	4.05	3.85	4.30	2.94	4.21	3.41	3.67
IV.3	4.64	4.30	5.66	4.76	4.51	4.12	4.79	3.51	4.75	3.98	4.23

r	A logP_s	*AC*log*P*	*AB*/log*P*	*mi*log*P*	A log*P*	*M*log*P*	logP_{Kowin}	*X*logP_2	*X*logP_3	*ACD*log*P*	C log*P*
A logP_s	1	0.947	0.641	0.993	0.935	0.951	0.918	0.658	0.947	0.964	0.958
*AC*log*P*		1	0.769	0.965	0.966	0.977	0.849	0.984	0.971	0.938	0.902
AB/log*P*			1	0.639	0.607	0.635	0.362	0.683	0.638	0.616	0.486
*mi*log*P*				1	0.966	0.972	0.938	0.978	0.973	0.975	0.972
A log*P*					1	0.991	0.925	0.991	0.994	0.951	0.944
*M*log*P*						1	0.908	0.994	0.984	0.937	0.938
logP_{Kow}							1	0.900	0.919	0.943	0.973
*X*logP_2								1	0.991	0.954	0.936
*X*logP_3									1	0.966	0.943
*ACD*log*P*										1	0.955
C log*P*											1

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). However, this is not the case. This is confirmed by the correlation coefficients obtained between different log*P* values of s-triazine derivatives in Table 4.

Table 4. Correlation coefficients (r) between the log*P* values calculated by different programs.

The fact that there are differences between the calculated values of log*P* of the investigated molecules indicates that different procedures for calculating partition coefficients result in different log*P* values.

Next, an agreement between different calculated log*P* values and chromatographic R_M^0 values was investigated. The correlation coefficients between R_M^0 obtained with different modifiers and log*P* are given in Table5.

Table 5. Correlation coefficients (r) between R_M^0 i log*P*

R_M^0	***A***log***P***$_s$	***AC***log*P*	***AB/I***log***P***	**mi**log***P***	***A***LOG***P***	***M***log***P***	log***P***$_{Kow}$	***X***log***P***$_2$	***X***log***P***$_3$	***ACD***log***P***	***C***log***P***
acetonitrile	0.849	0.754	0.342	0.857	0.795	0.794	0.872	0.782	0.793	0.804	0.858
acetone	0.774	0.612	0.138	0.768	0.675	0.669	0.877	0.658	0.667	0.757	0.829
tetrahydrofuran	0.584	0.479	0.078	0.605	0.572	0.509	0.750	0.518	0.593	0.702	0.649
dioxane	0.755	0.595	0.086	0.753	0.691	0.682	0.894	0.667	0.691	0.770	0.816
methanol	0.715	0.586	0.044	0.736	0.700	0.668	0.832	0.886	0.846	0.750	0.795
ethanol	0.872	0.880	0.528	0.886	0.883	0.905	0.838	0.886	0.872	0.825	0.822

By comparing the calculated values for defining the lipophilicity of the investigated molecules it is evident that ethanol as a modifier gives the highest degree of correlation (calculated mean value of correlation coefficient is 0.836). The modifier that immediately followed ethanol was acetonitrile.

QSSR analysis of the investigated newly synthesized s-triazine derivatives

In defining QSSR model which would best explain the correlation between the retention behavior of investigated s-triazine 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), standard deviation (sd), Fischer ratio (F).

In the case of the correlation of the retention parameter as a dependent variable and one of the lipophilicity descriptors, log *P*, extremely low values of the correlation coefficient were obtained. This leads us to a conclusion that mathematical models defined in such a way are not precise enough and thus some errors could be expected in predicting lipophilicity of the investigated molecules.

In order to find more quality and more reliable mathematical model for defining the best correlation between the retention constant of the investigated newly synthesized s-triazine derivatives and different lipophilicity parameter values, log*P*, multiple linear regression was used. Multiple linear regression is a mathematical model which takes into account simultaneously a number of different factors, significant for a variable. In other words, it is possible to define more precisely the functional dependence between the chromatographic retention constant R_M^0 and the structure of the investigated molecule. In MLR mathematical analysis, physicochemical parameters (molecule descriptors) are used as

independent variables, while retention constant is used as a dependent variable. The quality of obtained correlations expressed by multiple linear regression equations between the retention constant and the calculated values of lipophilicity parameters, log*P*, for different modifiers was estimated, too, on the basis of the statistical parameters values.

The dependency between the retention constant Rm^0 and two variable lipophilicity parameters were examined, as two independent variables:

$$R_M^0 = a + b\ logP_1 + c\ logP_2 \quad (3)$$

In order to estimate the retention of the investigated molecules, each modifier has been selected one model with satisfactory correlation coefficient values out of a great number of obtained models of relationships between retention and lipophilicity parameter. The only exception is tetrahydrofuran which did not prove to be reliable enough for defining models when estimating retention of the examined molecules. Hence, it can be assumed that mathematical models derived in such a way can predict retentions of investigated newly synthesized s-triazine derivatives (equations 4-8)

For acetone:

$$\boldsymbol{R_M^0} = 0.6093 - 0.4741\ \boldsymbol{AC}\ \log\boldsymbol{P} + 0.7547 \log \boldsymbol{P_{Kowin}}$$

$$\boldsymbol{n} = 14; \quad \boldsymbol{r} = 0.9347; \quad \boldsymbol{sd} = 0.29190; \quad \boldsymbol{F\text{-}test} = 38.0148 \quad (4)$$

For acetonitrile:

$$\boldsymbol{R_M^0} = 0.1111 - 1.5671\ \boldsymbol{AC}\ \log\boldsymbol{P} + 2.0381\ \boldsymbol{mi}\ \log\boldsymbol{P}$$

$$\boldsymbol{n} = 14; \quad \boldsymbol{r} = 0.9031; \quad \boldsymbol{sd} = 0.6234; \quad \boldsymbol{F\text{-}test} = 24.3328 \quad (5)$$

For dioxane:

$$\boldsymbol{R_M^0} = 0.9574 - 0.5922\ \boldsymbol{A}\ \mathrm{LOG}\boldsymbol{P} + 0.9310 \log\boldsymbol{P_{Kowin}}$$

$$\boldsymbol{n} = 14; \quad \boldsymbol{r} = 0.9650; \quad \boldsymbol{sd} = 0.2566; \quad \boldsymbol{F\text{-}test} = 73.4081 \quad (6)$$

For methanol:

$$\boldsymbol{R_M^0} = 0.5707 + 0.6721 \log\boldsymbol{P_{Kowin}} - 0.3570\ \boldsymbol{X}\ \mathrm{LOG}\boldsymbol{P_2}$$

$$\boldsymbol{n} = 14; \quad \boldsymbol{r} = 0.9535; \quad \boldsymbol{sd} = 0.2343; \quad \boldsymbol{F\text{-}test} = 55.0411 \quad (7)$$

For ethanol:

$$\boldsymbol{R_M^0} = -3.6665 + 1.9446\ \boldsymbol{M}\ \log\boldsymbol{P} - 0.6357\boldsymbol{X}\ \mathrm{LOG}\boldsymbol{P_2}$$

$$\boldsymbol{n} = 14; \quad \boldsymbol{r} = 0.9134; \quad \boldsymbol{sd} = 0.3673; \quad \boldsymbol{F\text{-}test} = 27.7168 \quad (8)$$

In order to check the validity of the shown mathematical models, the calculations of the retention parameter values ($\boldsymbol{R}_M^0$) were performed, using these equations, and their comparison with experimentally obtained data was made (data obtained from listed literature).

A good correlation between the experimentally obtained retention constant values and values calculated by using the chosen mathematical models was observed. Their compatibility is also confirmed in the following plots.

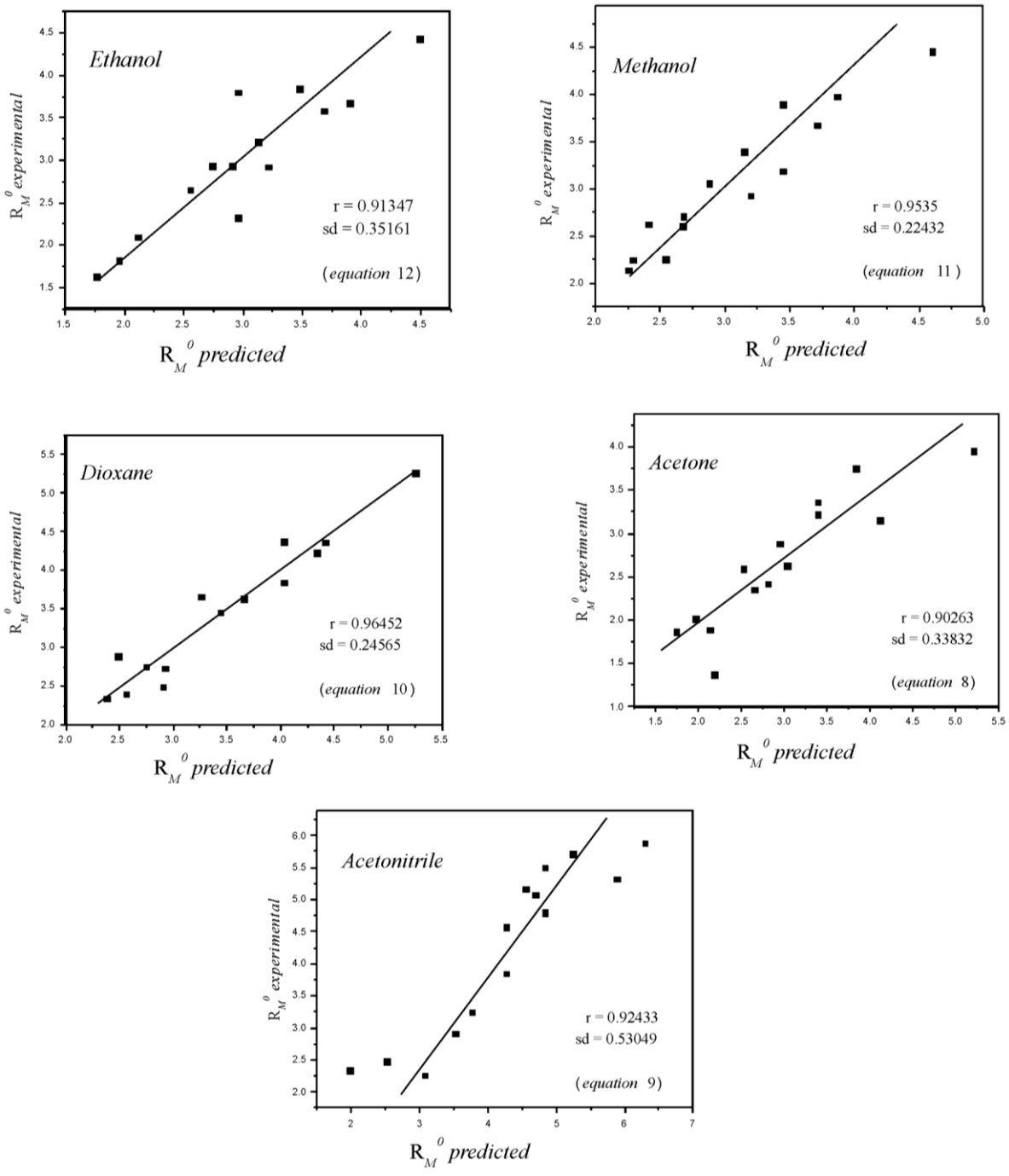


Figure 1. Correlation between experimentally obtained values and calculated values R_M^0 on different modifiers

The best correlations were obtained with dioxane as a modifier (equation 6). The modifier that immediately followed was methanol (equation 7).

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

In this sense, one should say that a balanced combination of descriptors determining the molecule structure has a significant role in model defining, which presents the correlation between retentive behavior and structure.

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

Conclusion

Experimentally obtained RP R_M^0 for different solvent mixtures are dependent on the type of organic modifier in the mobile phase. Correlations of different quality were obtained between R_M^0 values and *A*log*P*$_s$, *AC*log*P*, *mi*log*P*, *AB*/log*P*, *A*log*P*, *M*log*P*, log*P*$_{Kowin}$, *X*log*P*$_2$, *X*log*P*$_3$, i *C*log*P* and *ACD*log*P*. According to the correlation coefficients R_M^0 is a useful property for evaluation of the relative lipophilicity of the compounds examined. The quality of obtained correlations expressed by multiple linear regression equations between the retention constant, R_M^0, and the calculated values of lipophilicity parameters, log*P*, for different modifiers was estimated, too, on the basis of the statistical parameters values. The best correlations were obtained with dioxane as a modifier. The modifier that immediately followed was methanol.

Acknowledgement

These results are part the project No. 31055, supported by the Ministry of Science and Technological Development of the Republic of Serbia, 2011-2014.

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