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ESTIMATION OF THE CORRELATION BETWEEN THE RETENTION OF s-TRIAZINE DERIVATIVES AND SOME MOLECULAR DESCRIPTORS

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In this study, 14 newly synthesized s-triazine derivatives were investigated by means of reversed-phase thin-layer chromatography (TLC) on C-18 stationary and two different mobile phases: acetonitrile-water and methanol-water. Quantitative structure-retention relationship (QSRR) was developed for a series of s-triazine compounds by the multiple linear regression (MLR) analysis. An MLR procedure was used to model the relationships between molecular descriptors and retention of s-triazine derivatives. Physico-chemical molecular descriptors were calculated from the optimized structures. Statistically significant and physically meaningful QSRRs were obtained.

KEY WORDS: lipophilicity, multiple linear regression, s-triazine

INTRODUCTION

1, 3, 5-Triazines (or s-triazines) are a class of compounds well known for a long time and are still being the object of considerable interest, mainly because of their applications in agriculture as the basis for various herbicides (1, 2). Furthermore, some s-triazines display important biological activities, such as cytotoxic (3), anticancer, or antibacterial, which makes them attractive in various medical applications. Due to different physical and chemical properties and different reactivity of s-triazine derivatives, they may be individually separated. Modeling and prediction of the physicochemical properties of organic compounds have been expanding rapidly in many scientific fields (4). Over the last several years, an increasing number of studies have focused on the correlations between chromatographic retention data of analytes and molecular structure parameters (5). This kind of research is a very important theoretical field in chromatography which can provide valuable data regarding (a) the prediction of retention for a new solute (6), (b) the identification of the most relevant structural descriptors and (c) the prediction of relative biological activities within a set of compounds (7). Chromatographic techniques may be considered as a traditional approach for the fast estimation of lipophilicity. Due to

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the variability of experimental conditions, the establishment of the universal lipophilicity scale is the major problem of this method. Although thin-layer chromatography (TLC) is a relatively old technique, it is used in the various quantitative structure-retention relationship (QSRR) studies of organic molecules. Besides the advantage of lipophilicity being determined in a rapid and simple way, the technique of planar chromatography implies a wide choice of adsorbents and solvents and exceedingly small amounts of substance for testing, as well (8, 9). In the case of TLC, the QSRR studies are usually based on the use of R_M value defined by the Bate-Smith equation (10):

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

where R_F is the retention factor, defined as the ratio of the distance traveled by the centre of the spot to the distance simultaneously traveled by the mobile phase. In the case of RP-TLC, R_M values are related to the molecular lipophilicity through linear correlation according to the equation:

$$R_M = R_M^0 + S\varphi \quad [2]$$

where φ stands for the concentration of the organic component in the mobile phase, and *S* is the slope. Extrapolation to pure water, based on the Soczewinski model leads to the estimations of lipophilicity, whereas Eqs. [1] and [2] are the bases for deriving data for the QSRR studies. In the RP models, it has been verified that the octanol-water partition coefficient log *P* is in the linear correlation with R_M^0 and therefore chromatographic data have often been used to calculate the lipophilicity parameters (R_M^0), and these are commonly used as quantitative TLC retention descriptors and QSRR models to predict the R_M values of different organic molecules (11). Few studies are focused on the QSRR of s-triazine derivatives, and they all are based on the use of some newly developed topological indices (connectivity index - Randić connectivity index) (12-14). Due to our interest in the possible biological activity of the newly prepared s-triazine derivatives, our work was mainly focused on the quantification of molecular lipophilicity as a source of the valuable information in QSRR investigations (15, 16). This work is an extension of some previous studies based on the simplest QSRR between the calculated log *P* values and R_M^0, when significant correlations were obtained (17, 18). Therefore, our aim was to estimate the lipophilicites for s-triazine compounds, to select suitable descriptors, and develop a statistical model that may be used to predict lipophilicity for a new solute in a satisfactory way, in order to better understand the separation mechanism through the studies of QSRR.

EXPERIMENTAL

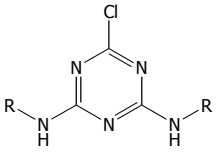
The investigated compounds were 1,3,5-triazines substituted at the position-s 4 and 6 by smaller and larger groups with various lipophilic characteristics (Table 1). Compounds were synthesized in the laboratory at the Department of Organic Chemistry in Faculty of Technology and Metallurgy, University of Belgrade (19, 20). Chromatographic analyses were performed on 10 × 10 cm high-performance thin-layer chromatography (HPTLC) plates coated with C-18 silica F_{254} (Merck, Darmstadt, Germany). All calculations were performed using the computer software Origin, Version 8.1 (21). The partition coeffi-

cients *C*log *P*, *A*log *P* and *mi*log *P* values were calculated for the compounds by applying different theoretical procedures (22).

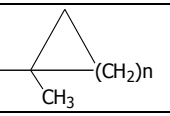
Statistical Methods

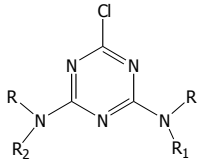
Full geometry optimization based on CS Chem-Office Software version 7.0. (Cambridge) (23). All molecules were constructed by using Chem Draw Ultra 7.0. and saved as the template structures. A set of molecular descriptors was selected to reflect geometrical, electronic, and physico-chemical properties of the compounds were calculated using the ChemSilico software (24).

Table 1. Chemical structures of the s-triazines studied

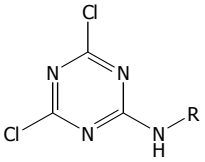


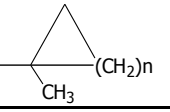
Series I	
Compound	**R**
I.1	-CH(CH_3)-C_6H_5
I.2	-CH(CH_3)-C_6H_4-4-CH_3
I.3	-CH(CH_3)-C_6H_4-4-Cl
I.4	-CH(CH_3)-C_6H_4-4-Br

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

RESULTS AND DISCUSSION

Analysis of R_M^0 values obtained with different mobile phase modifiers

Besides a very good fit of Equation [2] the statistics from Table 2 illustrate different calculated R_M^0 values for various modifiers used. The statistics obtained (Table 2) illustrate that the linear equation is a very good fit to the experimental data. Different mutual correlations were observed between R_M^0 values calculated for different modifiers (Table 3). The slope and intercept values in Table 3 varied depending on the mobile phase used.

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

Compound	methanol - water			acetonitrile - water		
	R_M^0	S	r	R_M^0	S	r
I.1	2.457	-3.087	0.996	2.110	-3.501	0.998
I.2	3.188	-3.738	0.997	2.786	-4.194	0.995
I.3	3.976	-4.570	0.992	2.887	-4.215	0.996
I.4	4.407	-4.984	0.999	2.896	-4.098	0.995
II.1	3.181	-3.829	0.995	2.388	-3.347	0.997
II.2	3.320	-3.868	0.994	2.753	-3.699	0.997
II.3	4.530	-5.070	0.998	3.000	-3.788	0.995
III.1	3.440	-4.086	0.991	2.356	-3.304	0.995
III.2	3.998	-4.452	0.994	3.284	-4.197	0.998
III.3	3.980	-4.471	0.985	3.101	-4.076	0.988
III.4	5.295	-5.764	0.995	3.556	-4.394	0.997
IV.1	1.526	-2.206	0.999	1.497	-2.592	0.997
IV.2	1.626	-2.242	0.988	1.590	-2.629	0.995
IV.3	1.756	-2.090	0.993	1.956	-2.821	0.996

Table 3. Correlations between R_M^0 values determined with different mobile phases.

Equations	R	SD	n
$R_M^0{}_{\text{MeOH}} = -1.187 + 1.751\ R_M^0{}_{\text{ACN}}$	0.945	0.391	14

* ***r*** - correlation coefficient, ***SD*** - standard deviation, ***n*** - number of replicates

Lipophilicity of analytes

The lipopholicity of bioactive compounds is an important physicochemical property. The hydrophobic nature of a drug can be represented by a rather simple term, the logarithm of the 1-octanol-water partition coefficient, log *P*. It is known that this property is significantly related to the activity of drugs and their transport through membranes. Instead of the classical method of measurement of log *P* values, partition chromatographic data can be employed and reversed-phase thin-layer chromatography is frequently used to estimate the lipophilicity of organic compounds. R_M^0 values are usually used for characterization of the hydrophobicity of substances. The calculated *C*log *P*, *A*log *P* and *mi*log *P* values were compared with the hydrophobicity values R_M^0 evaluated from the chromatographic results. The graphs obtained for these correlations are presented in Figure 1.

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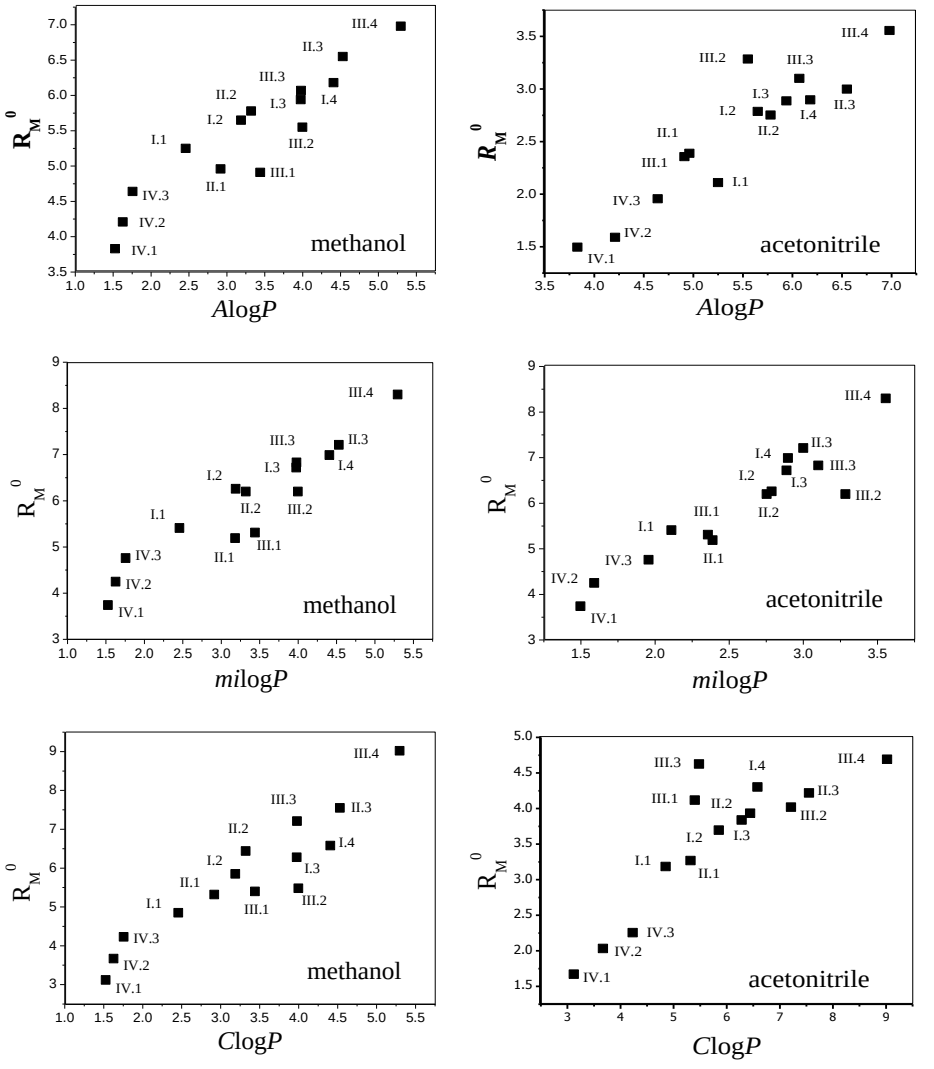

Figure 1. The correlations between the R_M^0 values and calculated *A*log *P*, *mi*log *P* and *C*log *P* values

These results are in accordance with previous reports of the retention behavior of some s-triazine derivatives (25).

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Structural descriptors of analytes

The molecular descriptors are the basic tool for any QSRR approach. They encode structural chemical information and are useful for a better understanding of molecular properties. The descriptors obtained after applying the variable selection routine served as the input data for MLR analysis and are presented in Table 4.

Table 4. The molecular descriptors used in this study

Comp.	*milogP*	*A*log*P*	*ClogP*	*pKa*	*logW*	*MR*	E_t	*G*	$^0\chi$	$^1\chi$	$^2\chi$	$^3\chi$	$^4\chi$
I.1	5.41	5.25	4.85	3.019	-4.400	106.361	3.391	820.19	17.648	12.114	10.766	8.457	7.126
I.2	6.26	5.66	5.85	4.216	-4.400	116.444	3.527	817.77	19.388	12.901	12.010	9.278	7.429
I.3	6.72	6.00	6.28	3.346	-4.410	115.971	5.063	777.07	19.388	12.901	12.010	9.278	7.429
I.4	6.99	6.18	6.58	3.162	-4.465	121.607	7.714	829.57	19.388	12.901	12.010	9.278	7.429
II.1	5.19	4.95	5.32	3.45	-4.000	90.399	33.636	628.69	14.924	9.965	9.988	7.322	6.491
II.2	6.20	5.78	6.44	3.884	-4.320	99.602	26.337	621.33	16.338	10.964	10.695	7.822	6.844
II.3	7.21	6.56	7.55	2.001	-3.000	108.804	41.901	613.97	17.752	11.964	11.402	8.322	7.197
III.1	5.31	4.91	5.40	4.155	-3.330	90.327	21.101	615.47	14.493	10.292	9.024	6.921	6.071
III.2	6.20	5.78	5.48	6.84	-4.980	98.796	30.761	675.09	16.233	11.147	9.847	8.289	6.659
III.3	6.83	6.07	7.21	4.691	-4.120	113.516	30.554	799.79	18.476	13.292	11.552	9.401	8.396
III.4	8.30	6.97	9.02	-	-	136.705	39.737	984.11	22.459	16.292	14.079	11.881	10.725
IV.1	3.74	3.82	3.12	1.715	-3.510	64.709	21.498	445.79	10.888	7.073	7.005	4.868	4.409
IV.2	4.25	4.21	3.67	1.778	-3.760	69.309	17.739	442.11	11.596	7.573	7.358	5.118	4.586
IV.3	4.76	4.64	4.23	0.955	-3.520	73.911	25.401	438.43	12.303	8.073	7.712	5.368	4.763

****mi*log *P*, *A*log *P*, *Clog P*** - the partition coefficients were calculated by applying different theoretical procedures, **p*Ka*** - dissociation constant, **log*W*** - water solubility, ***MR*** - molar refractivity, E_t - total energy, ***G*** - Gibbs energy, $^0\chi$, $^1\chi$, $^2\chi$, $^3\chi$, $^4\chi$ - connectivity index (Randić connectivity index) chi - 0, 1, 2, 3, 4 (respectively).

The multiple linear regression (MLR) analysis is the most widely used linear correlation method. It is based on the principle of polylinearity (Eq. 3):

$$y = x_0 + x_1 D_1 + x_2 D_3 + ... + x_m D_m \qquad [3]$$

where D_1, D_2, D_3 and D_n are descriptors, n is the number of descriptors. As a general rule, the samples (N) should be larger than 2^m (m is the number of descriptors used in the correlation). As the number of descriptors increase-s, however, the MLR becomes problematic, for example, redundancy of information when descriptors are correlated. In this paper, the retention was the dependet variable, y, and the structural descriptors obtained from molecular modeling were the independent variables. The quality criteria of the fit in the regression analysis were the coefficient of determination (*r*) and standard deviation (*SD*).

The regression models with the best statistics for ***methanol*** as modifier of mobile phase was that including 1-octanol-water partition coefficient (*mi*log *P*), Gibbs energy (*G*), total energy (E_t) and connectivity index - $^0\chi$, $^2\chi$, $^4\chi$ for ***acetonitrile*** as a second modifier of mobile phase: Gibbs energy (*G*), total energy (E_t), dissociation constant (p*Ka*), partition coefficient (*A*log *P*) and connectivity index - $^3\chi$, $^4\chi$. Resulting models were summarized in Table 5.

Table 5. Multiple linear regression equations between the selected molecular descriptors and lipophilicity parameters, R_M^0

Modifier					
Methanol	*r*	*SD*	*Acetonitrile*	*r*	*SD*
$R_M^0 = -1.943 + 0.851 \mathbf{milogP} + 0.009 E_t$	**0.955**	0.371	$R_M^0 = -0.826 + 0.536\ \mathbf{Alog\ P_s} + 1.367 \mathbf{pK_a}$	**0.982**	0.118
$R_M^0 = -1.747 + 1.082 \mathbf{milogP} - 0.082\ {}^0\chi$	0.953	0.379	$R_M^0 = 0.415 - 0.005 G + 0.682\ {}^4\chi$	0.956	0.197
$R_M^0 = -1.727 + 1.057 \mathbf{milogP} - 0.118\ {}^5\chi$	0.952	0.383	$R_M^0 = -1.007 + 0.637\ \mathbf{Alog\ P_s} + 0.004\ E_t$	0.946	0.219
$R_M^0 = -1.862 + 0.917 \mathbf{milogP} - 3.908 G$	0.949	0.392	$R_M^0 = -0.845 + 0.549\ \mathbf{Alog\ P_s} + 0.052\ {}^3\chi$	0.944	0.222
$R_M^0 = -0.637 - 0.008 G + 1.185\ {}^4\chi$	0.932	0.452	$R_M^0 = -0.921 + 0.595\ \mathbf{Alog\ P_s} + 0.035\ {}^4\chi$	0.943	0.225

From the selected regression equations and statistics presented in Table 5, some general conclusions can be made. Equations present that the retention depend-s mostly on the lipophilicity of the analytes as expressed by the logarithm of their 1-octanol-water partition coefficient. This is in accordance with the significance of hydrophobic interactions in a typical RP system. Besides, the connectivity indices (different order-s) as descriptors found to be important factors affecting the retention and therefore the lipophilicity, determined chromatographically. The results given in Table 5 suggest that all proposed models are reasonable QSRR models.

CONCLUSION

In the present study, QSRR methodology was used to investigate the connection between the chemical structure of s-triazine derivatives, their physicochemical properties activity and the chromatographic retention. The descriptors selected that are most important for chromatographic behavior of the s-triazine derivatives are lipophilicity and connectivity indices. Ten multiple linear regression QSRR models (in generally for methanol and acetonitrile modifiers) based on the most relevant descriptor were developed. The MLR statistics confirmed the importance of the hydrophobic interactions in the total retention mechanism of the investigated s-triazine compounds. Predictive ability of the MLR model and equations based on physically meaningful parameters allow us to estimate the lipophilicity of similar compounds.

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ИСПИТИВАЊЕ КОРЕЛАЦИЈЕ РЕТЕНЦИЈЕ *s*-ТРИАЗИНСКИХ ДЕРИВАТА И НЕКИХ МОЛЕКУЛСКИХ ДЕСКРИПТОРА

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Испитано је хроматографско понашање четири групе новосинтетисаних деривата *s*-триазина хроматографијом на обрнутим фазама (C-18 HPTLC) са метанолом и ацетонитрилом као модификаторима покретне фазе. На основу добијених резултата, применом вишеструке регресије, развијени су математички модели који омогућавају процену хроматографског понашања испитиваних молекула на основу њихове хемијске структуре (Quantitative structure-retention relationship (QSRR) модел. Познавање квантитативних зависности између структуре и ретенционе константе испитиваних деривата *s*-триазина доприноси бољем разумевању њихових структурних и физичко-хемијских особина.

Кључне речи: липофилност, мултипли-линеарна регресија, *s*-триазини

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