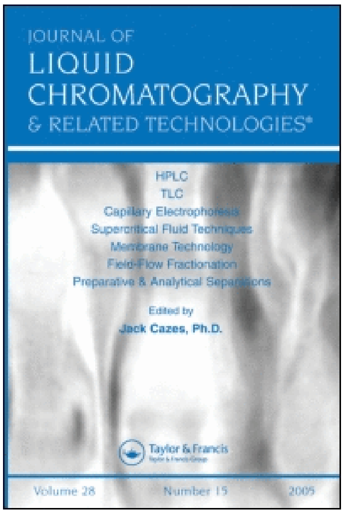

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Use of RP-TLC and Structural Descriptors to Predict the log *P* Values of Higher Fatty Acids, Hydroxy Acids, and Their Esters

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Use of RP-TLC and Structural Descriptors to Predict the log *P* Values of Higher Fatty Acids, Hydroxy Acids, and Their Esters

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ABSTRACT

Selected higher fatty acids, hydroxy acids, and their esters were chromatographed on RP-TLC plates using methanol : water as mobile phase. R_F values obtained by RP-TLC and log *P* values by Rekker were used for the new methods of calculation of partition coefficients for investigated compounds. The partition coefficient values estimated by the Rekker method for higher fatty acids, hydroxy acids, and their esters were also correlated with the numerical values of selected structural descriptors. The most accurate prediction of the partition coefficient values of the acids and esters was achieved by use of biparametric equations relating to the topological index *A* and electrotopological

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state $E_{\Sigma OH}$. These methods enable differentiation between the values of log P for the geometric isomers of 9-octadecenoic acids, namely for oleic acid and elaidic acid.

Key Words: RP-TLC method; Higher fatty acids; Hydroxy acids; Esters; Partition coefficient; Structural descriptors.

INTRODUCTION

The problem of calculating isomers' log P values presents an important analytical and physicochemical issues.

The definition of lipophilicity pertains to the phenomenon of water molecules' interaction with apolar fragments of organic molecules. Hydrophobic interactions are particularly important for biological processes, therefore the hydrophobic effect of organic compounds has been justifiably the subject of extensive investigations.

The biological activity of organic compounds depends on multiple factors such as their structure, distribution of electrons, as well as hydrophobic–hydrophilic character of such compounds. Biologically active substances are strongly affected by the hydrophobic–hydrophilic equilibrium, which can be expressed by the partition coefficient of these substances between water and an organic solvent.[1,2] Among many systems popularly used for this purpose is *n*-octanol–water, since it best reflects actual conditions of the biological milieu with regard to the arrangement of polar and non-polar phases.[3] This is why, in order to describe lipophilicity of the examined substance, one uses the logarithm of its partition coefficient (log P) in *n*-octanol–water system. The traditional method of specifying this parameter, i.e., extraction, is based upon quantitative determination of the examined substance concentration at equilibrium between the two phases mentioned. It possesses, however, numerous flaws. Among other things, it makes possible examination of substances only that are chemically pure and stable; it is also time-consuming and frequently unfeasible because of unwanted emulsion formation.[4,5] Reversed-phase thin-layer chromatography (RP-TLC) and different computational procedures are alternative methods for lipophilicity estimations.[6–9]

To assess hydrophobic–hydrophilic properties of organic compounds, one can make use of some physicochemical parameters that reveal relationships between chemical structures and biological activities. The most frequently used quantities describing molecular structures with singular numbers are topological indexes originating from the graph theory.

The aim of this work was application of RP-TLC and structural descriptors (topological indexes and electrotopological states) for calculation and prediction of partition coefficients for higher fatty acids, hydroxy fatty acids, and their esters. The subjects of investigation were: oleic acid, elaidic acid, ricinoleic acid, methyl ricinoleate, α-hydroxypalmitic acid, methyl α-hydroxypalmitate, 12-hydroxystearic acid, methyl 12-hydroxystearate, 9,10-dihydroxystearic acid, and methyl 9,10-dihydroxystearate.

EXPERIMENTAL

Chemicals

If not otherwise specified, all used chemicals were analytical grade. TLC-solvents were obtained from Merck, Darmstadt, Germany. Commercial samples of oleic acid, elaidic acid, ricinoleic acid, methyl ricinoleate, α-hydroxypalmitic acid, methyl α-hydroxypalmitate, 12-hydroxystearic acid, methyl 12-hydroxystearate, 9,10-dihydroxystearic acid, and methyl 9,10-dihydroxystearate (Sigma-Aldrich, USA) were used as test solutes in chloroform.

Separation of Higher Fatty Acids, Hydroxy Fatty Acids, and Their Esters by TLC

RP-TLC was performed on RP-18F_{254} RP-TLC plates (E. Merck, Darmstadt, Germany). Solutions of higher fatty acids, hydroxy fatty acids, and their esters (concentrations 0.169%) were spotted on a chromatographic plate in quantities of 2 μL. Methanol, and mixture containing methanol and water in the volume proportions 9.5 : 0.5, and 9 : 1 were used as mobile phases. After development, the plates were dried at room temperature for 24 hr to evaporate the solvents. Finally, the spots of compounds investigated were observed after visualization in iodine vapour.

Partition Coefficients

log *P* by the Method of Rekker

The log P_{Rek} partition coefficients were calculated from fragmental constants, according to the method of Rekker,[10–12] using equation:

$$\log P_{\text{Rek}} = \sum_{1}^{n} a_n f_n \qquad (1)$$

where a_n is the number of a given structural fragment n in a molecule and f_n is the hydrophobic fragmental constant of the given structural fragment n. The f_n values are:

$$f_{CH_3} = 0.724; \quad f_{CH_2} = 0.519; \quad f_{CH} = 0.315; \quad f_{COOH} = -0.942$$
$$f_{COO} = -1.200; \quad f_H = 0.2045; \quad f_{CH_2=CH} = 0.834; \quad f_{OH} = -1.448$$

New Methods of Calculation of Partition Coefficients

Partition Coefficients for Oleic and Elaidic Acids

New methods of calculation of partition coefficients, on the basis of the retention parameter values (R_F) obtained by TLC on RP-18 stationary phase and log P values by Rekker's method, are proposed for oleic acid and elaidic acid, i.e., by use of Eqs. (2) and (3):

$$\log P_{\text{oleic acid}} = \left(\frac{\bar{R}_F}{R_{F1}}\right) \times \log P_{\text{Rek}} \qquad (2)$$

$$\log P_{\text{elaidic acid}} = \left(\frac{\bar{R}_F}{R_{F2}}\right) \times \log P_{\text{Rek}} \qquad (3)$$

where R_{F1} is the R_F value of oleic acid, R_{F2} is the R_F value of elaidic acid, and

$$\bar{R}_F = \frac{R_{F1} + R_{F2}}{2}$$

Partition Coefficients for Hydroxy Acids and Their Esters

New methods of determination of partition coefficients are also proposed for ricinoleic acid, methyl ricinoleate, α-hydroxypalmitic acid, methyl α-hydroxypalmitate, 12-hydroxystearic acid, methyl 12-hydroxystearate, 9,10-dihydroxystearic acid, and methyl 9,10-dihydroxystearate. The R_F values of hydroxy acids and their methyl esters obtained on RP-18 plates, as well as log P values by the method of Rekker, were applied for these new methods of calculation of log P, i.e., by use of Eqs. (4) and (5), respectively:

$$\log P_{\text{acid}} = \left(\frac{\bar{R}_F}{R_{F1}}\right) \times \log P_{\text{Rek}} \qquad (4)$$

$$\log P_{\text{ester}} = \left(\frac{\bar{R}_F}{R_{F2}}\right) \times \log P_{\text{Rek}} \qquad (5)$$

where R_{F1} is the R_F value of suitable acid, R_{F2} is the R_F value of suitable methyl ester, and

$$\bar{R}_F = \frac{R_{F1} + R_{F2}}{2}$$

Structural Descriptors

Topological indexes based on connectivity (Gutman (M, M^v),[13–15,20] and Randić (${}^0\chi$, ${}^1\chi$, ${}^2\chi$, ${}^0\chi^v$, ${}^1\chi^v$, ${}^2\chi^v$),[13–15,20] and Pyka (χ_{012})[15,17,18] indexes) and on the distance matrix (Rouvray (R),[13–15,20] Wiener (W),[13,16] and Pyka (^{0}B, ^{1}B, A)[15,17,18] indexes) were calculated for the compounds investigated. The Rouvray, Wiener, and Pyka indexes were calculated by building the distance matrix and determining its elements by means of values given by Barysz and Pyka.[17,19] The electrotopological states of carbon atoms bearing carboxyl groups, oxygen atoms of carboxyl groups, and oxygen atoms of hydroxyl groups were obtained from the internet.[21] Elements necessary to calculate the earlier mentioned indexes are listed in Table 1. The methods used to calculate the topological indexes have been reviewed elsewhere.[13–15,20]

RESULTS AND DISCUSSION

Numerical values of partition coefficients, calculated according to Eq. (1) using the method of Rekker and the R_F values obtained by RP-TLC method, are listed in Table 2. The log P_{Rek} partition coefficients calculated according to the method of Rekker lead to identical numerical values for the geometric isomers of 9-octadecenoic acids, namely for oleic and elaidic acids. The partition coefficients (log *P*) values, calculated using the new methods proposed on the basis of Eqs. (2)–(5) for the all investigated compounds, are also listed in Table 2.

The combination of the data obtained by RP-TLC method and the log P_{Rek} calculated from fragmental constants (according to the method of Rekker), enable differentiation between the values of log *P* for the oleic acid and the elaidic acid.

Topological indexes based on adjacency matrix and numbers of hydrogen bonds acceptors[21] are presented in Table 3. Selected topological indexes based on the distance matrix and the electrotopological states are listed in Table 4.

Using structural descriptors, obtaining statistically optimal correlation equations that would describe log *P* according to Rekker is one problem. Another is obtaining such correlation equations that would allow, in turn, obtaining a correlation equation generating varying values of log *P* for isomers, i.e., for oleic acid and elaidic acid, because the Rekker method for

Table 1. The elements needed for calculation of topological indexes.

Atomic group	Delta values $\delta^{[13-15]}$	Valence delta values $\delta^{\nu[13-15]}$	Atom	Diagonal elements d_{ii}[19]	Type of bond	Off-diagonal elements d_{ij}[19]	Path	d_{ij} values[10]	Atom (skeletal hydride group)	Intrinsic state values I[20]
$-CH_3$	1	1	C	0	C–C	1.000	$C{=}C_{(j)}$ / $C_{(i)}$	1.323	$>CH-$	1.33
$=CH_2$	2	2	O	0.25	C–O	0.750			$-CH_2-$	1.50
$\equiv CH$	3	3			C=O	0.375			$>C=$	1.67
$=C=$	4	4			C=C	0.500			$=CH-$	2.00
$-OH$	1	5					$C{=}C$ / \\ $C_{(i)}$ $C_{(j)}$	1.500	$-CH_3$	2.00
$=O$	2	6							$=O$	7.00
									$-OH$	6.00
									$-O-$	3.50
							$C_{(j)}$ / $C{=}C$ / $C_{(i)}$	2.291		

Table 2. R_F, log *P* by Rekker and calculated log *P* values using methods proposed in this work.

Solute	R_F obtained using methanol : water (v/v)			log P_{Rek} by Rekker according to Eq. (1)	log *P* calculated using Eqs. (2)–(5) from log P_{Rek} and the R_F obtained using methanol : water (v/v)			Average value of log *P*
	9 : 1	9.5 : 0.5	10 : 0		9 : 1	9.5 : 0.5	10 : 0	
Oleic acid	0.23	0.41	0.57	7.678	6.676	7.022	7.408	7.035
Elaidic acid	0.17	0.34	0.53	7.678	9.033	8.468	7.968	8.489
Ricinoleic acid	0.45	0.61	0.73	6.022	5.420	5.479	5.733	5.544
Methyl ricinoleate	0.36	0.50	0.66	6.492	7.304	7.206	6.836	7.115
α-Hydroxypalmitic acid	0.34	0.48	0.64	5.396	4.444	4.778	5.059	4.760
Methyl α-hydroxypalmitate	0.22	0.37	0.56	5.862	7.461	6.733	6.281	6.825
12-Hydroxystearic acid	0.35	0.49	0.65	6.434	5.882	6.237	6.286	6.135
Methyl 12-hydroxystearate	0.29	0.46	0.62	6.900	7.613	7.125	7.067	7.286
9,10-Dihydroxystearic acid	0.58	0.67	0.75	4.782	4.534	4.604	4.750	4.629
Methyl 9,10-dihydroxystearate	0.52	0.62	0.74	5.248	5.551	5.460	5.283	5.431

Table 3. Number of hydrogen bonds acceptors and topological indexes based on adjacency matrix for compounds investigated.

Solute	No. of hydrogen bond acceptors (#HA)[21]	M	$^0\chi$	$^1\chi$	$^2\chi$	χ_{012}	M^v	$^0\chi^v$	$^1\chi^v$	$^2\chi^v$	χ^v_{012}
Oleic acid	2	96	14.2613	9.2476	6.2914	9.3968	152	13.4097	8.8217	5.7280	8.7833
Elaidic acid	2	96	14.2613	9.2476	6.2914	9.3968	152	13.4097	8.8217	5.7280	8.7833
Ricinoleic acid	3	102	15.1315	9.4579	6.9252	9.9702	182	13.7271	8.7129	5.9773	8.9416
Methyl ricinoleate	3	106	15.8386	10.0185	7.0716	10.3915	194	14.6882	9.1017	6.0928	9.3390
α-Hydroxypalmitic acid	3	75	13.3995	8.8349	6.4252	9.1284	155	11.9951	8.0899	5.5318	8.1271
Methyl α-hydroxypalmitate	3	79	14.1066	9.3956	6.5906	9.5592	167	12.9561	8.4787	5.7167	8.5635
12-Hydroxystearic acid	3	83	14.8137	9.8081	7.2787	10.1883	163	13.4093	9.193	6.264	9.1743
Methyl 12-hydroxystearate	3	87	15.5208	10.3687	7.4251	10.6116	175	14.3703	9.4519	6.4464	9.5668
9,10-Dihydroxystearic acid	4	80	15.1066	10.2187	7.7746	10.6271	184	13.1494	9.1546	6.3913	9.1632
Methyl 9,10-dihydroxystearate	4	84	15.8137	10.7794	7.921	11.0527	196	14.1104	9.6594	6.5737	9.6405

Table 4. Topological indexes based on distance matrix and electrotopological states for compounds investigated.

	Indexes based on distance matrix					Electrotopological state[21]			
Solute	R	W	A	^0B	^1B	C with COOH group (E_C)	O with C=O (E_{O1})	O with COOH or $COOCH_3$ (E_{O2})	$E_{\Sigma OH}$ (without OH with COOH)
Oleic acid	2327.878	1164.190	533.750	1.8879	0.1742	−0.6642	10.3241	8.5082	0
Elaidic acid	2454.438	1227.470	562.180	1.8374	0.1649	−0.6642	10.3241	8.5082	0
Ricinoleic acid	2547.024	1273.887	570.352	1.9429	0.1768	−0.6887	10.3302	8.5092	9.7939
Methyl ricinoleate	2728.222	1364.736	598.594	2.0171	0.1825	−0.1008	10.9204	4.6095	9.8245
α-Hydroxypalmitic acid	2124.250	1062.500	497.507	1.8239	0.1706	−1.0944	10.3817	8.5091	9.0883
Methyl α-hydroxypalmitate	2424.000	1212.375	553.508	1.8440	0.1661	−0.5064	10.9719	4.4806	9.4045
12-Hydroxystearic acid	2843.750	1422.200	634.387	1.8339	0.1570	−0.6775	10.3393	8.5183	9.8452
Methyl 12-hydroxystearate	3039.625	1520.190	704.528	1.8423	0.1514	−0.0896	10.9296	4.6186	9.8757
9,10-Dihydroxystearic acid	3055.250	1528.125	668.270	1.8091	0.1626	−0.7285	10.3515	8.5204	19.8132
Methyl 9,10-dihydroxystearate	3259.375	1630.187	698.750	1.9720	0.1677	−0.1405	10.9417	4.5954	19.9027

these substances yields the same value. The best correlation equations obtained as follow:

$$\log P_{\mathrm{Rek}} = 0.4787(\pm 0.1029) \times {}^{0}\chi^{\nu} - 1.3840(\pm 0.1184) \times \#\mathrm{HA} + 3.9275(\pm 1.4053) \quad (6)$$

$$n = 10; \quad R^2 = 95.52\%; \quad F = 74.5; \quad s = 0.236; \quad P < 0.0001$$

$$\log P_{\mathrm{Rek}} = 0.9825(\pm 0.0731) \times {}^{1}\chi^{\nu} - 1.6188(\pm 0.0508) \times \#\mathrm{HA} + 2.3132(\pm 0.6065) \quad (7)$$

$$n = 10; \quad R^2 = 99.32\%; \quad F = 508.3; \quad s = 0.092; \quad P < 0.0001$$

$$\log P_{\mathrm{Rek}} = 1.0910(\pm 0.0648) \times \chi^{\nu}_{012} - 0.1680(\pm 0.0046) \times E_{\Sigma\mathrm{OH}} - 1.9396(\pm 0.5642) \quad (8)$$

$$n = 10; \quad R^2 = 99.49\%; \quad F = 681.4; \quad s = 0.080; \quad P < 0.0001$$

$$\log P_{\mathrm{Rek}} = 0.9920(\pm 0.0654) \times \chi^{\nu}_{012} - 1.6380(\pm 0.0457) \times \mathrm{HA} + 2.2271(\pm 0.5432) \quad (9)$$

$$n = 10; \quad R^2 = 99.46\%; \quad F = 642.9; \quad s = 0.082; \quad P < 0.0001$$

$$\log P_{\mathrm{Rek}} = 1.0833(\pm 0.0668) \times {}^{1}\chi^{\nu} - 0.1661(\pm 0.0047) \times E_{\Sigma\mathrm{OH}} - 1.8252(\pm 0.5794) \quad (10)$$

$$n = 10; \quad R^2 = 99.45\%; \quad F = 631.6; \quad s = 0.083; \quad P < 0.0001$$

Table 5 puts together values of partition coefficients for the examined fatty acids and their derivatives calculated using Eqs. (9) and (10).

The coefficients appear in these equations are not mutually correlated. These equations are characterized by a high correlation coefficient; however, they do not allow differentiating between oleic and elaidic acids. That means, log P values calculated from these equations will always be the same for both acids, which are isomers. The reason for this happening is that in Eqs. (6)–(10) all parameters are same for both acids. If one wishes to differentiate between these two acids, the correlation equation will have to be modified by introducing an index or parameter that would be different for these two acids. Only topological indexes based on distance matrix allow differentiating between geometrical isomers having cis- and trans-configuration. The best equation of this type is as follows:

$$\log P_{\mathrm{Rek}} = 0.007989(\pm 0.001013) \times A - 0.1882(\pm 0.01092) \times E_{\Sigma\mathrm{OH}} + 3.2748(\pm 0.5484) \quad (11)$$

$$n = 10; \quad R^2 = 97.85\%; \quad F = 159.4; \quad s = 0.163; \quad P < 0.0001$$

The log P values calculated from Eq. (11) are shown in Table 5.

Table 5. log *P* value calculated on the base structural descriptors [Eqs. (9)–(12)] for investigated compounds.

	log P_{Rek} calculated using equations			
Solute	(9)	(10)	(11)	(12)
Oleic acid	7.664	7.732	7.539	7.486[a]
Elaidic acid	7.664	7.732	7.766	
Ricinoleic acid	6.183	5.987	5.987	7.714[a]
Methyl ricinoleate	6.577	6.403	6.207	
α-Hydroxypalmitic acid	5.375	5.430	5.538	5.971
Methyl α-hydroxypalmitate	5.808	5.798	5.926	6.192
12-Hydroxystearic acid	6.414	6.499	6.489	5.517
Methyl 12-hydroxystearate	6.608	6.774	7.044	5.908
9,10-Dihydroxystearic acid	4.765	4.802	4.884	6.475
Methyl 9,10-dihydroxystearate	5.238	5.334	5.110	7.032
				4.906
				5.134

[a]Predicted log *P* values.

The topological index *A*, in the above equation, the only one being based on distance matrix is the least correlated with $E_{\Sigma\mathrm{OH}}$ ($r = -0.6587$). This means, such an equation can serve to calculate log *P* for oleic and elaidic acids, as well as log *P* values for the remaining acids and their derivatives (see Table 5).

With oleic acid and elaidic acid removed from Eq. (11), a new equation is thus obtained:

$$\log P_{\mathrm{Rek}} = 0.00802(\pm 0.001140) \times A - 0.1847(\pm 0.0177) \times E_{\Sigma\mathrm{OH}} + 3.2031(\pm 0.5994) \qquad (12)$$

$$n = 8; \quad R^2 = 95.62\%; \quad F = 54.6; \quad s = 0.177; \quad P < 0.0005$$

The log *P* values for oleic and elaidic acids predicted from Eq. (12), as well as log *P* values calculated for the remaining compounds tested, are also included in Table 5.

The log *P* values calculated using the new proposed Eqs. (11) and (12) have different values for oleic acid and elaidic acid.

The results from these investigations indicate that some topological indexes are most useful for study of QSPR for the higher fatty acids, hydroxy acids, and their esters. Structural descriptors, namely topological indexes based on distance matrix and adjacency matrix, as well as electrotopological states, can be used for calculation and prediction of partition coefficients of investigated compounds. From the data presented in this work, it is apparent that the topological index A describes additional important elements of chemical structures of investigated compounds not given by the other topological indexes and electrotopological states.

These new methods of calculation of partition coefficients (log P) on the basis of the proposed equations of state broadly supplement well-established methods and applications, i.e., methods of normal measurements in the *n*-octanol–water system. Because of experimental difficulties, including solubility limits, various stabilities, formation of emulsions or impurities of the studied compounds, the evaluation of log P values by the proposed methods from this paper is analytically well-founded.

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