

# Selected Traditional Structural Descriptors and $R_M$ Values for Estimation and Prediction of Lipophilicity of Homologous Series of Saturated Fatty Acids

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**ABSTRACT:** An homologous series of carboxylic FA, from methanoic to triacontanoic, were characterized by selected structural descriptors based on distance matrix ( $W, A, {}^0B, {}^1B$ ), adjacency matrix ( $M, M^v, {}^0\chi, {}^1\chi, {}^2\chi, {}^0\chi^v, {}^1\chi^v, {}^2\chi^v, F, N_2$ ), and information theory ( $I_{SA}, \bar{I}_{SA}$ ) as well as electrotopological states. Saturated FA, from pentanoic to eicosanoic as well as from heptanoic to tricontanoic acids, were separated by reversed-phase high-performance TLC (RP-HPTLC) using mobile phases of methanol/water. The relationships existing between experimental partition coefficients ( $\log P_{exp}$ ), partition coefficients obtained from an Internet database (IAlogP and ClogP<sup>TM</sup>), and  $R_M$  values (obtained by means of RP-HPTLC, where  $R_M$  is the hydrophobicity index) or structural descriptors (based on adjacency matrix:  $M, M^v, {}^0\chi, {}^1\chi, {}^2\chi, {}^0\chi^v, {}^1\chi^v, {}^2\chi^v, F, N_2$  and information theory:  $I_{SA}, \bar{I}_{SA}$ ) of saturated FA were investigated. Comparison and estimation of the usefulness of  $R_M$  values and selected structural descriptors for calculating and predicting partition coefficients of saturated FA are the novel components of the work presented. The authors found that both values for  $R_M$  and structural descriptors can serve for calculating and predicting the partition coefficients of FA investigated; but the selected traditional structural descriptors better describe the partition coefficients than the  $R_M$  values.

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**KEY WORDS:** Homologous series, partition coefficient, regression analysis,  $R_M$  value, RP-HPTLC, saturated fatty acids, structural descriptors.

Saturated as well as unsaturated FA are present mainly as TAG in natural fats and oils. They are also transported as FFA and are present in blood serum. Saturated and unsaturated FA occur in plants and even in bacterial species (1,2). Problems with FA metabolism can cause illness, which often can be detected by measurement of FA concentration (3).

Lipophilicity is one of the parameters of a chemical substance that influences its biological activity. Lipophilicity also can help describe the pharmacodynamic and pharmacokinetic aspects of drug action (4,5).

Lipophilicity is defined by the partition of a compound between a nonaqueous and an aqueous phase. The  $n$ -octanol–water partition coefficient ( $\log P_{exp}$ ) is generally accepted as a useful parameter in quantitative structure-activity relationship studies (QSAR) for the prediction of biological or

pharmacological activity of compounds (6,7). Measurement of partition coefficients is not a simple matter. Measurement of partition coefficients by equilibration methods is frequently difficult owing to the presence of impurities or compound instability, a strong preference of the compound for one of the two phases, or by stable emulsion formation. Practical problems arise for polar and highly lipophilic compounds ( $\log P_{exp} > 4$ ) (4,5). Partition chromatographic techniques (5,8–10) and theoretical methods (4–6,8–16) have been widely used as a reliable alternative to the classical determination of  $\log P_{exp}$ .

We have investigated previously the optimal conditions for the separation of homologous series of saturated FA by reversed-phase high-performance TLC (RP-HPTLC) and described the relationships between physicochemical properties (retention parameters, molar volume, heat of combustion, experimental partition coefficient, resolidification point, refractive index, heat of crystallization, m.p., and b.p.) and structural descriptors (based on distance matrix:  $W, A, {}^0B, {}^1B$ ; adjacency matrix:  $M, M^v, {}^0\chi, {}^1\chi, {}^2\chi, {}^0\chi^v, {}^1\chi^v, {}^2\chi^v, F, N_2$ ; and information theory:  $I_{SA}, \bar{I}_{SA}$  as well as electrotopological states) (17–21).

The aim of this work was to compare  $R_M$  values (where  $R_M$  is the hydrophobicity index) obtained by using RP-HPTLC with selected structural descriptors for calculating and predicting  $n$ -octanol–water partition coefficients of homologous series of saturated FA. The following  $n$ -octanol–water partition coefficients were investigated: (i)  $\log P_{exp}$ , obtained experimentally (15,16); (ii) IAlogP, the theoretical method of calculation of  $n$ -octanol–water partition coefficients based on the set of 238 MolconnZ molecular indices generated from 13,000 organic structures with accurately measured  $\log P$  values. Interactive analysis (IA), using neural networks technology to derive a set of 10-fold cross-validated networks, was used to develop the  $\log P$  predictor (15,16). (iii) ClogP<sup>TM</sup>, which is a theoretical method of calculation of  $n$ -octanol–water partition coefficients based on its estimation of these interactions on the principles defined by Hammett. Not only is ClogP one of the most accurate calculations available, it produces results that are based on established chemical interactions, unlike other programs that are based solely on statistics (15,16).

## EXPERIMENTAL PROCEDURES

**Partition TLC.** The carboxylic acids investigated in this study are listed in Table 1. Solutions of the acids were prepared from analytical-grade chemicals (Larodan Chemicals, Malmö, Swe-

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**TABLE 1**  
**Experimental Values of Octanol–Water Partition Coefficient and  $R_M$**

Acid (symbol of acid)	Partition coefficient			$R_M$ value <sup>a</sup>	
	$\log P_{\text{exp.}}$ <sup>b</sup>	IAlogP <sup>c</sup>	ClogP <sup>d</sup>	$R_{M(95:5)}$ <sup>e</sup>	$R_{M(100\%MeOH)}$ <sup>f</sup>
Methanoic (C1)	-0.54	-0.73	-0.54	—	—
Ethanoic (C2)	-0.17	-0.44	-0.19	—	—
Propanoic (C3)	0.33	0.09	0.34	—	—
Butanoic (C4)	0.79	0.60	0.86	—	—
Pentanoic (C5)	1.39	1.10	1.39	-0.810	—
Hexanoic (C6)	1.92	1.62	1.92	-0.686	—
Heptanoic (C7)	2.42	2.15	2.45	-0.550	-0.602
Octanoic (C8)	3.05	2.68	2.98	-0.436	-0.500
Nonanoic (C9)	3.42	3.22	3.51	-0.310	-0.438
Decanoic (C10)	4.09	3.80	4.04	-0.194	-0.327
Undecanoic (C11)	4.42	4.35	4.57	-0.063	-0.226
Dodecanoic (C12)	4.60	4.91	5.10	0.064	-0.176
Tridecanoic (C13)	—	5.45	5.63	0.194	-0.066
Tetradecanoic (C14)	6.11	5.98	6.15	0.358	0.087
Pentadecanoic (C15)	—	6.50	6.68	0.491	0.222
Hexadecanoic (C16)	7.17	7.00	7.21	0.650	0.368
Heptadecanoic (C17)	—	7.47	7.74	0.857	0.537
Octadecanoic (C18)	8.23	7.91	8.27	0.964	0.635
Nonadecanoic (C19)	—	8.33	8.80	1.187	0.753
Eicosanoic (C20)	9.29	8.71	9.33	1.288	0.899
Heneicosanoic (C21)	—	9.06	8.86	—	1.016
Docosanoic (C22)	—	9.36	10.39	—	1.091
Tricosanoic (C23)	—	9.53	10.51	—	1.180
Tetracosanoic (C24)	—	9.58	11.44	—	—
Pentacosanoic (C25)	—	9.62	11.97	—	—
Hexacosanoic (C26)	—	9.65	12.50	—	—
Heptacosanoic (C27)	—	7.97	13.03	—	—
Octacosanoic (C28)	—	8.03	13.60	—	—
Nonacosanoic (C29)	—	8.07	14.09	—	—
Triacosanoic (C30)	—	8.10	14.62	—	—

<sup>a</sup> $R_M$  = hydrophobicity index, a parameter used to describe the suitability of reversed-phase high-performance TLC as a method for determining the lipophilic character of compounds.

<sup>b</sup> $\log P$  was obtained experimentally (15,16).

<sup>c</sup> $\log P$  was developed by Interactive Analysis, using neural working technology to derive a set of 10-fold cross-validated networks (15,16).

<sup>d</sup> $\log P$  was calculated using ClogP method (15,16).

<sup>e</sup> $R_M$  values were obtained as a result of experiment by using methanol/water, 95:5 (vol/vol) as the mobile phase.

<sup>f</sup> $R_M$  values were obtained as a result of experiment using 100% methanol as the mobile phase.

den). Analytical-grade methanol was obtained from Polish Chemical Reagents (Gliwice, Poland).

RP-HPTLC was performed on  $10 \times 20$  cm glass-backed RP-18 HPTLC plates without a concentrating zone (#1.05914; Merck, Darmstadt, Germany). Solutions of the acids, 20  $\mu\text{g}$  in 5  $\mu\text{L}$  chloroform, were spotted on the plates. The plates were developed at room temperature in a classical flat-bottomed chamber (#022.5250; Camag, Muttenz, Switzerland) that had been saturated in advance for 30 min. The development distance was 7.5 cm. The mobile phases were: methanol/water, 95:5 (vol/vol), and 100% methanol. The substances analyzed were visualized in iodine vapor. The chromatograms were run in triplicate.  $R_F$  values were measured and converted to  $R_M$  values according to Equation 1:

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

where  $R_F$  is the retardation factor, that is, the ratio of the distance covered by the center of the spot to the distance simultaneously covered by the mobile-phase front.

**Structural descriptors.** The Rouvray-Crafford (R) (22), Wiener (W) (22), Pyka (A, <sup>0</sup>B, <sup>1</sup>B) (23), Gutman (M, M<sup>v</sup>) (22), Randić (<sup>0</sup> $\chi$ , <sup>1</sup> $\chi$ , <sup>2</sup> $\chi$ , <sup>0</sup> $\chi^v$ , <sup>1</sup> $\chi^v$ , <sup>2</sup> $\chi^v$ ) (21), Platt (F) (22), and Scantlebury (N<sub>2</sub>) (22) indexes and the indexes based on information theory ( $I_{SA}$ ,  $\bar{I}_{SA}$ ) (22) as well as the electrotopological states (16,22) were calculated for the acids investigated. The Wiener, Rouvray-Crafford, and Pyka indexes were calculated by building the distance matrix and determining its elements by means of values given by Barysz *et al.* (24). The electrotopological states (dssC, dO, sOH) were obtained from Internet data (16).

## RESULTS AND DISCUSSION

Experimental *n*-octanol–water partition coefficients values (15,16) as well as theoretical *n*-octanol–water partition coefficient values obtained from an Internet database (15,16) are presented in Table 1.  $R_M$  values obtained by RP-HPTLC also are listed in Table 1.

The relationships between *n*-octanol–water partition coefficient (experimental  $\log P_{\text{exp}}$ , as well as theoretical calculated

**TABLE 2**  
**Functions Describing Relationships Between Log  $P$  and Structural Descriptors<sup>a</sup>**

Structural descriptors ( $I_i$ )	$\log P_{\text{exp}}^b$		IAlogP <sup>c</sup>		ClogP <sup>d</sup>	
	Function	Determination coefficient $R^2$ (%)	Function	Determination coefficient $R^2$ (%)	Function	Determination coefficient $R^2$ (%)
R	P3rd <sup>h</sup>	97.80	$P^f$	96.01	$P^f$	99.04
W	P3rd <sup>h</sup>	97.80	$P^f$	95.97	$P^f$	99.04
<sup>0</sup> B	No correlation		P2nd <sup>g</sup>	73.21	No correlation	
A	P3rd <sup>h</sup>	98.88	$P^f$	96.08	$P^f$	<b>99.07</b>
<sup>1</sup> B	P3rd <sup>h</sup>	96.45	P3rd <sup>h</sup>	98.38	$P^f$	<b>99.24</b>
M	L <sup>e</sup>	<b>99.52</b>	P2nd <sup>g</sup>	<b>99.13</b>	L <sup>e</sup>	<b>99.90</b>
M <sup>v</sup>	L <sup>e</sup>	<b>99.52</b>	P2nd <sup>g</sup>	<b>99.13</b>	L <sup>e</sup>	<b>99.90</b>
<sup>0</sup> $\chi$	L <sup>e</sup>	<b>99.75</b>	P3rd <sup>h</sup>	<b>99.98</b>	L <sup>e</sup>	<b>99.96</b>
<sup>1</sup> $\chi$	L <sup>e</sup>	<b>99.81</b>	P3rd <sup>h</sup>	<b>99.99</b>	L <sup>e</sup>	<b>99.97</b>
<sup>2</sup> $\chi$	L <sup>e</sup>	<b>99.56</b>	P3rd <sup>h</sup>	<b>99.93</b>	L <sup>e</sup>	<b>99.92</b>
<sup>0</sup> $\chi^v$	L <sup>e</sup>	<b>99.72</b>	P3rd <sup>h</sup>	<b>99.98</b>	L <sup>e</sup>	<b>99.95</b>
<sup>1</sup> $\chi^v$	L <sup>e</sup>	<b>99.75</b>	P3rd <sup>h</sup>	<b>99.99</b>	L <sup>e</sup>	<b>99.96</b>
<sup>2</sup> $\chi^v$	L <sup>e</sup>	<b>99.79</b>	P3rd <sup>h</sup>	<b>99.99</b>	L <sup>e</sup>	<b>99.97</b>
F	P2nd <sup>g</sup>	<b>99.59</b>	P3rd <sup>h</sup>	<b>99.95</b>	L <sup>e</sup>	<b>99.84</b>
N <sub>2</sub>	P2nd <sup>g</sup>	<b>99.59</b>	P3rd <sup>h</sup>	<b>99.95</b>	L <sup>e</sup>	<b>99.84</b>
I <sub>SA</sub>	P2nd <sup>g</sup>	<b>99.81</b>	P3rd <sup>h</sup>	<b>99.98</b>	L <sup>e</sup>	<b>99.84</b>
I <sub>SA</sub>	P3rd <sup>h</sup>	<b>99.62</b>	P3rd <sup>h</sup>	<b>99.68</b>	P3rd <sup>h</sup>	<b>99.55</b>
dssC	P2nd <sup>g</sup>	44.85	P2nd <sup>g</sup>	49.10	No correlation	
dO	P3rd <sup>h</sup>	97.50	P3rd <sup>h</sup>	<b>99.04</b>	P3rd <sup>h</sup>	96.08
sOH	P3rd <sup>h</sup>	97.47	P3rd <sup>h</sup>	<b>99.02</b>	P3rd <sup>h</sup>	96.02

<sup>a</sup>Values presented in boldface have determination coefficients  $R^2 > 99\%$ .

<sup>b-d</sup>For definitions of these terms see Table 1.

<sup>e</sup>Linear function:  $\log P = a(I_i) + b$ .

<sup>f</sup>Power function:  $\log P = a(I_i)^b$ .

<sup>g</sup>Polynomial of second degree:  $\log P = a(I_i)^2 + b(I_i) + c$ .

<sup>h</sup>Polynomial of third degree:  $\log P = a(I_i)^3 + b(I_i)^2 + c(I_i) + d$ .

*n*-octanol–water partition coefficients: IAlogP and ClogP) values and structural descriptors were investigated. The relationship between experimental  $\log P_{\text{exp}}$  values, obtained from the literature (16), for many of the saturated acids from methanoic to eicosanoic, except acids C13, C15, C17, and C19, and structural descriptors were analyzed. The relationships obtained were described by second- or third-degree polynomials and by linear functions (Table 2). Correlations for relationships between  $\log P_{\text{exp}}$  and topological index <sup>0</sup>B as well as between  $\log P_{\text{exp}}$  and electrotopological state of the carbon atom of the carboxylic group (dssC) were not found. Correlation equations with the highest values for the correlation coefficients were obtained with all indexes based on the adjacency matrix and also with the index of atomic composition and index of average atomic composition ( $R^2 > 99\%$ ).

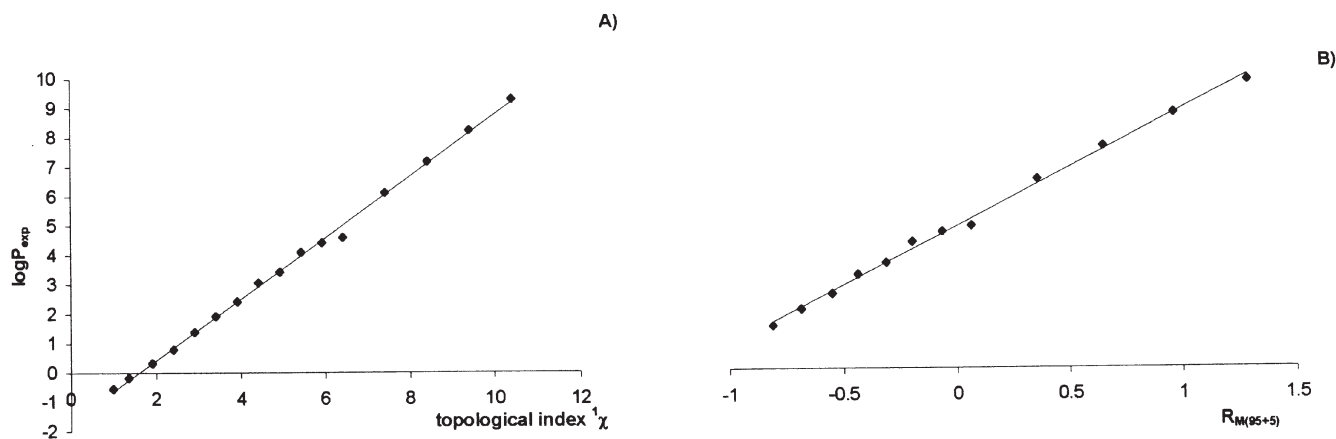
The relationships between IAlogP and structural descriptors were analyzed and are described for acids from methanoic to hexacosanoic in Table 2. Heptacosanoic, octacosanoic, nonacosanoic, and triacontanoic acids were not taken into consideration because the values of  $\log P$  for these acids were significantly different from the values calculated for the rest of the acids. The relationships between IAlogP and structural descriptors are presented in Table 2, in the case of topological indexes R, W, and A by a power function and by second- or third-degree polynomials in the case of the rest of the structural descriptors (Table 2). Regression equations with the highest correlation coefficients were obtained for relationships with all indexes based on the adjacency matrix, index of atomic composition, and index of average atomic composition, as well

as with the electrotopological state of the oxygen atom from the hydroxide group (dO and sOH) ( $R^2 > 99\%$ ).

The relationships between ClogP values and structural descriptors for acids from methanoic to triacontanoic also were investigated. These relationships are described either by a power function, by third-degree polynomials, or by linear functions (Table 2). In the case of topological index <sup>0</sup>B as well as the electrotopological state of the carbon atom of the carboxylic group, no correlation was found. Regression equations with correlation coefficients close to 1.0 were obtained for relationships with indexes based on the adjacency matrix and index of atomic composition, as well as the index of average atomic composition. For all mentioned relationships,  $R^2 > 99\%$ .

For comparison, the  $R_M$  values were used as experimental structural descriptors for calculating partition coefficients of the saturated FA investigated. Pentanoic to eicosanoic acids were separated by means of RP-HPTLC using RP-18 plates without a concentrating zone and with a mobile phase of methanol/water, 95:5 (vol/vol). Heptanoic to tricosanoic acids were separated on RP-18 plates without a concentrating zone using 100% methanol. For separation of short-chain ethanoic to butanoic FA and long-chain tetracosanoic to triacontanoic FA, the RP-HPTLC method used was not effective. Relationships between all partition coefficients ( $\log P_{\text{exp}}$ , IAlogP, and ClogP) and  $R_M$  values were described by a linear function. However, the relationship between IAlogP and  $R_{M(100\%MeOH)}$  is best described by a second-degree polynomial equation.  $R_{M(100\%MeOH)}$  values better describe IAlogP than  $R_{M(95:5)}$  values.

On the basis of correlation equations (Table 2), there exists



**FIG. 1.** Relationship between experimental  $\log P_{\text{exp}}$  and (A) topological index  ${}^1\chi$  for acids from methanoic to eicosanoic, except acids C13, C15, C17, and C19; and (B)  $R_{M(95:5)}$  values for acids from pentanoic to eicosanoic, except acids C13, C15, C17, and C19.

the possibility of calculating the partition coefficient values for the saturated FA investigated. These equations describe the relationship between partition coefficients ( $\log P_{\text{exp}}$ , IAllogP, and ClogP) and indices based on adjacency matrix, index of atomic composition or index of average atomic composition, and  $R_M$  values. The relationships between  $\log P_{\text{exp}}$  values of FA investigated and topological index  ${}^1\chi$  as well as  $R_{M(95:5)}$  values are presented in Figures 1A and 1B, respectively. Equations describing these relationships are as follows:

$$\log P_{\text{exp}} = 1.042 (\pm 0.012)({}^1\chi) - 1.653 (\pm 0.069) \quad [2]$$

$n = 16 \quad R^2 = 99.90\% \quad F = 7398 \quad s = 0.13 \quad P < 0.001$

$$\log P_{\text{exp}} = 3.784 (\pm 0.068)R_{M(95:5)} + 4.589 (\pm 0.044) \quad [3]$$

$n = 12 \quad R^2 = 99.67\% \quad F = 3058 \quad s = 0.15 \quad P < 0.001$

There are no data in the literature concerning the experimental coefficients in an *n*-octanol–water system for tridecanoic acid (C13), pentadecanoic acid (C15), heptadecanoic acid (C17), and nonadecanoic acid (C19). On the basis of Equation 2,  $\log P$  values for these acids are predicted to be 5.55 for C13, 6.92 for C15, 7.63 for C17, and 8.68 for C19. However, the  $\log P_{\text{exp}}$  values predicted on the basis of  $R_M$  values (Eq. 3) for tride-

canoic, pentadecanoic, heptadecanoic, and nonadecanoic acids are 5.32, 6.45, 7.83, and 9.08, respectively.

The relationships between the IAllogP values for the FA investigated and topological index  ${}^2\chi^v$ , as well as  $R_{M(100\%MeOH)}$  values, are presented in Figures 2A and 2B, respectively. Equations describing these relationships are as follows:

$$\text{IAllogP} = -0.0179 (\pm 0.0005)({}^2\chi^v)^3 + 0.1776 (\pm 0.0074)({}^2\chi^v)^2 + 1.0136 (\pm 0.0284)({}^2\chi^v) - 0.7855 (\pm 0.0290) \quad [4]$$

$n = 26 \quad R^2 = 99.99\% \quad s = 0.04 \quad F = 159384 \quad P < 0.001$

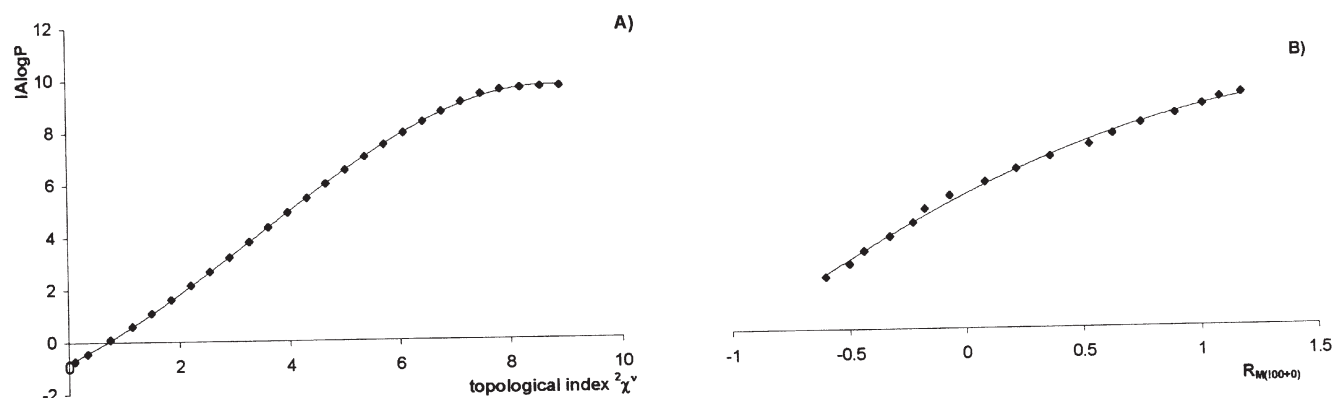
$$\text{IAllogP} = 5.502 (\pm 0.051) + 4.718 (\pm 0.099)R_{M(100\%MeOH)}^2 - 1.182 (\pm 0.133) \quad [5]$$

$n = 17 \quad R^2 = 99.65\% \quad F = 2257 \quad s = 0.14 \quad P < 0.001$

The relationship between the ClogP values of FA investigated and topological index  ${}^2\chi^v$  as well as  $R_{M(95:5)}$  values are presented in Figures 3A and 3B, respectively. Equations describing these relationships are as follows:

$$\text{ClogP} = 1.486 (\pm 0.005)({}^2\chi^v) - 0.797 (\pm 0.030) \quad [6]$$

$n = 30 \quad R^2 = 99.98\% \quad F = 91795 \quad s = 0.08 \quad P < 0.001$



**FIG. 2.** Relationship between IAllogP and (A) topological index  ${}^2\chi^v$  for acids from methanoic to hexacosanoic; and (B)  $R_{M(100\%MeOH)}$  values for acids from heptanoic to tricosanoic.

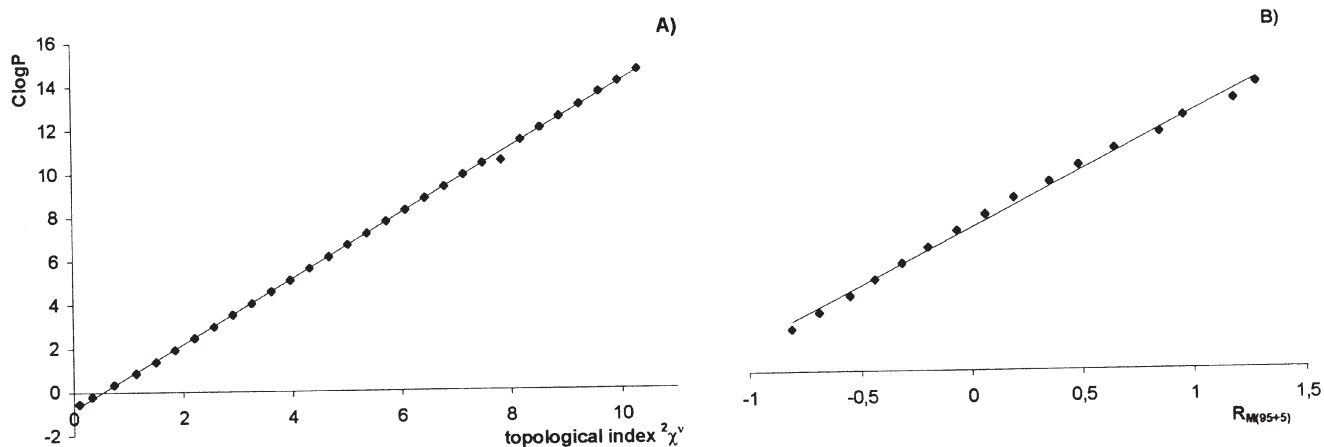


FIG. 3. Relationship between ClogP and (A) topological index  ${}^2\chi^v$  for acids from methanoic to triacontanoic; and (B)  $R_{M(95:5)}$  values for acids from pentanoic to eicosanoic.

$$\text{ClogP} = 3.744 (\pm 0.068) R_{M(95:5)} + 4.658 (\pm 0.046) \quad [7]$$

$n = 16 \quad R^2 = 99.53\% \quad F = 2986 \quad s = 0.18 \quad P < 0.001$

$$\text{ClogP} = 3.725 (\pm 0.072) R_{M(95:5)} + 4.672 (\pm 0.049) \quad [13]$$

$n = 15 \quad R^2 = 99.51\% \quad F = 2663 \quad s = 0.18 \quad P < 0.001$

The relationships between  $\log P_{\text{exp}}$ , IAllogP, ClogP, and the rest of the topological indexes investigated based on adjacency matrix, index of atomic composition, and index of average atomic composition are described also by statistically significant correlation equations similar to Equations 2, 4, and 6.

Values of partition coefficient can be predicted by omitting heptanoic acid in correlation equations. Correlation Equations 2–7 were recalculated and, for example, the values of  $\log P_{\text{exp}}$ , IAllogP, and ClogP were predicted. These equations for  $\log P_{\text{exp}}$  are as follows:

$$\log P_{\text{exp}} = 1.04 (\pm 0.013) ({}^1\chi) - 1.652 (\pm 0.073) \quad [8]$$

$n = 15 \quad R^2 = 99.81\% \quad F = 6803 \quad s = 0.14 \quad P < 0.001$

$$\log P_{\text{exp}} = 3.772 (\pm 0.073) R_{M(95:5)} + 4.598 (\pm 0.0475) \quad [9]$$

$n = 11 \quad R^2 = 99.66\% \quad F = 2639 \quad s = 0.16 \quad P < 0.001$

The equations for IAllogP are as follows:

$$\text{IAllogP} = -0.018 (\pm 0.0001) ({}^2\chi^v)^3 + 0.179 (\pm 0.008) ({}^2\chi^v)^2 + 1.008 (\pm 0.029) ({}^2\chi^v) - 0.784 (\pm 0.029) \quad [10]$$

$n = 25 \quad R^2 = 99.99\% \quad s = 0.04 \quad F = 155830 \quad P < 0.001$

$$\text{IAllogP} = 5.501 (\pm 0.051) + 4.668 (\pm 0.123) R_{M(100\% \text{MeOH})} - 1.130 (\pm 0.154) R_{M(100\% \text{MeOH})}^2 \quad [11]$$

$n = 16 \quad R^2 = 99.56\% \quad s = 0.10 \quad F = 1763 \quad P < 0.001$

The equations for ClogP are as follows:

$$\text{ClogP} = 1.486 (\pm 0.005) ({}^2\chi^v) - 0.795 (\pm 0.031) \quad [12]$$

$n = 29 \quad R^2 = 99.97\% \quad F = 85978 \quad s = 0.08 \quad P < 0.001$

The values of  $\log P_{\text{exp}}$ , IAllogP, and ClogP obtained from the literature and predicted on the basis of Equations 8–13 are compared in Table 3.

As might be expected, the partition coefficients ( $\log P_{\text{exp}}$ , IAllogP, and ClogP) for heptanoic acid predicted by use of Equations 8, 10, and 12 are more accurate than those predicted by use of Equations 9, 11, and 13. Thus, the topological indexes based on adjacency matrix and information theory better describe the partition coefficients ( $\log P_{\text{exp}}$ , IAllogP, and ClogP) of investigated FA than  $R_M$  values obtained using RP-HPTLC.

The examples just presented show that the possibility exists of calculating and predicting values of FA partition coefficients on the basis of relationships obtained by topological indexes values or  $R_M$  values obtained by RP-HPTLC.

For this purpose, topological indices based on the adjacency matrix ( $M, M^v, {}^0\chi, {}^1\chi, {}^2\chi, {}^0\chi^v, {}^1\chi^v, {}^2\chi^v, F, N_2$ ) and index of atomic composition ( $I_{SA}$ ) as well as index of average atomic composition ( $\bar{I}_{SA}$ ) performed best. The strong correlation between topological indices and partition coefficients probably arises from the fact that both are additive quantities. The equations that relate partition coefficients to  $R_M$  values have some limitations because correlation equations  $\log P = f(R_M)$  use a smaller number of measurement points as a basis. However, in using RP-HPTLC, FA from pentanoic to tricosanoic can be separated.

The possibility of predicting physicochemical properties of chemical compounds, including  $\log P$ , is important because the experimental  $\log P$  values are estimated, in many cases for impure substances. Another problem is that sometimes during experimental estimation of the partition coefficient, an emulsion can be formed, which also can change the results. That is why prediction of  $\log P$  values from topological indices would be a desirable alternative to experimental estimation.



**TABLE 3**  
**Predicted Log *P* Values for Heptanoic Acid**

Partition coefficient	Structural descriptors or $R_M$ value	Value obtained from literature	Predicted log <i>P</i> for heptanoic acid using equation	$\Delta \log P^a$
log $P_{\text{exp}}$	$^1\chi$	2.42	2.42 (Eq. 8)	0.00
	$R_{M(95+5)}$	2.42	2.52 (Eq. 9)	-0.10
lAlogP	$^2\chi^v$	2.15	2.12 (Eq. 10)	0.03
	$R_{M(100\% \text{MeOH})}$	2.15	2.28 (Eq. 11)	-0.13
ClogP	$^2\chi^v$	2.45	2.48 (Eq. 12)	-0.03
	$R_{M(95:5)}$	2.45	2.62 (Eq. 13)	-0.17

<sup>a</sup> $\Delta \log P$  = the difference between the log *P* value obtained from the literature and the predicted value.

## REFERENCES

- Carballeira, N.M., A. Guzman, J.T. Nechev, K. Lahtchev, A. Ivanova, and K. Stefanov, Unusual Lipid Composition of a *Bacillus* sp. Isolated from Lake Pomorie in Bulgaria, *Lipids* 35:1371–1375 (2000).
- Carballeira, N.M., C. Miranda, C.M. Lozano, J.T. Nechev, A. Ivanova, M. Ilieva, I. Tzvetkova, and K. Stefanov, Characterization of Novel Methyl-Branched Chain Fatty Acids from a Halophilic *Bacillus* Species, *J. Nat. Prod.* 64:256–259 (2001).
- Murray, R.K., D.K. Granner, P.A. Mayes, and V.W. Rodwell, *Harper's Biochemistry* (in Polish), Wydawnictwo Lekarskie PZWL, Warsaw 1995, pp. 131–335.
- Kubinyi, H., The Quantitative Analysis of Structure–Activity Relationships, in *Burger's Medicinal Chemistry and Drug Discovery. Principles and Practice*, 5th edn., edited by M.E. Wolff, John Wiley & Sons, 1995, Vol. 1, pp. 497–571.
- Józwiak, K., H. Szumiło, and E. Soczewiński, Lipophilicity, Methods and Determination and Role in Biological Effect of Chemical Substances, *Wiad. Chem.* (in Polish) 55:1047–1074 (2001).
- Mannhold, R., and R.F. Rekker, The Hydrophobic Fragmental Constant Approach for Calculating log *P* in Octanol–Water and Aliphatic Hydrocarbon/Water Systems, *Perspect. Drug Discovery Des.* 18:1–18 (2000).
- Rekker, R.F., and R. Mannhold, *Calculation of Drug Lipophilicity*, VCH, Weinheim, 1992, pp. 2–104.
- Kwietniewski, L., M. Janicka, and J.K. Różyło, The Effect of Mobile Phase Composition on Solute Retention in Reversed-Phase Planar Chromatography, *J. Planar Chromatogr. Mod. TLC* 11:350–352 (1998).
- Kastner, P., J. Klimes, P. Velenovska, and V. Klimesova, Study of Lipophilicity of Potential Antituberculous Compounds by Reversed-Phase Thin-Layer Chromatography, *Ibid.* 15:200–203 (2002).
- Dross, K., R.F. Rekker, G. de Vries, and R. Mannhold, The Lipophilic Behaviour of Organic Compounds: 3. The Search for Interconnections Between Reversed-Phase Chromatographic Data and log  $P_{\text{oct}}$  Values, *Quant. Struct.-Act. Relat.* 18:549–557 (1999).
- Hansch, C., and A.J. Leo, *Substituent Constants for Correlation Analysis in Chemistry and Biology*, John Wiley, New York 1979, pp. 2–132.
- Meylan, W.M., and P.H. Howard, Atom/Fragment Contribution Method for Estimating Octanol–Water Partition Coefficients, *J. Pharm. Sci.* 84:83–92 (1995).
- Tetko, I.V., V. Yu. Tanchuk, and L. Lai, Application of Associative Neural Networks for Prediction of Lipophilicity in ALOGPS 2.1 Program, *J. Chem. Inf. Comput. Sci.* 42:1136–1145 (2002).
- Wang, R., Y. Fu, and L. Lai, A New Atom-Additive Method for Calculating Partition Coefficients, *Ibid.* 37:615–621 (1997).
- Tetko, I.V., and V. Yu. Tanchuk, Virtual Computational Chemistry Laboratory, VCC-lab 2002, <http://146.107.217.178/servlets/vcclab?action=alogps> (accessed September 2003)
- Interactive Analysis log *P* Predictors, <http://www.logp.com> (accessed January 2002).
- Pyka, A., and K. Bober, Investigation of Homologous Series of Fatty Acids by TLC. Part I. Comparison of Separations of Fatty Acids on RP-18 Plates With and Without Concentrating Zone, *J. Planar Chromatogr. Mod. TLC* 15:332–340 (2002).
- Pyka, A., and K. Bober, Selected Structural Descriptors and  $R_M$  Values for Calculation and Prediction of Molar Volume of Homologous Series of Saturated Fatty Acids, *Indian J. Chem. Sec. A* 42A:1360–1367 (2003).
- Pyka, A., and K. Bober, Investigation of an Homologous Series of Fatty Acids by TLC. Part II. Comparison of Separations of Fatty Acids on RP-18 Plates with Different Mobile Phases, *J. Liq. Chromatogr. Rel. Technol.* 26:2663–2671 (2003).
- Pyka, A., and K. Bober, Investigation of a Homologous Series of Fatty Acids by TLC. Part III. Application of Terms Describing the Separation of Homologous Series of Saturated Fatty Acids in TLC, *J. Planar Chromatogr. Mod. TLC* 16:303–307 (2003).
- Pyka, A., and K. Bober, Structural Descriptors in Evaluation of Selected Physicochemical Properties of Fatty Acids, *Riv. Ital. Sostanze Grasse* 81:231–238 (2004).
- Devillers, J., and A.T. Balaban, *Topological Indices and Related Descriptors in QSAR and QSPR*, Gordon and Breach, Amsterdam, 1999, pp. 21–562.
- Pyka, A., Correlation of Topological Indices with the Chromatographic Separation of Isomers, *J. Planar Chromatogr. Mod. TLC* 4:316–318 (1991).
- Barysz, M., G. Jashari, R.S. Hall, V.K. Srivastava, and N. Trinajstić, On the Distance Matrix of Molecules Containing Heteroatoms. Chemical Applications of Topology and Graph Theory, *Stud. Phys. Theor. Chem.* 28:222–230 (1983).

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