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A Comparative Study of the Molecular Lipophilicity Indices of Vitamins A and E, and of Some Precursors of Vitamin A, Estimated by HPLC and by Different Computation Methods

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Summary. Lipophilicity indices for vitamins A and E, and for some precursors of vitamin A, have been determined for the first time by reversed-phase high-performance liquid chromatography (RPHPLC) on C_{18} and C_8 columns. For each column the mobile phases were methanol–water mixtures with methanol in volume proportions from 86 to 90% (*v*/*v*) in 1% steps. The regression correlation coefficients obtained for both stationary phases were excellent (usually >0.999). To compare the experimental lipophilicity estimated for the compounds by use of $\log k'_w$, S, φ_0, the means of k' and $\log k'$, and the scores of k' and $\log k'$ corresponding to the first principal component, and $\log P$ values calculated by use of different computer software a correlation matrix was constructed. Better correlations were obtained in both cases between the mean of k' and the mean of $\log k'$, and scores corresponding to the first principal component obtained by applying principal-components analysis to the matrix of retention factors and computed $\log P$ values. The best correlations were found between the mean of k' and scores corresponding to the first principal component determined on C_8 and most of the computed $\log P$ values.

Key Words: vitamins, carotenoids, lipophilicity, lipophilicity indices, HPLC, PCA

Introduction

The lipophilic vitamins are a group of organic substances required to regulate the proper functioning of cells. Vitamin A affects many physiologic processes, including growth, reproduction, and the immune response. High doses of vitamin A and other retinoids have serious effects, including teratogenicity, chronic toxicity, and acute hypervitaminosis [1, 2]. The biological activity of carotenoids includes enhancement of the immune response, reduction of photoinduced or chemically induced neoplasm, reduced mutagenesis and sister-chromatid exchange, reduced cellular transformation, and inhibited micronuclei formation in epithelial cells [3, 4]. Vitamin E plays a role in counteracting the biological effects of oxyradicals and seems to be essential for maintenance of a normal neurological structure and function [5, 6].

The partition coefficients of compounds between octanol and water, K_{ow}, are extensively used in the biological, biochemical, and environmental sciences as descriptors of lipophilic character [7]. Lipophilicity can be determined experimentally, by use of a variety of methods, and/or computed by use of fairly elaborate algorithms. The successful use of partition coefficients in quantitative structure–activity relationships (QSAR), quantitative structure–property relationships (QSPR), and quantitative structure–retention relationships (QSRR) is well established [8–10]. The compatibility of experimental and theoretical approaches to the determination of the lipophilicity of organic compounds remains a focus of scientific interest [7–11].

Reverse-phase high-performance liquid chromatography (RPHPLC) has been used in recent decades for indirect determination of K_{ow} as a measure of the lipophilicity of compounds [7, 10]. This technique has significant advantages over the classical 'shake-flask' method: consumption of the investigated compounds is minimal; high-purity chemicals and additional analytical quantification are not required; and retention time only must be determined [12–14]. In many scientific papers concerned with the biological activity of compounds, the scientists operate with computed lipophilicities only (denoted in this paper by log P). For vitamins only two values of log K_{ow} (determined by the 'shake-flask' method) are reported in the literature – 6.30 for retinoic acid and 5.68 for retinol [15].

The objective of this work was to analyze and compare experimental lipophilicities estimated by use of chromatographic retention indices (log k'_w, S, φ_0, the means of k' and log k', and the scores corresponding to the first principal components of k' and log k') and computed log P values of the compounds obtained by use of different software.

Theory

Methods

Reverse-phase high-performance liquid chromatography (RPHPLC) can furnish a variety of indices (descriptors) that can be used to estimate lipophilicity. The most popular lipophilicity indices measured by RPHPLC are derived from the retention time, t_R, by use of the Soczewiński–Wachtmeister equation:

$$\log k' = \log k'_w - S\varphi \quad (1)$$

where
$$\log k' = \log\left(\frac{t_R - t_0}{t_0}\right) \quad (2)$$

and t_0 is the retention time of an unretained solute. k'_w refers to the isocratic k' value for pure water as mobile phase, and is usually an extrapolated value, S is related to the solvent strength of pure organic modifier as mobile phase and is specific to the solvent and stationary phases used, and φ is the volume fraction of the organic solvent in the mobile phase [16–18].

Another recently introduced retention-related quantity is the isocratic chromatographic hydrophobicity index, φ_0. According to Valkó the φ_0 value represents the volume fraction of the organic solvent in the mobile phase for which the amount of solute in the mobile phase is equal to that in the stationary phase, i.e. the retention factor is 1 ($\log k' = 0$), i.e. $\varphi_0 = \log k'_w / S$ [19, 20]. In addition, we also used the lipophilicity scale obtained by applying principal-components analysis (PCA) directly to the matrix retention data (k' and $\log k'$) obtained for all the compounds and combinations of methanol and water. The scores corresponding to the first principal component seem to be one of the best solutions for the lipophilicity scale resulting from retention data [21–23].

log *P*

All the molecules were drawn in Hyperchem [24] and optimized using the MM+ molecular mechanics force field. The optimized geometries were loaded into Alchemy 2000 [25], Chem3D Ultra 8.0 [26], and Dragon Plus version 5.4 [27] software to calculate different log *P* values. We derived a set of 21 log *P* values of which four were given by Dragon 5.4 ($MLogP^1$ – Moriguchi method, $MLogP^2$ – squared Moriguchi method, $ALogP^1$ – Ghose-Crippen method, $ALogP^2$ – Squared Ghose-Crippen method), two by Alchemy (AILogPc, AILogP), four by ChemDraw Ultra 8.0 ($LogP^1$ – Crippen method, $LogP^2$ – Viswanadhan method, $LogP^3$ – Broto method, ClogP). Eleven values calculated by applying different algorithms (fragmental methods, atomistic methods) were obtained by using the internet module ALOGP-vcclab [28, 29] (ALogPs, ACLogP, AB/LogP, COSMOFraq, miLogP, ALogP, MLogP, K_{ow}WIN, $XLogP^2$, $XLogP^3$, AverageLogP). The calculated values of log *P* are listed in *Table I*.

Table I. Log *P* values calculated by use of different software

Log P	Lutein	Astaxanthin	Zeaxanthin	Retinol	Retinoic acid	9-*cis*-retinal	All-*trans* retinal	α-Tocopherol	γ-Tocopherol	δ-Tocopherol
LogP[1]	8.51	6.57	8.22	4.69	4.65	4.38	4.38	9.98	9.49	9.00
LogP[2]	8.69	6.85	8.37	4.62	4.73	4.32	4.32	9.60	9.13	8.67
LogP[3]	8.80	6.83	9.12	4.75	5.13	5.25	5.25	10.59	10.17	9.76
ClogP	11.23	8.84	11.06	6.40	6.74	6.38	6.38	12.05	11.60	11.2
AILogPc	2.64	2.53	2.64	3.10	3.12	3.05	3.05	2.69	2.76	2.82
AILogP	7.57	7.57	7.57	3.77	3.78	3.69	3.83	5.88	6.21	6.48
MLogP[1]	7.06	5.27	7.06	4.53	4.38	4.45	4.45	6.24	6.04	5.84
MLogP[2]	49.84	27.82	49.84	20.53	19.18	19.79	19.79	38.90	36.50	34.15
ALogP[1]	9.46	8.35	9.52	5.32	5.53	5.57	5.57	10.42	9.93	9.44
ALogP[2]	89.60	69.80	90.72	28.27	30.53	31.06	31.06	108.48	98.59	89.17
ALogPs	8.29	7.40	8.10	6.38	5.66	6.52	6.52	8.84	8.81	8.76
ACLogP	10.91	9.78	10.83	5.84	5.44	6.16	6.16	10.45	10.13	9.82
AB/LogP	10.00	9.13	10.00	6.36	6.55	6.45	6.45	10.00	10.00	9.82
COSMOFraq	12.63	10.12	12.07	6.55	6.04	7.22	7.22	11.48	10.94	10.36
miLogP	9.31	8.6	9.28	5.92	5.80	6.10	6.10	9.04	8.98	8.60
ALogP	9.47	8.35	9.32	5.32	5.53	5.51	5.51	10.42	9.93	9.44
MLogP	7.06	5.28	6.89	4.53	4.38	4.67	4.67	6.24	6.04	5.84
K_{ow}WIN	14.82	13.27	14.50	7.62	7.85	7.82	7.82	12.18	11.63	11.08
XLogP[1]	7.93	6.58	6.76	4.15	4.24	4.47	4.47	9.95	9.73	9.50
XLogP[2]	11.01	10.27	10.36	5.68	6.30	6.46	6.46	10.70	10.33	9.97
AverageLogP	10.14	8.88	9.81	5.83	5.78	6.14	6.14	9.93	9.65	9.32

Experimental

Lutein, astaxanthin, 9-*cis*-retinal, all-*trans*-retinal, and δ-tocopherol were obtained from Sigma (Redox, Bucharest, Romania), zeaxanthin, retinol, and retinoic acid were from Fluka (Redox, Bucharest, Romania), and α and γ-tocopherols were from Acros Organics (Redox, Bucharest, Romania) (*Fig. 1*).

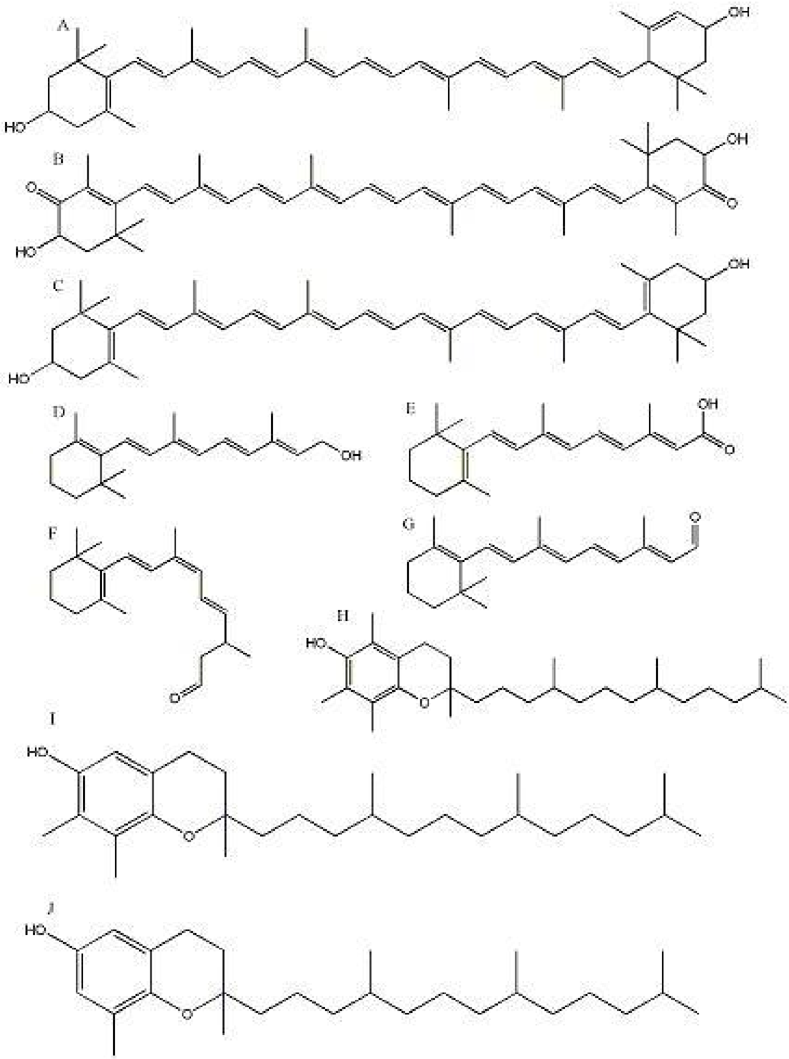

Fig. 1. Chemical structures of some vitamin A precursors (A, lutein; B, astaxanthin; C, zeaxanthin), A vitamins (D, retinol; E, retinoic acid; F, 9-*cis*-retinal; G, all-*trans*-retinal), and E vitamins (H, α-tocopherol; I, γ-tocopherol; J, δ-tocopherol)

Diethyl ether and methanol were obtained from POCh (Gliwice, Poland). Water was purified by use of a Millipore Waters (Milford, MA, USA) Milli-Q system. All chemicals were of analytical grade purity. Standard solutions (10 µg mL^{-1}) were prepared in diethyl ether.

Chromatography was performed with an Agilent 1100 Series LC system consisting of a vacuum degassing unit, a binary high-pressure pump, a standard automatic sample injector, a column thermostat, and a diode-array detector (DAD). The system was connected to an 1100 MSD mass spectrometer. The chromatographic behavior of the compounds was studied on C_{18} (3 mm × 125 mm, 5-µm particle size, LiChroCART, Purosphere RP-18e) and C_8 (4.6 mm × 150 mm, 5-µm particle size, Zorbax, Eclipse XDB-C8) columns. The mobile phases were mixtures of methanol and water containing methanol in volume proportions from 86 to 90% (v/v) in 1% steps. This range of the methanol volume fraction was optimum for all the compounds investigated with regard to retention time. Even in such a narrow range of methanol content the retention time of δ-tocopherol, for example, varied from 5 to 23 min. The flow rate of 1 mL min^{-1}.

Table II. The ions used for SIM

No.	Compound.	Molecular weight	Ions
1	Lutein	568.887	391, 551, 552
2	Astaxanthin	596.854	391, 551, 597
3	Zeaxanthin	568.887	391, 392, 279
4	Retinol	286.457	181, 269, 285
5	Retinoic acid	300.443	300, 301
6	9-*cis*-Retinal	284.444	161, 285, 286
7	All-*trans*-retinal	284.444	161, 285, 286
8	α-Tocopherol	430.715	430, 431
9	γ-Tocopherol	416.691	416, 417
10	δ-Tocopherol	602.664	402, 403

The injection volume was 10 µL. The temperature was kept constant at 25°C. Because some of the compounds do not adsorb in the UV range, detection was performed by mass spectrometry in selected-ion-monitoring (SIM) mode with electropositive ionization at 60 eV. The ions monitored are listed in *Table II*.

Results and Discussion

The chromatographic results obtained on both C_{18} and C_8 columns are presented in *Tables III* and *IV*. The standard deviations (*s*) of *mk*′ and *m*log *k*′, estimated for both columns, were highest for δ-tocopherol, as a consequence of its highest retention times. The regression correlation coefficients are indicative of good linearity throughout the range of concentration of methanol used as organic modifier. The correlation coefficient (*r*) was always >0.999, except for retinol ($r = 0.963$) and δ-tocopherol ($r = 0.969$) on the C_8 column. For both columns there was strong correlation between log k'_w and *S* ($r_{C18} = 0.996$; $r_{C8} = 0.993$). According to some authors this correlation might indicate that the lipophilicity and specific hydrophobic surface area intercorrelated and the analyzed compounds form a congeneric series [30, 31]. The results obtained indicate lipophilicity is highest for δ-tocopherol (log $k'_{w(C18)} = 14.86$; log $k'_{w(C8)} = 11.75$) followed by the other two tocopherols and the carotenoids (log $k'_w > 8$). The least lipophilic compound was retinol (log $k'_{w(C18)} = 0.97$; log $k'_{w(C8)} = 2.65$). The retinoids are of intermediate lipophilicity (log $k'_{w(C18)}$ ~7 and log $k'_{w(C8)}$ ~6). The high correlation among the all the lipophilicity indices estimated from the retention factors is very well illustrated in *Figs 2a–2b*.

Table III. Lipophilicity indices obtained on the C_{18} column

No.	Name	*mk*′ (±*s*)	*m*log *k*′ (±*s*)	log k'_w	*S*	φ_0	Score PC1/*k*′	Score PC1/log *k*′
1	Lutein	10.99 (±3.393)	1.02 (±0.136)	8.60	−0.086	−99.90	−4.07	−0.507
2	Astaxanthin	10.98 (±3.398)	1.02 (±0.136)	8.62	−0.086	−99.85	−4.04	−0.506
3	Zeaxanthin	10.93 (±3.348)	1.02 (±0.135)	8.55	−0.085	−99.95	−3.90	−0.503
4	Retinol	0.22 (±0.027)	−0.64 (±0.058)	0.97	−0.018	−52.69	20.48	3.245
5	Retinoic Acid	6.06 (±1.570)	0.77 (±0.114)	7.11	−0.072	−98.71	7.41	0.060
6	9-cis-Retinal	6.05 (±1.449)	0.77 (±0.105)	6.63	−0.067	−99.59	7.55	0.060
7	All-*trans*-retinal	6.21 (±1.505)	0.78 (±0.106)	6.72	−0.067	−99.60	7.18	0.035
8	α-Tocopherol	11.14 (±3.529)	1.03 (±0.139)	8.74	−0.088	−99.74	−4.32	−0.519
9	γ-Tocopherol	10.79 (±3.392)	1.02 (±0.138)	8.67	−0.087	−99.68	−3.68	−0.489
10	δ-Tocopherol	17.34 (±9.948)	1.18 (±0.247)	14.86	−0.155	−95.61	−22.62	−0.877

The log *P* values computed theoretically by use of different software are highly correlated (*Fig. 3*). The mean retention factors correlated best with calculated log *P* values. For both columns better correlations were obtained between the means of *k*′ and log *k*′ and scores corresponding to the first principal component obtained by applying principal-component analysis to the matrix of retention factors and computed log *P* values (*Table V*).

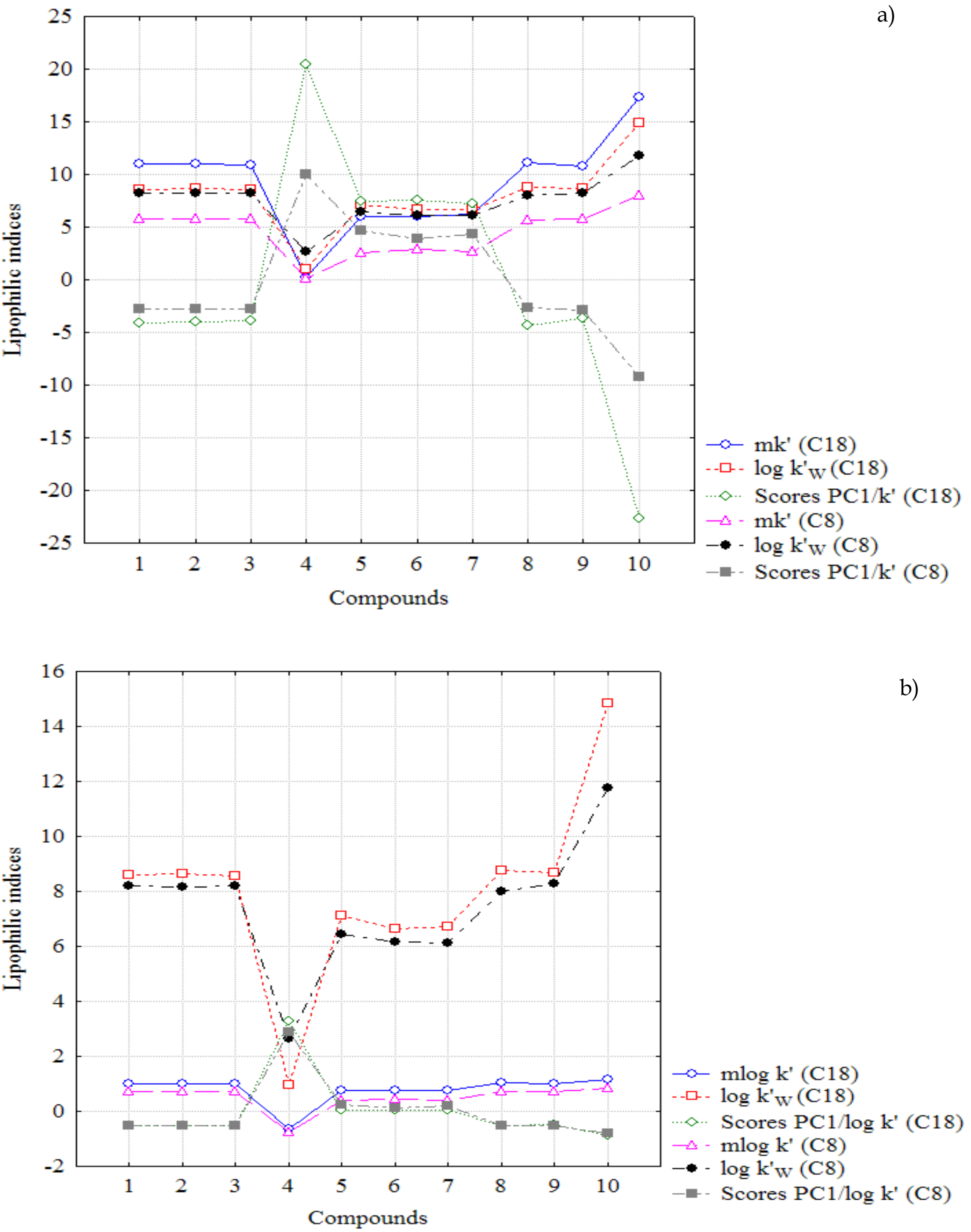

Fig. 2. Profiles of lipophilicity indices: (a) indices derived from *k*′ and log k'_w (C_{18} and C_8); (b) indices derived from log *k*′ and log k'_w (C_{18} and C_8)

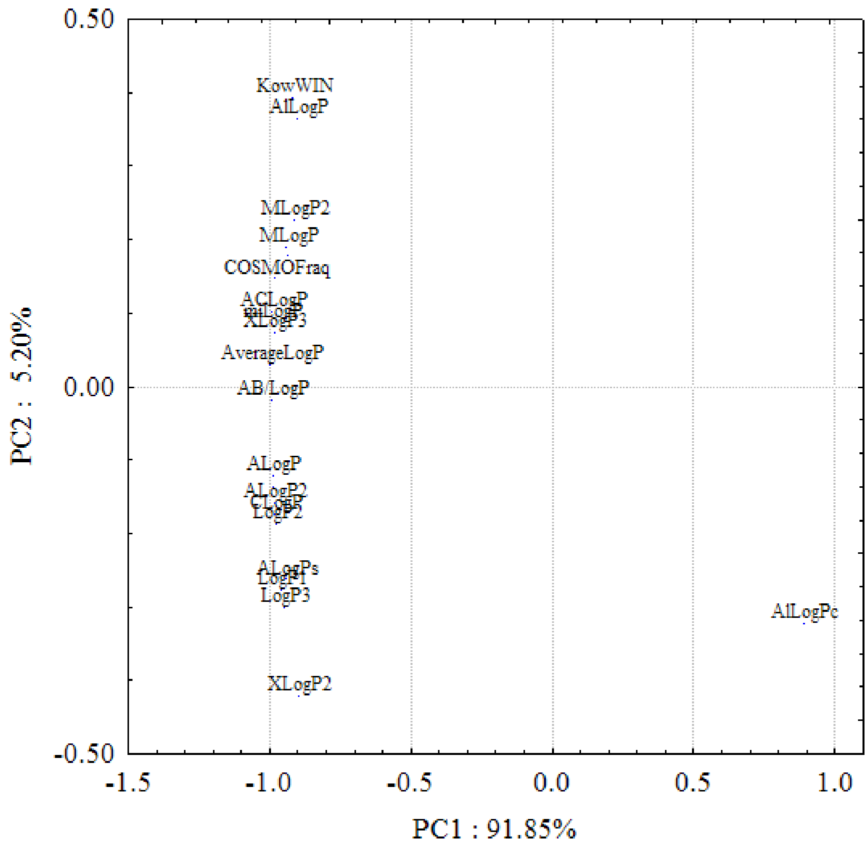

Fig. 3. Loadings scatterplot corresponding to PC1 and PC2 obtained for the calculated log *P* values

Table IV. Lipophilicity indices obtained on the C_8 column

No.	Name	*mk'* (±*s*)	*m*log *k'* (±*s*)	log k'_w	*S*	φ_0	Score PC1/*k'*	Score PC1/ log *k'*
1	Lutein	5.74 (±1.766)	0.742 (±0.134)	8.22	−0.085	−96.74	−2.78	−0.529
2	Astaxanthin	5.75 (±1.758)	0.743 (±0.137)	8.18	−0.084	−96.79	−2.79	−0.531
3	Zeaxanthin	5.75 (±1.766)	0.743 (±0.134)	8.21	−0.085	−96.75	−2.80	−0.530
4	Retinol	0.17 (±0.024)	−0.776 (±0.064)	2.65	−0.039	−68.05	10.04	2.870
5	Retinoic Acid	2.52 (±0.634)	0.391 (±0.109)	6.45	−0.069	−93.68	4.71	0.257
6	9-cis-Retinal	2.90 (±0.687)	0.452 (±0.103)	6.17	−0.065	−94.96	3.90	0.122
7	All-*trans*-retinal	2.68 (±0.635)	0.418 (±0.103)	6.13	−0.065	−94.44	4.39	0.198
8	α-Tocopherol	5.69 (±1.692)	0.740 (±0.131)	8.01	−0.083	−96.95	−2.62	−0.522
9	γ-Tocopherol	5.75 (±1.794)	0.743 (±0.135)	8.28	−0.086	−96.67	−2.84	−0.530
10	δ-Tocopherol	7.98 (±4.108)	0.862 (±0.202)	11.75	−0.124	−94.96	−9.21	−0.804

Table V. Correlation table

log *P*	C18							C8						
	mk'	*m*log *k'*	log *k'*w	*S*	φ_0	Score PC1/*k'*	Score PC1/log *k'*	*mk'*	*m*log *k'*	log *k'*w	*S*	φ_0	Score Score PC1/*k'*	Score PC1/log *k'*
LogP[1]	0.779	0.554	0.631	−0.626	−0.338	−0.760	−0.554	**0.836**	0.618	0.714	−0.712	−0.440	**−0.828**	−0.619
LogP[2]	0.786	0.571	0.629	−0.620	−0.358	−0.763	−0.572	**0.850**	0.637	0.719	−0.714	−0.460	**−0.839**	−0.638
LogP[3]	**0.806**	0.611	0.675	−0.665	−0.406	−0.786	−0.612	**0.856**	0.670	0.749	−0.741	−0.503	**−0.848**	−0.671
CLogP	0.797	0.595	0.647	−0.636	−0.385	−0.775	−0.595	**0.858**	0.658	0.735	−0.727	−0.485	**−0.847**	−0.659
AILogPc	−0.686	−0.584	−0.493	0.461	0.431	0.642	0.583	−0.783	−0.653	−0.608	0.575	0.523	0.756	0.653
AILogP	0.742	0.573	0.567	−0.549	−0.385	−0.711	−0.572	**0.823**	0.641	0.679	−0.664	−0.480	**−0.806**	−0.641
MLogP[1]	0.653	0.504	0.478	−0.459	−0.337	−0.620	−0.504	0.735	0.570	0.585	−0.568	−0.423	−0.716	−0.571
MLogP[2]	0.620	0.488	0.448	−0.427	−0.332	−0.586	−0.487	0.702	0.551	0.555	−0.535	−0.417	−0.683	−0.551
ALogP[1]	**0.811**	0.625	0.651	−0.635	−0.420	−0.784	−0.625	**0.880**	0.691	0.744	−0.730	−0.522	**−0.866**	−0.692
ALogP[2]	0.793	0.608	0.633	−0.618	−0.406	−0.766	−0.608	**0.862**	0.674	0.725	−0.711	−0.508	**−0.847**	−0.675
ALogPs	0.795	0.549	0.649	−0.646	−0.326	−0.782	−0.549	**0.852**	0.618	0.727	−0.727	−0.432	**−0.847**	−0.618
ACLogP	0.787	0.611	0.606	−0.587	−0.413	−0.754	−0.610	**0.869**	0.681	0.713	−0.695	−0.516	**−0.851**	−0.682
AB/LogP	**0.826**	0.628	0.662	−0.648	−0.415	**−0.800**	−0.628	**0.896**	0.696	0.761	−0.750	−0.519	**−0.883**	−0.696
COSMO Fraq	0.740	0.599	0.559	−0.534	−0.424	−0.704	−0.598	**0.826**	0.668	0.667	−0.642	−0.520	**−0.805**	−0.668
miLogP	0.788	0.615	0.608	−0.588	−0.418	−0.755	−0.615	**0.871**	0.686	0.716	−0.697	−0.521	**−0.852**	−0.686
K_{ow}WIN	0.671	0.563	0.482	−0.453	−0.409	−0.629	−0.563	0.766	0.630	0.601	−0.572	−0.498	−0.740	−0.630
XLogP[2]	**0.810**	0.583	0.693	−0.691	−0.364	−0.799	−0.583	**0.850**	0.640	0.755	−0.756	−0.463	**−0.847**	−0.641
XLogP[3]	**0.822**	0.679	0.655	−0.630	−0.491	−0.786	−0.678	**0.897**	0.744	0.756	−0.731	−0.589	**−0.878**	−0.744
Average LogP	**0.801**	0.625	0.628	−0.609	−0.426	−0.770	−0.625	**0.879**	0.695	0.731	−0.713	−0.528	**−0.862**	−0.695
m*k'*(C18)	1.000	**0.839**	**0.967**	**−0.959**	−0.632	**−0.996**	**−0.841**	**0.987**	**0.868**	**0.992**	**−0.986**	−0.711	**−0.992**	**−0.869**
mlog *k'*(C18)		1.000	**0.850**	−0.796	**−0.952**	**−0.801**	−1.000	**0.831**	**0.995**	**0.863**	−0.798	**−0.978**	**−0.812**	**−0.995**
log *k'*w(C18)			1.000	**−0.996**	−0.671	**−0.973**	**−0.851**	**0.916**	**0.856**	**0.988**	**−0.985**	−0.728	**−0.929**	**−0.857**
S(C18)				1.000	0.599	**0.973**	0.798	**−0.902**	**−0.804**	**−0.980**	**0.988**	0.660	**0.920**	**0.805**
φ_0 (C18)					1.000	0.581	**0.951**	−0.624	**−0.927**	−0.672	0.584	**0.992**	0.595	**0.926**
PC1/*k'*(C18)						1.000	**0.802**	**−0.974**	**−0.829**	**−0.990**	**0.994**	0.661	**0.984**	**0.830**
PC1/log *k'*(C18)							1.000	**−0.832**	**−0.995**	**−0.864**	**0.800**	**0.978**	**0.813**	**0.995**
m*k'*(C8)								1.000	**0.872**	**0.964**	**−0.952**	−0.711	**−0.998**	**−0.873**
mlog *k'*(C8)									1.000	**0.881**	**−0.819**	**−0.964**	**−0.852**	**−1.000**
log *k'*w(C8)										1.000	**−0.993**	−0.740	**−0.971**	**−0.882**
S(C8)											1.000	0.657	**0.965**	**0.820**
φ_0 (C8)												1.000	0.683	**0.964**
PC1/*k'*(C8)													1.000	**0.853**
PC1/log *k'*(C8)														1.000

Emboldening indicates correlation ≥0.8

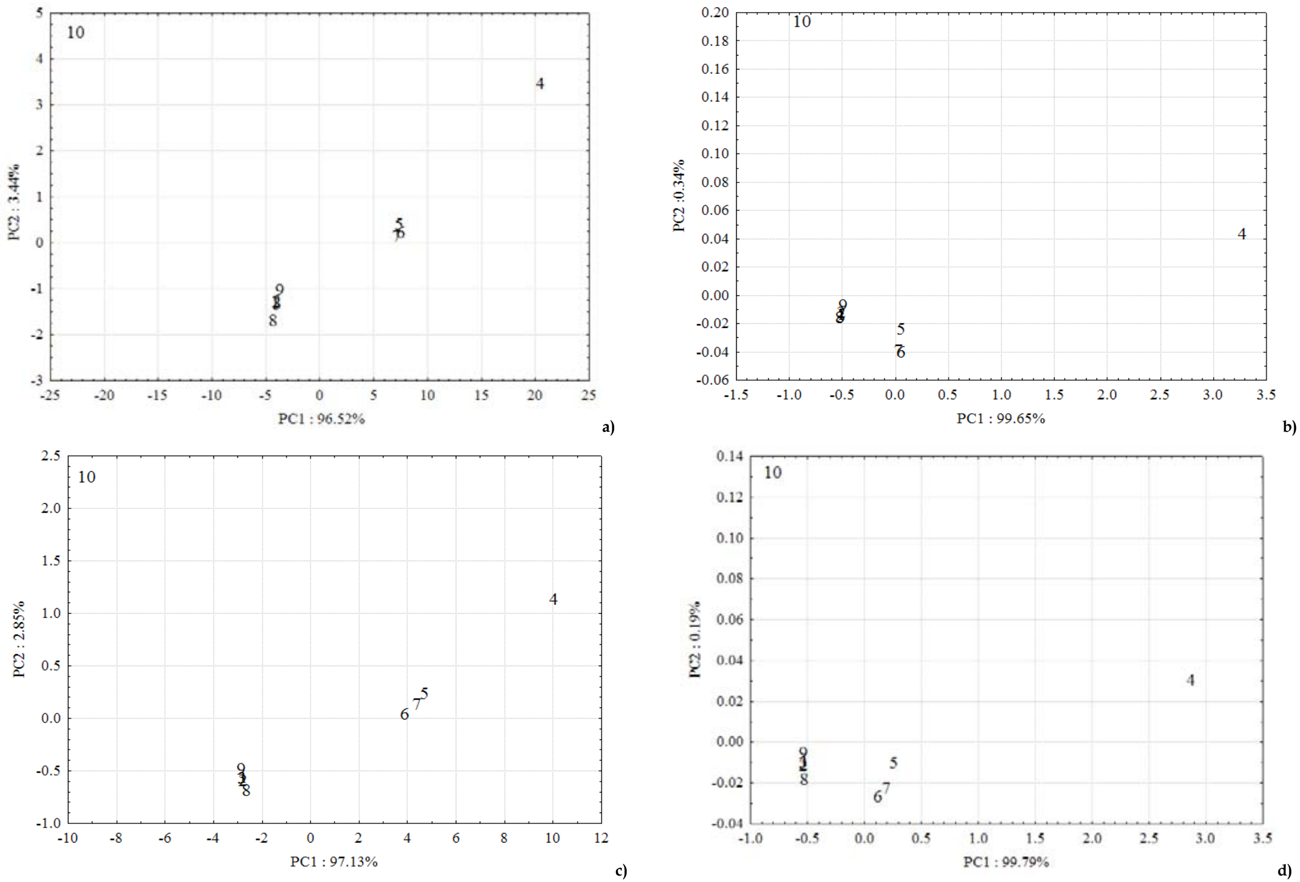

Fig. 4. Congeneric lipophilicity charts obtained from the scatterplot of scores corresponding to PC1 and PC2: (a) and (b) for *k′* and log *k′*, respectively, on C_{18}; (c) and (d) for *k′* and log *k′*, respectively, on C_8

We must mention that application of PCA revealed the first principal component accounts for 96.53% (k') and 99.67% ($\log k'$) for the C_{18} column and 97.12% (k') and 99.79% ($\log k'$) for the C_8 column. In addition, scatter-plots of scores on to the plane described by PC1 and PC2 for each column described above (*Figs 4a–4d*) clearly illustrate that the corresponding 'congeneric lipophilicity charts' are very similar.

The highest correlations were found between the mean of k' and scores corresponding to the first principal component determined on the C_8 column, and most of the computed $\log P$ values. These findings can be explained by analyzing the structure of the compounds. It is known that strong interactions between long-chain molecules and C_{18} (or stationary phases with even longer carbon chains) may lead to inconclusive results in the determination of lipophilicity. For both the mean of k' and scores similar correlations were obtained with computer-estimated $\log P$ values. The best correlations were obtained between the mean of k' and scores on C_8 and AlogP[1] ($r = 0.880$ and $r = -0.866$, respectively), AB/LogP ($r = 0.896$ and $r = -0.883$, respectively), and XLogP[3] ($r = 0.897$ and $r = -0.878$, respectively). It is interesting to remark that similar best correlations were obtained on C_{18} also: AlogP[1] ($r = 0.811$ and $r = -0.784$, respectively), AB/LogP ($r = 0.826$ and $r = -0.800$, respectively), and XLogP[3] ($r = 0.822$ and $r = -0.786$, respectively). The good agreement between $\log K_{ow}$ (6.30) and $\log k'_w$ (6.45 on C_8 and 7.11 on C_{18}) for retinoic acid is also clearly apparent.

Conclusions

Different indices of lipophilicity for vitamins A and E and for some precursors of vitamin A have been determined for the first time by reversed-phase high-performance liquid chromatography on C_{18} and C_8 columns using methanol–water mixtures as mobile phases. Excellent regression correlation coefficients were obtained for both stationary phases. Good correlation was found between the mean of k' and scores corresponding to the first principal component obtained by applying principal-component analysis to the matrix of retention factors and computed $\log P$ values. Owing to the better agreement between different experimental indices of lipophilicity and computed $\log P$ values, the C_8 column seems to be more suitable for estimating the lipophilicity of the compounds investigated.

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