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Revisiting thin-layer chromatography as a lipophilicity determination tool—A comparative study on several techniques with a model solute set

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ABSTRACT

The lipophilicity of a compound is a fundamental property related to pharmaceutical and biomedical activity. As many approaches are mixed together in every-day published studies, the subject needs some standardization. The paper presents a comparative study on several approaches of TLC lipophilicity determination: a single TLC run, extrapolation of a retention, principal component analysis of a retention matrix, PARAFAC on a three-way array and a PLS regression. All techniques were applied to 35 model solutes with simple molecules, using nine concentrations of six modifiers: acetonitrile, acetone, dioxane, propan-2-ol, methanol and tetrahydrofurane. The elaborated comparative analysis formed several general recommendations. Methanol and dioxane were the best modifiers, while acetonitrile gave the worst and inacceptable correlation of retention with lipophilicity. Surprisingly, good correlations were obtained for the single TLC runs and this method is underestimated in the literature. The advanced chemometric processing proposed recently, such as PCA, PARAFAC and PLS did not show a visible advantage comparing to classical methods. A need to use a robust regression and robust correlation measures, due to presence of significant outliers, was also noticed and studied.

1. Introduction

The lipophilicity of a compound, defined as a partitioning coefficient between water and n-octanol, is a fundamental property related to pharmaceutical and biomedical actions. It can be determined in different ways, but searching for new better methods is a field of continuous research [1]. The chromatographic determination of lipophilicity [2] is currently one of the major approaches presented in the literature due to simple instrumentation and a wide range of measurable lipophilicity values. Computational methods are also in development [3], but they are imperfect and experimental methods are preferred.

Historically, the idea of liquid chromatography lipophilicity assessment can be traced back even to 1940s and several comprehensive reviews on this topic, regarding high performance liquid chromatography (HPLC) are available for the interested reader [1,4–8]. Many analyticians use also thin-layer chromatography (TLC) for lipophilicity determination due to more reduced cost, less environmental pollution and a wider range of measured retention. There are hundreds of papers describing lipophilicity determination by TLC for very diverse classes of solutes, although no review is strictly dedicated to TLC.

Lipophilicity measurements are done mostly in reversed-phase (RP) chromatography with a non-polar (such as C8 or C18) phase [2,9]. Some studies were performed on less hydrophobic (such as cyanopropyl) one, but these gave generally worse results. Some new and better approaches, such as immobilised artificial membrane (IAM) [10], are not common mainly due to high costs of analysis.

The current state of knowledge is that the main mechanism of a retention in RP systems is based on partitioning between mobile and stationary phases; other factors are almost negligible [4]. Therefore, a retention factor $\log k$ (equivalent to R_M in TLC) can be treated as $\log P$ (logarithm of partitioning coefficient) between these phases. While the stationary phase is non-polar as n-octanol, the retention for pure water is strictly correlated with lipophilicity ($\log P_{OW}$), or even—according to some authors, it can be treated as its surrogate [11].

Direct obtaining of retention data for water as a modifier is impossible in both HPLC and TLC methods—the retention time would be extremely long and the R_F value almost equal to zero. Several workarounds are used to cope with this problem. The simplest way is using as small as possible concentration of the modifier. The retention is then less related with lipophilicity, but still linearly bound by Collander equation [4]:

$$\log P_{OW} = aR_M + b \quad (1)$$

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Table 1
The analyzed compounds with the corresponding reference numbers and experimental literature lipophilicities.

1	0.46	Acetaminophen	13	1.81	Dimethylaminbenzaldehyde (4-)	25	1.41	Phenylacetic acid
2	1.16	Acetanilide	14	3.50	Diphenylamine	26	1.25	Phenylhydrazine
3	0.83	Aminobenzoic (4-) acid	15	2.47	Ethyl hydroxybenzoate (4-)	27	0.16	Phloroglucine
4	0.62	Aminophenol (2-)	16	2.27	Eugenol	28	0.80	Resorcinol
5	0.48	Aminopiridine (2-)	17	2.02	Hydroxyquinoline (8-)	29	1.28	Salicylamide
6	0.89	Aminosalicylic (4-) acid	18	2.14	Indol	30	2.26	Salicylic acid
7	3.39	Antraquinone	19	−0.70	Isoniazide	31	−0.62	Sulfanilamide
8	1.86	Benzocaine	20	2.70	Naphtol (2-)	32	−2.16	Sulfanilic acid
9	1.87	Benzoic acid	21	2.25	Naphtylamine (1-)	33	3.30	Thymol
10	0.20	Benzoquinone	22	1.91	Nitrophenol (4-)	34	1.39	Toluidine (4-)
11	−0.07	Caffeine	23	1.46	Phenol	35	1.20	Vanillin
12	−1.80	Dihydralazine	24	3.80	Phenyl salicylate			

The more accurate way is examining the retention in a sequence of modifier's concentrations and find a linear dependence formed by Soczewiński–Wachtmeister equation [12]:

$$\log k = \log k_w + S\varphi \quad (2)$$

... where φ is a concentration of a modifier (given usually as a volume fraction). The extrapolated intercept term $\log k_w$ is then a partitioning coefficient between a stationary phase and pure water. This approach is a common practice in TLC due to a short time of plate development and small amounts of the solvents used. The plates can be run even simultaneously if several TLC chambers are available.

Third workaround, used almost only in HPLC, is a single gradient run. The method was firstly proposed in the late 1990s [13] and then significantly improved to reduce analysis time [14]. Although there are some technical possibilities to use a gradient technique in TLC plates, the equipment is very rare and – to the best of our knowledge – no one tried to determine the lipophilicity by this method.

In the late 1990s a chemometric approach was proposed to extract the lipophilicity values from the retention data [15]. The retention matrix (solutes × modifier concentrations) is processed by Principal Component Analysis (PCA). The first principal component, explaining majority of the variance, is always correlated with a solute's lipophilicity. This idea was used by the same authors for different solutes sets [16–19]. An extended approach relying on typical multivariate calibration (prediction of lipophilicity by Principal Component Regression and Partial Least Squares) was also presented [20]. This approach can be extended to multidimensional methods such as PARAFAC when several modifiers are studied, but so far, it has not been done in the literature.

Another issue, treated differently among the literature, is the analysis of some reference compounds with known lipophilicity to form a "calibration curve" [21–23]. Although the difference between $\log k_W$ and $\log P_{OW}$ can be often neglected, such a calibration makes lipophilicity prediction more standardized and accurate.

If an extrapolation is used, every modifier can be theoretically applied for the analysis, but there are often significant differences in practice. It is generally argued [4,11] that the modifier should be as water-like as possible and generally methanol would be the best choice. This rule is not taken into account by many researchers, who use almost all water-miscible solvents. Acetone (avoided in HPLC due to a high UV absorbance), propan-2-ol, ethanol and dioxane (not often used in HPLC due to high pressure and viscosity) are very common in TLC lipophilicity measurements.

As many approaches are mixed together in every-day published studies, the subject needs some standardization. While the problem is very comprehensively discussed in the case of HPLC [24], comparative studies by TLC were almost undone. The papers published so far in this field describe a relationship between slope and intercept [25], an effect of a modifier on some steroids set [26], a comparison of several modifiers [27] and a trial to standardize the conditions [28], where acetone (while not water-like modifier) was proposed as the best choice.

The current study, done on 35 simple compounds with known literature lipophilicity, was undertaken to point the attention to several important questions:

1. What correlations between single R_M values (from one plate) and lipophilicity values can be expected with different modifiers and if one TLC plate (without extrapolations) can be used as a surrogate of several concentrations followed by extrapolation? How large is a difference between modifiers? What values of Collander equation can we obtain?
2. What dependences between the extrapolated $\log k_W$ and experimental lipophilicity can be obtained using different modifiers? Are some modifiers generally better?
3. Do PCA analysis and other multivariate methods (including non-proposed three-way decomposition by PARAFAC) perform better than a single extrapolation?

2. Experimental

35 model compounds with simple molecules (Table 1) were of appropriate purity and were obtained from different manufacturers (Sigma–Aldrich, USA; Fluka, Germany and POCH, Poland). The chromatographic plates (RP18) were with F254 fluorescence indicator from Merck (Darmstadt, Germany). The 1 mg/mL solutions in methanol (analytical grade, POCH, Gliwice, Poland) were applied in 5 μL amounts, 5 mm from a plate border. The plates were

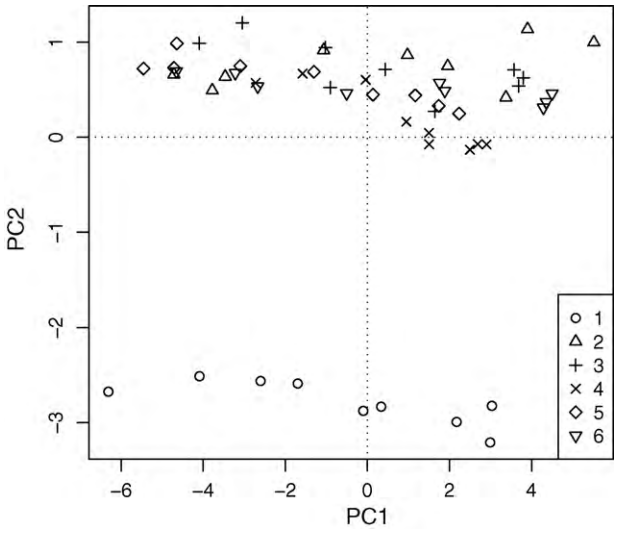

Fig. 1. PCA analysis of retention indices for all modifiers: acetonitrile (1) has visibly different properties than the others. For modifier numbering, see Section 2.

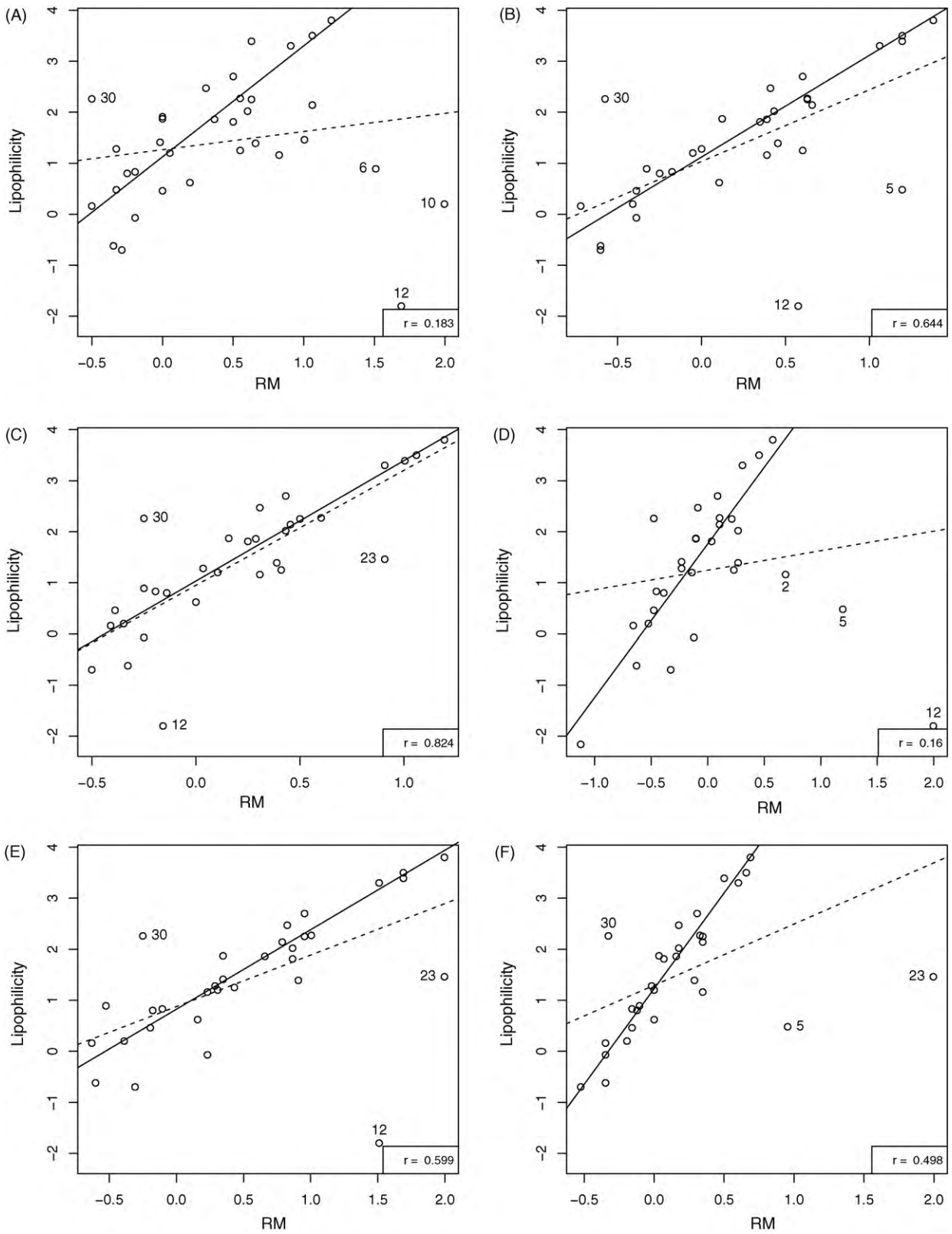

Fig. 2. Dependence between R_M and log P_{OW} (lipophilicity) in TLC systems containing 50% of modifier: (A) acetonitrile, (B) acetone, (C) dioxane, (D) propan-2-ol, (E) methanol, and (F) tetrahydrofuran. The LTS regression is marked by solid line, classical OLS regression by dashed line.

developed to 5 mm from the opposite border (9 cm of total distance) in horizontal DS Teflon chambers (ChromDes, Lublin, Poland) using a face-down mode (saturated conditions), then dried in ambient temperature and visualized under UV 254 nm. All experiments were performed in air-conditioned room with a constant temperature $24 \pm 0.5\,^{\circ}$C. In all the cases, R_F values were collected as the retention indices and then converted to R_M (equivalent of $\log k$) by following formula: $R_M = \log(1 - R_F)/R_F$. Computations were performed with Matlab R2009b (three-way analysis) and GNU R 2.10.1 (other calculations) software. The reference lipophilicities (deter-

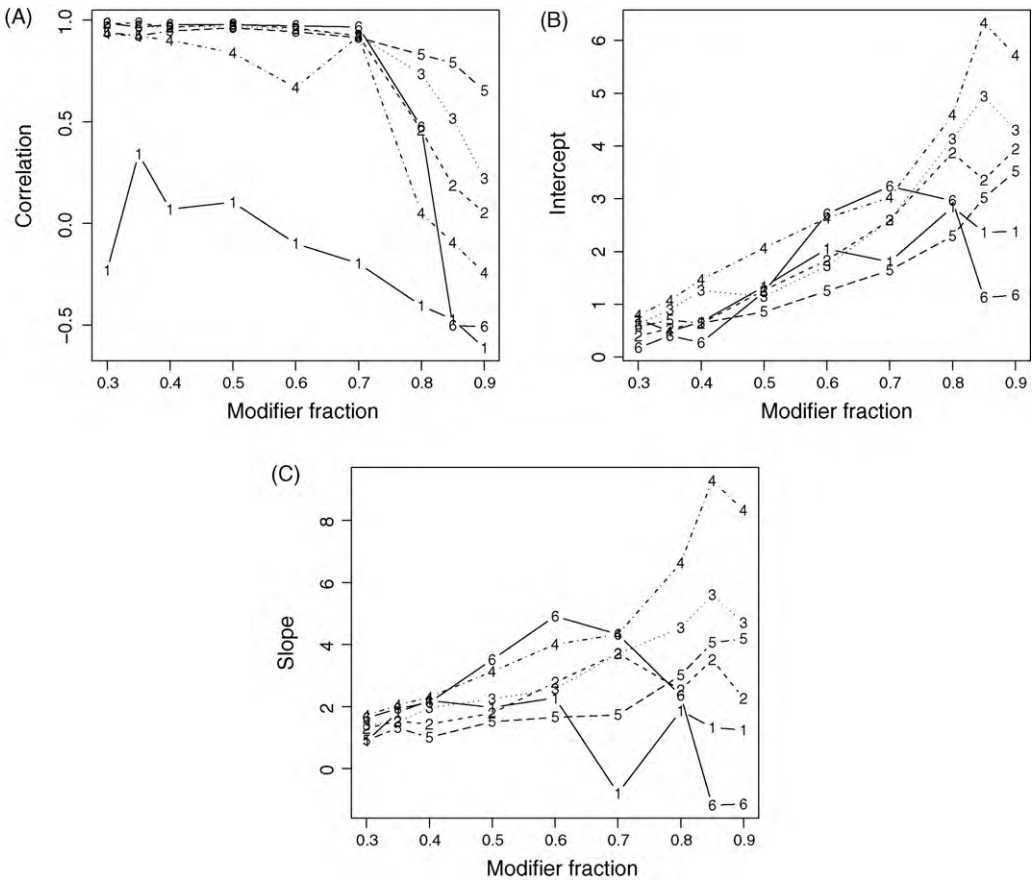

Fig. 3. Correlation (r) between R_M and lipophilicity (A) and parameters of Collander equation: intercept (B) and slope (C) as a function of modifier fraction in mobile phase. For modifier numbering see Section 2.

mined experimentally by a shake-flask method) were taken from www.vcclab.org database.

Six modifiers: acetonitrile (1), acetone (2), dioxane (3), propan-2-ol (4), methanol (5) and tetrahydrofurane (6) was used. Each modifier was used at 9 concentrations in water: 30, 35, 40, 50, 60, 70, 80, 85 and 90% (v/v).

3. Results and discussion

The compounds used in the investigation were chosen to be very simple model solutes, being representative—i.e. having quite large diversity of functional groups and features. The solute set coveres wide range from extremely polar compounds (dihydralazine, sulfanilic acid), to hydrophobic ones (antraquinone, diphenylamine). The range of lipophilicity is from −2.16 to 3.8.

Preliminary chromatographic analysis with buffered mobile phases confirmed very weak changes of retention, when pH varied in range 5–8. It could be suspected, that the analyzed compounds were not ionized in these conditions, therefore for further experiments water-based phases were used. The results also matched to reference experimental values, given for non-ionized form of compounds. Repetitive analysis in the conditioned room proved the differences in R_F values around 0.01, comparably to measurement accuracy.

Preliminary analysis of the retention matrix with unscaled Principal Component Analysis (Fig. 1) showed a visible difference of acetonitrile TLC systems (denoted as circles and number 1), regardless of the concentrations used. The inspection of the retention dataset showed significantly worse correlation with the lipophilicity obtained with acetonitrile and a visible difference of retention in comparison to the others.

3.1. Determining the lipophilicity from a single TLC run

Inspecting the correlation, we have found that in the case of each modifier several compounds are outliers, showing mainly higher retention than the lipophilicity (Fig. 2). Their presence can significantly affect the obtained slope and intercept of Collander equation. Their removal would be a subjective decision. Moreover, in a particular case, there can be more outliers. Therefore, it is a need to use a robust regression method here, minimizing the sum of trimmed residuals instead of their full sum (Least Trimmed Squares—LTS). LTS results are marked by a solid line and indicate well the major linear trend in the data. On the contrary, classical ordinary least squares (OLS), denoted as a dashed line, is very often far away from the desired result.

Analyzing the correlation between R_M in a single chromatographic run and the lipophilicity, it can be seen (Fig. 3A), that very strong correlation (above 0.9) was obtained for all modifiers except acetonitrile and propan-2-ol in a quite wide range 30–70%. The worst correlation was obtained with acetonitrile and this modifier cannot be recommended for the lipophilicity evaluation without extrapolation.

The intercept of the Collander equation increases with a modifier concentration (Fig. 3B). In the range 30–70% (the same as above) it increases almost linearly. The same trend, but not so evident, is seen for the slope (Fig. 3C). It should be also noted, that this trend could be found only by the robust regression. When OLS regression was used, the outliers disturbed whole dependence totally (results not shown).

The above analysis suggests that lipophilicity can be estimated even from a single TLC run, while the compounds do not differ substantially with lipophilicity and a proper modifier is applied.

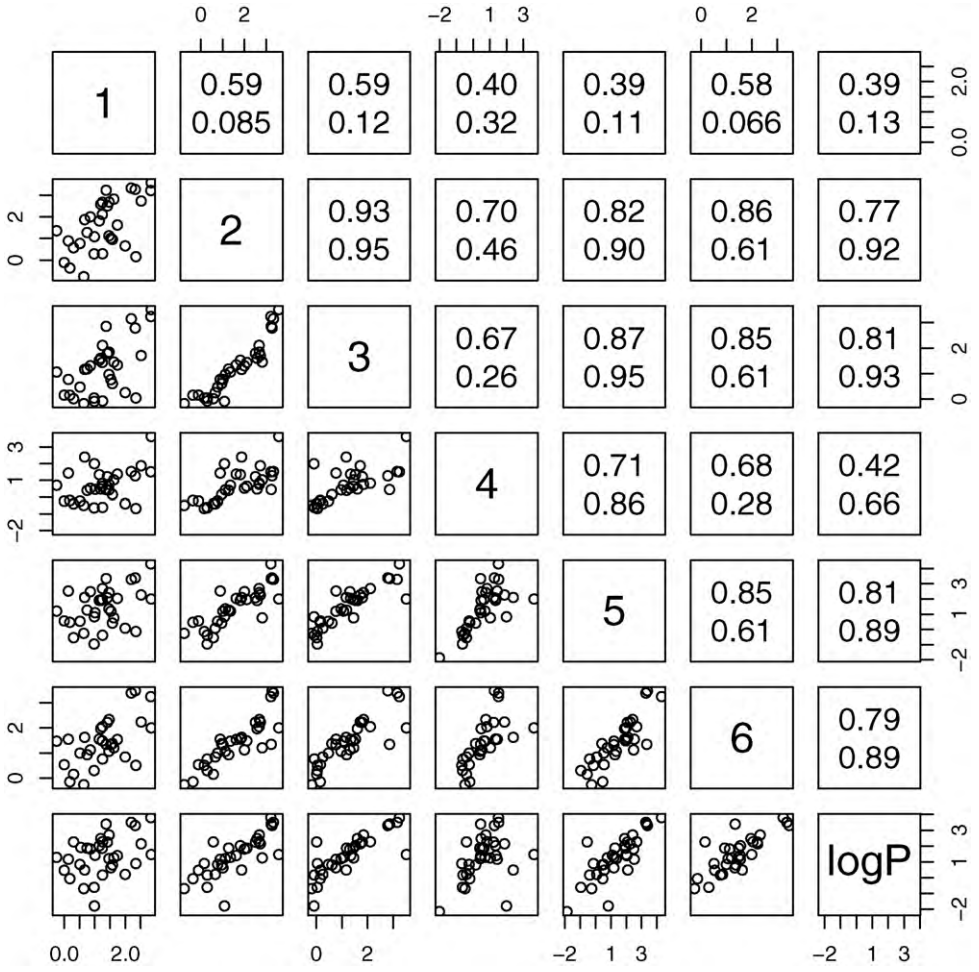

Fig. 4. Correlation (r) between extrapolated R_{MW} and lipophilicity. Correlations (upper) and robust correlations (lower) are given in upper triangle. For modifier numbering see Section 2.

As methanol has the lowest slope and intercept, it can be recommended here. On the contrary, the results with acetonitrile are almost unpredictable.

Regardless of the modifier, such an analysis requires a "calibration dataset" of compounds being chromatographed for obtaining the Collander equation (acting as a calibration curve) and converting R_M to $\log P_{OW}$ for the investigated compounds.

3.2. Determining the lipophilicity from extrapolated retention

The same retention dataset was then used to calculate the extrapolated R_M values, interpreted as a partitioning coefficient between water and a stationary phase. Extrapolation also was done using a robust linear regression (LTS). Extrapolation by classical OLS resulted with a visibly worse correlation with the lipophilicity. Robust regression can deal with some errors in nonlinearity at a small or large modifier concentration, fitting automatically a straight line only to a linear part.

Dependence between them and lipophilicities is shown on Fig. 4. Due to the presence of outlying compounds, two correlations are given—classical Pearson correlation coefficient (upper) and robust (insensitive to outliers) median correlation coefficient [29]. Surprisingly, the correlation between the extrapolated retention and real lipophilicity is visibly worse than that of a single TLC run. Moreover, there are several cases (for example with acetonitrile), when a main cloud of compounds is less correlated than a whole dataset (robust correlation is worse than the classical coefficient). The reason is that only several compounds, outlying from the main cloud to opposite sides, contribute to the correlation.

Although the theoretically extrapolated retention should be insensitive to a modifier, this assumption cannot be confirmed in practice. Acetonitrile and propan-2-ol have significantly worse correlation, whereas for other modifiers the correlations are better and similar. Methanol and dioxane are the best ones.

3.3. Determining the lipophilicity from principal components of a retention matrix

Next, a PCA approach to lipophilicity was tested. The retention matrices of each modifier were subjected to PCA and a first principal component (PC1), being a linear combination containing as much data information as possible, was correlated with the lipophilicity of solutes. The results are shown in Fig. 5. Comparing Figs. 4 and 5 one can see that the correlation of PCs is worse than that of the extrapolated retention values, mainly due to more outliers. Robust correlation measures are similar, but a PC method does not outperform classical extrapolation in any case. Additionally, as PC values cannot be used as strict surrogates of $\log P$, there is a need to use reference compounds in the same conditions.

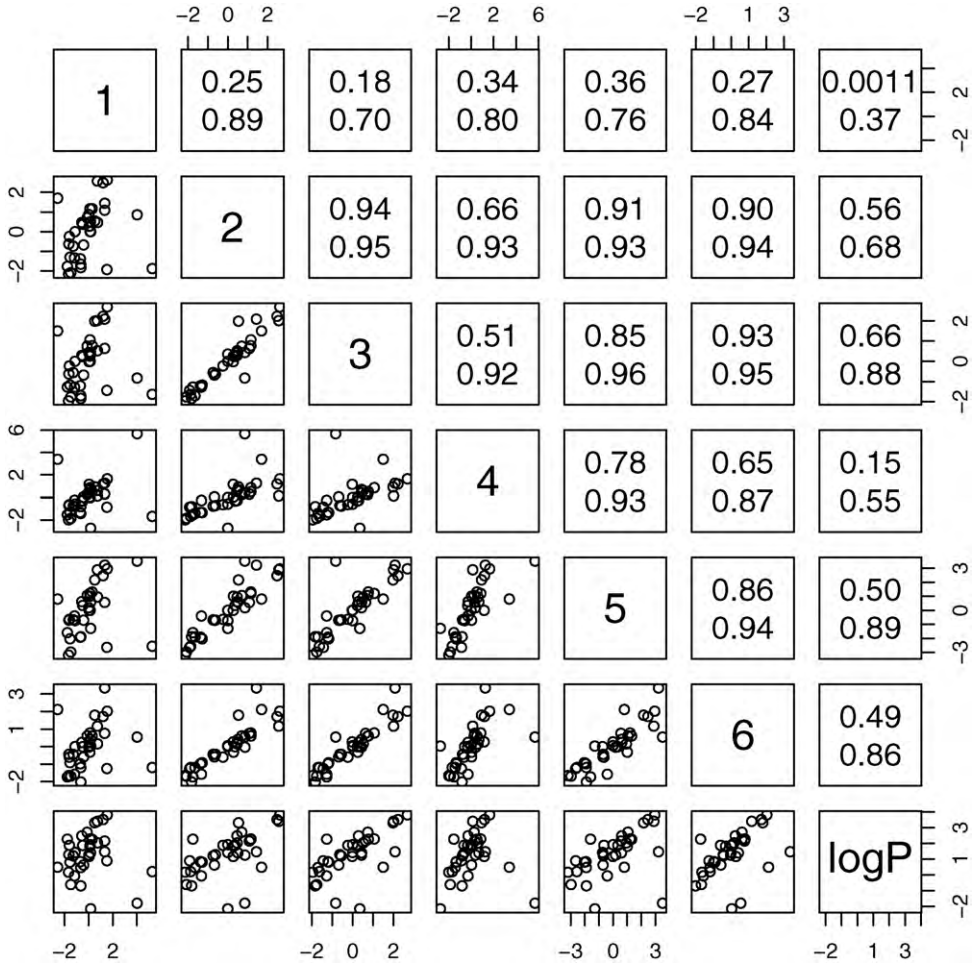

Fig. 5. Correlation (r) between PC1 derived from data matrix and lipophilicity with corresponding correlation coefficients. For modifier numbering see Section 2.

3.4. Determining the lipophilicity by augmented PCA and PARAFAC

An extension of the above technique, not done before in the literature, is using a dataset of several modifiers and decomposing all the data in a one step, correlating first component with the lipophilicity. It can be done by augmenting several retention matrices columnwise before performing PCA, or by creating a three-way array and decomposing it by PARAFAC [30]. Both approaches were done and the results are depicted in Fig. 6. It can be seen, that correlation of lipophilicity is comparable to one-modifier PCA, but slightly worse. This method can be treated as some kind of averaging of all modifiers results.

3.5. Determining the lipophilicity using PLS regression

We have also tested PLS models on a whole matrix. An optimal 5-factor PLS model had RMSECV ≈0.3 and external RMSEP ≈0.5, which was almost twice better comparing to a linear extrapolation. But as such a model must be made on a large matrix of many model compounds, a multivariate calibration in lipophilicity estimation, although once described, couldn't be treated as a very promising alternative.

3.6. Conclusions

We have performed several TLC lipophilicity estimations for 35 model compounds, comparing 6 modifiers inside each method. From this comparative study, following general conclusions can be made:

1. Methanol is theoretically and practically most recommended modifier for lipophilicity estimation. Dioxane gives similar results, but it is less water-like. Propan-2-ol and acetonitrile give visibly worse results, practically disqualifying them for this purpose.
2. A rare method, but underestimated, is the determination of lipophilicity from a single TLC run with an optimal concentration of well chosen modifier. This requires applying of a reference compounds to obtain the Collander equation, but this variant is very attractive, even with this extension. The resulted retention is even better correlated with lipophilicity than the extrapolated retention indices.
3. Due to frequent presence of outliers and some linearity disturbances, an automatic extrapolation of retention should be done by a robust regression. LTS (Least Trimmed Squares) is here proposed as a good choice.
4. Regardless of Pearson correlation coefficient, it is a good idea to compute and inspect its robust median variant, because several outliers can worsen the correlation value, even if a main trend is very linear.
5. Recent proposals based on PCA, even extended to PARAFAC (three dimensions), do not seem to be a good alternatives. They result in similar or even worse correlation but require a reference compounds to be chromatographed.

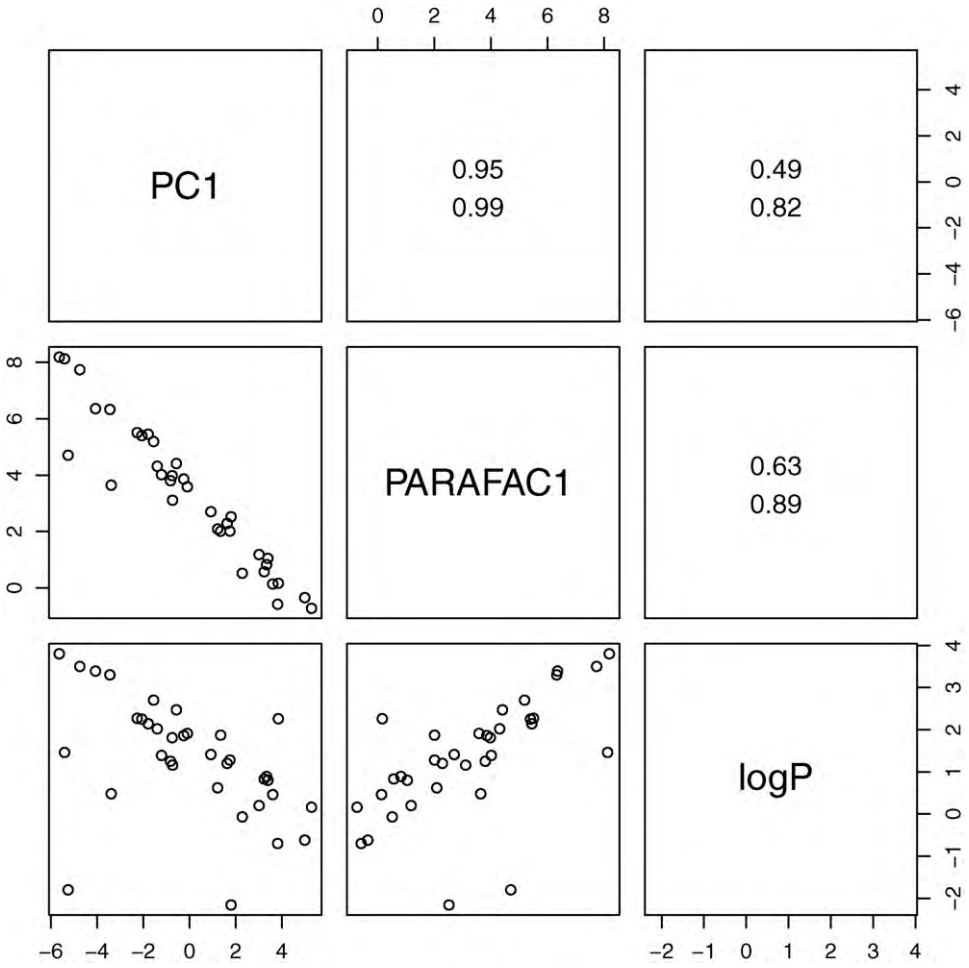

Fig. 6. Correlation (r) between PC1 derived from whole data matrix, first factor of PARAFAC and lipophilicity with corresponding correlation coefficients. For modifier numbering see Section 2.

6. A PLS model have better prediction ability but it requires a large calibration study before its creation followed by a complicated model validation.

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References

[1] C. Giaginis, A. Tsantili-Kakoulidou, Alternative measures of lipophilicity: from octanol-water partitioning to iam retention, J. Pharm. Sci. 97 (2008) 2984–3004.
[2] S. Gocan, G. Cimpan, J. Comer, Lipophilicity measurements by liquid chromatography, Adv. Chromatogr. 44 (2006) 79–176.
[3] R. Mannhold, G. Cruciani, K. Dross, R. Rekker, Multivariate analysis of experimental and computational descriptors of molecular lipophilicity, J. Comput.-Aided Mol. Des. 12 (1998) 573–581.
[4] T. Braumann, Determination of hydrophobic parameters by reversed-phase liquid chromatography: theory, experimental techniques, and application in studies on quantitative structure-activity relationships, J Chromatogr. 373 (1986) 191–225.
[5] J. Dorsey, M. Khaledi, Hydrophobicity estimations by reversed-phase liquid chromatography. Implications for biological partitioning processes, J. Chromatogr. A 656 (1993) 485–499.
[6] K. Valkó, Application of high-performance liquid chromatography based measurements of lipophilicity to model biological distribution, J. Chromatogr. A 1037 (2004) 299–310.
[7] A. Nasal, D. Siluk, R. Kaliszan, Chromatographic retention parameters in medicinal chemistry and molecular pharmacology, Curr. Med. Chem. 10 (2003) 381–426.
[8] A. Nasal, R. Kaliszan, Progress in the use of hplc for evaluation of lipophilicity, Curr. Comput.-Aided Drug Des. 2 (2006) 327–340.
[9] T. Braumann, H.-G. Genieser, C. Lllmann, B. Jastorff, Determination of hydrophobic parameters by reversed-phase high-performance liquid chromatography. Effect of stationary phase, Chromatographia 24 (1987) 777–782.
[10] K. Valkó, M. Plass, C. Bevan, D. Reynolds, M. Abraham, Relationships between the chromatographic hydrophobicity indices and solute descriptors obtained by using several reversed-phase, diol, nitrile, cyclodextrin and immobilised artificial membrane-bonded high-performance liquid chromatography columns, J Chromatogr. A 797 (1998) 41–55.
[11] W. Lambert, Modeling oil-water partitioning and menbrane permeation using reversed-phase chromatography, J. Chromatogr. A 656 (1993) 469–484.
[12] E. Soczewiński, Mechanistic molecular model of liquid-solid chromatography: retention-eluent composition relationships, J. Chromatogr. A 965 (2002) 109–116.
[13] K. Valkó, Chromatographic hydrophobicity index by fast-gradient rp-hplc: a high-throughput alternative to log p/log d, Anal. Chem. 69 (1997) 2022–2029.
[14] S. Donovan, M. Pescatore, Method for measuring the logarithm of the octanol-water partition coefficient by using short octadecyl-poly(vinyl alcohol) high-performance liquid chromatography columns, J. Chromatogr. A 952 (2002) 47–61.
[15] C. Sârbu, S. Todor, Evaluation of lipophilicity by principal components analysis, J. Planar Chromatogr. Mod. TLC 11 (1998) 123–126.
[16] C. Sârbu, S. Todor, Determination of lipophilicity of some non-steroidal anti-inflammatory agents and their relationships by using principal component analysis based on thin-layer chromatographic retention data, J. Chromatogr. A 822 (1998) 263–269.
[17] C. Sârbu, B. Malawska, Evaluation of lipophilicity of piperazine derivatives by thin layer chromatography and principal component analysis, J. Liq. Chrom. Rel. Technol. 23 (2000) 2143–2154.
[18] C. Sârbu, K. Kuhajda, S. Kevresan, Evaluation of the lipophilicity of bile acids and their derivatives by thin-layer chromatography and principal component analysis, J. Chromatogr. A 917 (2001) 361–366.
[19] C. Sârbu, Evaluation of lipophilicity of some pesticides by thin layer chromatography and principal component analysis, Rev. Roum. Chim. 47 (2002) 1113–1118.

[20] C. Sârbu, B. Tiperciuc, Modelling, by multivariate regression methods, of the chromatographic retention (lipophilicity) of new oxadiazoline derivatives, J Planar Chromatogr. Mod. TLC 19 (2006) 342–347.
[21] A. Gumieniczek, A. Berecka, D. Matosiuk, H. Hopkała, Standardized reversed-phase thin-layer chromatographic study of the lipophilicity of five anti-diabetic thiazolidinediones, J. Planar Chromatogr. Mod. TLC 20 (2007) 261–265.
[22] L. Komsta, K. Sztanke, P. M[ą]czka, M. Ucherek, R. Skibiński, A. Gumieniczek, Determination of the lipophilicity of twenty-seven imidazo[2,1-c][1,2,4]triazine derivatives with strong biological activity by reversed-phase tlc. comparison with results obtained by use of computational algorithms, J. Planar Chromatogr. Mod. TLC 22 (2009) 327–331.
[23] M. Ucherek, L. Komsta, R. Skibiński, B. Modzelewska-Banachiewicz, A. Gumieniczek, Lipophilicity evaluation of the products obtained in the reaction of n^3-substituted amidrazones with cis-1,2-cyclohexanedicarboxylic anhydride, Chromatographia 69 (2009) 1169–1174.
[24] C. Giaginis, S. Theocharis, A. Tsantili-Kakoulidou, Contribution to the standardization of the chromatographic conditions for the lipophilicity assessment of neutral and basic drugs, Anal. Chim. Acta 573–574 (2006) 311–318.
[25] G. Biagi, A. Barbaro, A. Sapone, M. Recanatini, Determination of lipophilicity by means of reversed-phase thin-layer chromatography. i. Basic aspects and relationship between slope and intercept of tlc equations, J. Chromatogr. A 662 (1994) 341–361.
[26] G. Biagi, A. Barbaro, A. Sapone, M. Recanatini, Determination of lipophilicity by means of reversed-phase thin-layer chromatography. ii. Influence of the organic modifier on the slope of the thin-layer chromatographic equation, J. Chromatogr. A 669 (1994) 246–253.
[27] G. Biagi, A. Barbaro, M. Recanatini, Determination of lipophilicity by means of reversed-phase thin-layer chromatography. iii. Study of the tlc equations for a series of ionizable quinolone derivatives, J. Chromatogr. A 678 (1994) 127–137.
[28] G. Völgyi, K. Deák, J. Vámos, K. Valkó, K. Takács-Novák, Rptlc determination of log p of structurally diverse neutral compounds, J. Planar. Chromatogr. Mod. TLC 21 (2008) 143–149.
[29] G.L. Shevlyakov, On robust estimation of a correlation coefficient, J. Math. Sci. 83 (1997) 434–438.
[30] R. Bro, Parafac. Tutorial and applications, Chemom. Intell. Lab. Syst. 38 (1997) 149–171.