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Characterization of solute-solvent interactions in liquid chromatography systems: A fast method based on Abraham's linear solvation energy relationships

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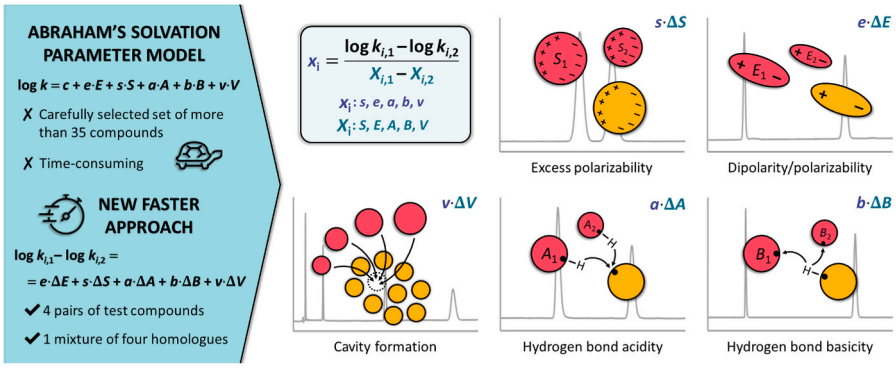
HIGHLIGHTS

- Fast characterization method based on Abraham solvation parameter model.
- Method applicable to both reversed-phase and HILIC.
- Evaluation of chromatographic selectivity based on main solute-solvent interactions.
- HILIC is compared to reversed-phase retention selectivity.
- Tanaka's method is analyzed by Abraham solvation parameter model.

GRAPHICAL ABSTRACT



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ABSTRACT

The Abraham's solvation parameter model, based on linear solvation energy relationships (LSER), allows the accurate characterization of the selectivity of chromatographic systems according to solute-solvent interactions (polarizability, dipolarity, hydrogen bonding, and cavity formation). However, this method, based on multilinear regression analysis, requires the measurement of the retention factors of a considerably high number of compounds, turning it into a time-consuming low throughput method. Simpler methods such as Tanaka's scheme are preferred. In the present work, the Abraham's model is revisited to develop a fast and reliable method, similar to the one proposed by Tanaka, for the characterization of columns employed in reversed-phase liquid chromatography and particularly in hydrophilic interaction liquid chromatography. For this purpose, pairs of compounds are carefully selected in order to have in common all molecular descriptors except for a specific one (for instance, similar molecular volume, dipolarity, polarizability, and hydrogen bonding basicity features, but different hydrogen bonding acidity). Thus, the selectivity factor of a single pair of test compounds can provide information regarding the extent of the dissimilar solute-solvent interactions and their influence on chromatographic retention. The proposed characterization method includes the determination of the column hold-up

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volume and Abraham's cavity term by means of the injection of four alkyl ketone homologues. Therefore, five chromatographic runs in a reversed-phase column (four pairs of test solutes and a mixture of four homologues) are enough to characterize the selectivity of a chromatographic system. Tanaka's method is also analyzed from the LSER point of view.

1. Introduction

It is well known that choosing the right combination of mobile and stationary phases is essential when it comes to developing a liquid chromatography separation method. In this sense, a reliable method for the characterization of chromatographic systems is a very convenient tool to evaluate the different solute-solvent interactions contributing to the partitioning process, the effect of changing the mobile phase composition on these interactions, and thus, for the comparison of different chromatographic modes. Among the different approaches reported in the literature [1], the high-throughput Tanaka's scheme and the more detailed but time-consuming Abraham's solvation parameter model are likely the most widely used characterization methods.

In 1989, Nobou Tanaka and coworkers proposed a test scheme for the characterization of octadecylsilane packing materials, based mainly on the selectivity (or separation) factor obtained from the injection of pairs of solutes [2]. In principle, the method was intended to provide a simple protocol, based on a few chromatographic runs, to assess the different solute-solvent interactions that perform retention in C18 columns (Table 1). In this context, hydrophobicity is referred to the surface coverage of the bonded phase (ligand density), measured by the selectivity factor between the test solutes *n*-pentylbenzene and *n*-butylbenzene that are only differentiated by one methylene group. The planar triphenylene is expected to better slot in between the alkyl chains of the bonded phase than the puckered *o*-terphenyl, and therefore these test compounds were proposed to evaluate the shape selectivity. Since caffeine is a much better hydrogen bond acceptor and a much poorer hydrogen bond donor than phenol, the differences in their retention are thought to provide a measure of the joint hydrogen bond abilities of the column, mainly attributed by Tanaka to the silanol activity of the packing material. Finally, the basic benzylamine, in contrast to the acidic phenol, is expected to be partially or fully protonated (and therefore positively charged) at neutral or acidic pH, showing then the column behavior regarding silanol activity and cation-exchange capacity.

Tanaka's scheme is probably the most widely used characterization method for reversed-phase columns. For instance, ACD/Labs provides a free web-based tool allowing the comparison of chromatographic columns to one another, with a database containing more than 350 columns characterized according to Tanaka's test [3].

Table 1
Tanaka's characterization scheme for commercial reversed-phase packing [2].

Property tested	Associated stationary phase characteristics	Chromatographic measurement	Mobile phase conditions
Amount of alkyl chains	Surface area and surface coverage	k(pentylbenzene)	80% methanol 20% water
Hydrophobic selectivity	Surface coverage	$\frac{k(\text{pentylbenzene})}{k(\text{butylbenzene})}$	80% methanol 20% water
Shape selectivity	Functionality of silane, surface coverage	$\frac{k(\text{triphenylene})}{k(o-\text{terphenyl})}$	80% methanol 20% water
Hydrogen bonding capacity	Amount of silanols, endcapping	$\frac{k(\text{caffeine})}{k(\text{phenol})}$	30% methanol 70% water
Cation exchange capacity at pH > 7	Amount of silanols and cation exchange sites	$\frac{k(\text{benzylamine})}{k(\text{phenol})}$	30% methanol 70% pH 7.6[a]
Cation exchange capacity at pH < 3	Amount of cation exchange sites at pH 3, silica pretreatment	$\frac{k(\text{benzylamine})}{k(\text{phenol})}$	30% methanol 70% pH 2.7[a]

[a] 0.02 M aqueous solution of phosphate buffer.

The Abraham's approach [4], also called solvation parameter model in its application to chromatography [5], is based on Linear Solvation Energy Relationships (LSER) and relates the logarithm of the retention factor (log k) of neutral solutes to the different contributions affecting retention in a chromatographic system by means of Eq. (1).

$$\log\ k = c + e{\cdot}E + s{\cdot}S + a{\cdot}A + b{\cdot}B + v{\cdot}V \quad (1)$$

Capital letters represent the solute descriptors, related to specific intermolecular interactions (E, S, A, and B) and the McGowan's molecular volume (V), while lower case letters account for chromatographic system coefficients (e, s, a, b, and v), which are related to the difference of the complementary effect of the mobile and stationary phases on these interactions. The constant term (c) elucidates the chromatographic phase ratio, normalization of descriptors, and other factors that are not solute-solvent interactions dependent. $e{\cdot}E$ term models excess polarizability solute-solvent contributions from n- and π-electrons, $s{\cdot}S$ accounts for dipolarity/polarizability interactions, $a{\cdot}A$ represents the hydrogen bonding donation from solute to solvent and $b{\cdot}B$ from solvent to solute, and $v{\cdot}V$ is related to the ease of the cavity formation in the solvent suitable for the size of the solute molecule (in fact, difference between the easiness of cavity formation in stationary and mobile phases). The sign and magnitude of the coefficients (lower case letters) lead to the characterization of chromatographic systems, explaining the interactions responsible for retention and allowing the comparison between different retention modes, columns, and mobile phases. Abraham's molecular descriptors can be obtained from free [6] and subscription [3] databases, which also provide a software for the calculation in case no experimental values are found.

The model, described in Eq. (1) for liquid chromatography, is a particular case of the more general Abraham LSER method developed to characterize a great diversity of physicochemical and biological processes, such as liquid/liquid and gas/liquid partitions, biopartitions, kinetic processes, toxicities, etc. [4,7–17]. This method [17] has been used from the decade of the 90s [18–20] to characterize many column/mobile phase systems and there are extensive literature reviews, compilations, and tutorials [1,5,21–23]. However, its every-day practice is limited because of the high number of measurements needed.

In Abraham's model (Eq. (1)), the determination of the system constant (c) and coefficients (e, s, a, b, and v) is based on multiple linear regression analysis of the retention factors (dependent variable) and molecular descriptors (E, S, A, B, and V; independent variables) of a set of carefully selected solutes. At least 35 compounds, structurally different in order to cover the maximum possible chemical space, are needed for a reliable characterization of the chromatographic system [23]. Consequently, this characterization method, requiring the injection of such a number of compounds and their replicates, is inevitably time consuming.

The main objective of the present work is to propose a fast method for the characterization of chromatographic systems using pairs of test compounds, like in the Tanaka's scheme, but starting from the Abraham's solvation parameter model. This method would be greener than the traditional one since it would require less measurements and consume lower volumes of organic solvents. Also, it would be much more sustainable in terms of time and economy.

The proposed fast method is intended to be potentially applicable to any liquid chromatographic mode, including Hydrophilic Interaction

Liquid Chromatography (HILIC). Nowadays, HILIC has become increasingly popular for the separation of polar and ionized analytes, particularly in the context of samples of biological interest, and manufacturers provide columns with a great variety of bonded phases. In the last decade, there has been a boost in the development of HILIC methodologies and, after reversed-phase, it is the liquid chromatographic mode with the highest number of applications [24–29]. HILIC uses polar bonded phase columns in combination with water-organic solvent eluents. Water from the eluent is preferentially adsorbed on the polar phase creating immobilized and/or semi-immobilized water-rich layers, which act as stationary phase [30–35]. Selectivity in HILIC is thus expected to be complementary to reversed-phase mode [36].

2. Materials and methods

2.1. Instrumentation

All measurements were performed on a Shimadzu (Kyoto, Japan) HPLC system. The instrument consisted of two LC-10ADVP pumps, an SIL-10ADVP autosampler, an SPD-M10AVP diode array detector, a CTO-10ASVP oven, and an SCL-10AVP controller. The system was controlled by LC Solutions software from Shimadzu.

The fully porous silica columns employed were: Chrom-Clone C18 (150 × 46 mm 5 μm 100 Å), Gemini C18 (150 × 46 mm 5 μm 110 Å), and Luna NH2 (150 × 46 mm 5 μm 100 Å) from Phenomenex (Torrance, CA, USA); YMC-Pack PVA-Sil (150 × 46 mm 5 μm 120 Å) and YMC-Triart Diol-HILIC (150 × 46 mm 5 μm 120 Å) from YMC Co. Ltd. (Kyoto, Japan); and ZIC-HILIC (150 × 46 mm 5 μm 200 Å) from Merck (Darmstadt, Germany).

2.2. Methods and chromatographic conditions

The mobile phases used were 60/40 (v/v) acetonitrile/water for reversed-phase columns and 90/10 (v/v) acetonitrile/water for HILIC columns. The mobile phase flow rate was generally 1 mL min^{-1}, except for the ZIC-HILIC column that was 0.5 mL min^{-1}, and the injection volume was 1 μL. All separations were performed at 25 °C, at least in duplicate. Detector wavelength was set at 272 nm for ketones, 300 nm for pentacene, picene, dibenz[*a,c*]anthracene, and dibenz[*a,h*]anthracene, and 200 nm for the rest of the tested solutes. The extra-column volume of the HPLC instrument was subtracted from all the gross retention volumes measured from the chromatograms.

2.3. Chemicals and solvents

The solutes used in this work were purchased from Acros Organics (Geel, Belgium), Alfa Aesar (Ward Hill, MA, USA), Sigma-Aldrich (St. Louis, MO, USA), TCI (Tokio, Japan), and Thermo Scienfitic (Waltham, MA, USA), all of high purity grade (≥98%).

HPLC-grade acetonitrile was purchased from Panreac (Barcelona, Spain). Water was obtained from a Milli-Q plus system from Millipore (Billerica, USA) with a resistivity of 18.2 MΩ cm.

2.4. Sample preparation

Stock solutions of the solutes were generally prepared at a concentration of 5 mg mL^{-1} dissolving each compound with methanol. 1,4-Dioxane was used instead for pentacene, picene, dibenz[*a,c*]anthracene, and dibenz[*a,h*]anthracene to increase their solubility.

n-Alkyl ketones were injected at stock solution concentration due to their lower UV absorbance, and the rest of the analytes were diluted to 0.5 mg mL^{-1} before injection. For pentacene and picene the supernatant from the stock solution was collected and injected because of its poor solubility.

2.5. Database screening and calculations

Preliminary selection of suitable test compounds from Abraham's database of solutes and molecular descriptors was performed through a script developed for this express purpose in MATLAB R2022b from The MathWorks Inc. (Natick, MA, USA). Non-linear regressions were performed by the Solver tool in MS Excel and TableCurve 2D software from SPSS Inc. (Chicago, IL, USA).

3. Results and discussion

3.1. Tanaka's test scheme from Abraham's model perspective

Tanaka's characterization scheme (Table 1) is based on the measurement of selectivity factors between pairs of test solutes according to Eq. (2).

$$\alpha_{1/2} = k_1 / k_2 \quad (2)$$

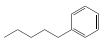
The subscripts 1 and 2 represent two solutes of very similar properties except for the measured selectivity (hydrophobic, shape, hydrogen bonding, or cation exchange selectivities).

However, a detailed examination of the different LSER solute-solvent interactions of the pairs of compounds proposed by Tanaka for the characterization of octadecylsilane columns reveals that differences in selectivity might be devoted to more than a single factor. This is clearly not the case of the pair chosen to characterize the hydrophobic selectivity, pentylbenzene and butylbenzene. As shown in Table 2, these two members of the *n*-alkyl benzene homologous series exhibit nearly the same excess polarizability (*E*) identical dipolarity/polarizability (*S*) and hydrogen bond acidity (*A*) and basicity (*B*) features but a different molecular volume (*V*). Therefore, the only contribution to the hydrophobic selectivity of pentylbenzene/butylbenzene is the cavity term, which is in good agreement with the measured property (surface coverage of bonded alkyl chains, Table 1). However, the pairs of test compounds accounting for shape selectivity and hydrogen bond capacity clearly exhibit notorious and multiple differences in terms of solute-solvent interactions and molecular volume.

Triphenylene and *o*-terphenyl were chosen by Tanaka in order to measure column shape selectivity because of their similar chemical structure but a clear different shape (Table 2). However, LSER descriptors in Table 2 show that they have similar hydrogen bonding properties but different volume, dipolarity and, particularly, polarizability. Both compounds have in common the absence of hydrogens covalently bound to electronegative atoms, and therefore they both lack hydrogen bonding donor capacities (*A*). In addition, they have the same number of electrons in benzene rings acting as hydrogen bond acceptors, resulting in similar hydrogen bond basicity (*B*). However, triphenylene has two less hydrogen atoms and one more condensed ring than *o*-terphenyl and thus it has a slightly smaller volume. More important, the complete delocalization of the 18-π-electron system of triphenylene in its four rings produces a much higher dipolarity/polarizability (*S*) and especially polarizability (*E*). Triphenylene shows a greater capability to participate in dispersion interactions due to their loosely bound π-electrons than *o*-terphenyl. These differences are clearly appreciable in their different physicochemical properties. For instance, triphenylene has much higher melting and boiling points (198 °C and 438 °C) than *o*-terphenyl (59 °C and 337 °C) [37]. Therefore, dissimilarities between retention factors of triphenylene and *o*-terphenyl can be attribute to their different planarity, to their different LSER interactions, or to both effects.

Caffeine, reversely to phenol, is a very poor hydrogen bond donor (*A*) due to the lack of hydrogens bonded to electronegative atoms, but it is an excellent hydrogen bond acceptor (*B*) because of the lone pairs of electrons of the two oxygen and the four nitrogen atoms. Therefore, differences in selectivity might be clearly attributed to hydrogen

Table 2
Molecular descriptors and structures of the Tanaka's test solutes for the measurement of the selectivity for hydrophobicity, shape, and hydrogen bonding capacity [6].

Compounds	*E*	*S*	*A*	*B*	*V*	Structures
(1) Pentylbenzene	0.59	0.51	0.00	0.15	1.42	
(2) Butylbenzene	0.60	0.51	0.00	0.15	1.28	
(1) Triphenylene	3.00	1.71	0.00	0.42	1.82	
(2) *o*-Terphenyl	1.95	1.35	0.00	0.38	1.93	
(1) Caffeine	1.50	1.82	0.08	1.25	1.36	
(2) Phenol	0.81	0.89	0.60	0.30	0.78	

bonding, although it is not possible to distinguish between acidity or basicity. In fact, selectivity measures should be partially cancelled since hydrogen bond basicity of caffeine is larger than that of phenol but hydrogen bond acidity is smaller and both properties commonly act in the same way (i.e. they decrease retention in reversed-phase). The difference in the number of heteroatoms in the molecule also leads to a very dissimilar behavior in terms of polarizability and dipolarity (*E* and *S*). Due to the above mentioned multiple dissimilar properties of caffeine and phenol, together with the molecular volume (*V*), the comparison of its chromatographic retention does not seem adequate for an accurate evaluation of hydrogen bonding interactions.

Since the presented Abraham's approach (Eq. (1)) is limited to neutral compounds, we are focusing on the properties involving pairs of unionized test solutes, and therefore cation exchange capacities evaluated with the basic benzylamine (pK_a 9.34 [37]) are not being assessed in this work.

3.2. Fundamentals of the proposed fast method based on Abraham's solvation model

Tanaka's selectivity characterization procedure can be applied to any pair of solutes to reflect different solute-solvent interactions. Therefore, for a particular chromatographic system (same column and mobile phase composition), we can combine Eqs. (1) and (2) for two different solutes (1 and 2) to obtain the decimal logarithm of their selectivity factor (log $\alpha_{1/2}$) according to Eq. (3).

$$\log\ \alpha_{1/2} = \log\ k_1 - \log\ k_2 = e\cdot(E_1 - E_2) + s\cdot(S_1 - S_2) + a\cdot(A_1 - A_2) + b\cdot(B_1 - B_2) + v\cdot(V_1 - V_2) \quad (3)$$

In Eq. (3), *e*, *s*, *a*, *b*, and *v* are the system coefficients for the specific chromatographic conditions, and *E*, *S*, *A*, *B*, and *V* the molecular descriptors of solutes 1 and 2. Notice that the system constant (*c*) in Eq. (1) is cancelled in Eq. (3) due to the subtraction of log *k* values. According to this equation, the selectivity factor depends on the diverse solute-solvent interactions of the system, indicated by the lower case coefficients, and the differences between the molecular properties of solute 1 in relation to solute 2, represented by the upper case descriptors. Thus, according to Eq. (4), it would be possible to estimate any system coefficient x_i (reflecting a particular solute-solvent interaction) provided that two solutes with four identical (or very similar) molecular descriptors and a significantly different fifth descriptor X_i can be found.

$$x_i \approx \frac{\log\ \alpha_{1/2}}{X_{i,1} - X_{i,2}} = \frac{\log\ k_1 - \log\ k_2}{X_{i,1} - X_{i,2}} \quad (4)$$

For instance, in the particular case of two compounds with similar *E*, *S*, *B*, and *V* descriptors, the system coefficient *a* could be calculated as Eq. (4a). The same reasoning can be applied to estimate the rest of the system coefficients.

$$a \approx \frac{\log\ k_1 - \log\ k_2}{A_1 - A_2} \quad (4a)$$

The proposed method should provide the same information as the full Abraham's characterization model, but with significant time savings since only an adequate pair of compounds is needed to estimate each system coefficient.

3.3. Selection of the test compound candidates

The development of the fast characterization method described in the previous section requires a selection of pairs of solutes with adequate descriptors. We searched within the Abraham's database for pairs of solutes with four very similar molecular descriptors (d_{Xi}) and a fifth one as different as possible (ΔX_i). The dissimilarity of a particular pair of solutes was evaluated according to the Euclidean distance of their four similar solute descriptors (d_{Xi}) and the difference in the molecular descriptor of interest (ΔX_i) by means of Eqs. (5) and (6), respectively.

$$d_{X_i} = \sqrt{\sum_{i\neq j=1}^{4} \left(X_{j,1} - X_{j,2}\right)^2} \quad (5)$$

$$\Delta X_i = X_{i,1} - X_{i,2} \quad (6)$$

When evaluating candidates for the estimation of an x_i system coefficient (Eq. (4)), differences between the related molecular descriptor ($X_{i,1}-X_{i,2}$) must be as large as possible whereas differences between the rest of descriptor pairs ($X_{j\neq i,1}-X_{j\neq i,2}$) must be necessarily small (ideally $d_{Xi} = 0$). For instance, for the evaluation of solute hydrogen bond acidity candidates Eqs. (5) and (6) can be expressed as Eqs. (5a) and (6a).

$$d_A = \sqrt{(E_1 - E_2)^2 + (S_1 - S_2)^2 + (B_1 - B_2)^2 + (V_1 - V_2)^2} \quad (5a)$$

$$\Delta A_i = A_{i,1} - A_{i,2} \quad (6a)$$

For the selection of suitable pairs of candidates, we looked for compounds that differ in the molecular descriptor of interest (Eq. (6)) not lower than 0.5 units, and dissimilarities for the other descriptors (Eq. (5)) not higher than 0.05. Additionally, solute candidates were required to absorb in the ultraviolet range in order to be easily detected, to be commercially available and relatively inexpensive, and soluble enough in the common solvents used in the preparation of reversed-phase and HILIC mobile phases. Finally, the acid/base properties of the selected compounds were also considered to be in their neutral form over the widest possible range within the column pH stability. Most of the HILIC columns available in the market have a silica matrix whose recommended operational pH range is between 2 and 7.5. Therefore, phenols with pK_a values above 9 were more appropriate candidates for hydrogen bond acidic test solutes, rather than, for instance, carboxylic acids, which are expected to be yet deprotonated at mildly acidic pH values. Anisoles, which lack acid/base properties, are interesting candidates in the characterization of hydrogen bond basicity. On the other hand, amines, anilines, and pyridines must be evaluated with care due to their basic nature. For example, 5-indanol and *N*,*N*-dimethylaniline were promising test compounds for the determination of *a* coefficient (ΔA = 0.56 and d_A = 0.02), but the basic behavior of the aniline (pK_a 5.07 [37]) makes it unsuitable for the characterization of chromatographic systems

with acidic mobile phases.

The pairs of solute candidates finally considered in this study and their molecular descriptors are presented in Table 3. Notice that these compounds are grouped according to the solute selectivity expected for each pair of solutes, and the remaining four molecular descriptors must be as similar as possible. The quotient $\Delta X_i/d_{Xi}$ also reported in the table is an indicator of the potential goodness of a specific pair of solute candidates, since the larger the difference between the same molecular descriptor for the test compounds (ΔX_i, Eq. (6)) and the lower the difference between the other four descriptors (d_{Xi}, Eq. (5)), the better. The molecular structures of the selected pairs of compounds cited in Table 3 are presented in Table S1 (supplementary material).

For the estimation of the contribution to retention of the solute excess polarizability two pairs of compounds were considered, 1,8-dihydroxyanthraquinone/1-chloroanthraquinone and dibenzofuran/1-chloro-3-phenylpropane. The anthraquinones have very similar structure, only the two OH groups are replaced by one H and one Cl. Thus, volume (*V*), dipolarity (*S*), and hydrogen bond basicity (*B*) are very similar, although the strong electronegativity of Cl makes the chloroanthraquinone much less polarizable than the dihydroxyanthraquinone giving a much lower *E* descriptor. Interestingly, the dihydroxy functionalized one does not act as hydrogen bond donor in their interactions with surrounding solvent molecules, most probably due to intramolecular hydrogen bonding between the hydroxy groups and the neighboring carbonyl and both compounds have no hydrogen bond donor ability at all ($A = 0$) [38,39]. The Cl atom in the structure of 1-chloro-3-phenylpropane may contribute to a lower polarizability and *E* descriptor than dibenzofuran, which is a very polarizable compound due to the complete delocalization of the 12-π-electrons in the two benzenes fused to the central furan ring. Both compounds have similar volume, dipolarity, small hydrogen bond basicity (because of the π-electrons of the aromatic rings) and no hydrogen bond donor atoms.

Regarding dipolarity/polarizability, on the one hand pentacene have the same type and number of atoms, bonds and even aromatic rings than dibenz[*a*,*c*]anthracene, dibenz[*a*,*h*]anthracene, and picene and thus, the same volume, excess molar refraction and hydrogen bond capabilities, but the linear disposition of aromatic rings in pentacene makes it much more dipolar than the other compounds (higher *S* descriptor). On the

Table 3
Pairs of solute candidates considered in the study, their corresponding molecular descriptors [6], differences between molecular descriptors of the two members of a particular pair of solutes (ΔX_i, Eq. (6)), the dissimilarity between the rest of molecular descriptors (d_X, Eq. (5)) and the ratio $\Delta X_i/d_{Xi}$.

Solute selectivity and compounds	*E*	*S*	*A*	*B*	*V*			
Excess polarizability (*E*)						**ΔE**	**d_E**	**$\Delta E/d_E$**
(1) 1,8-Dihydroxyanthraquinone	**2.46**	1.79	0.00	0.56	1.65	0.56	0.01	41
(2) 1-Chloroanthraquinone	**1.90**	1.79	0.00	0.57	1.65			
(1) Dibenzofuran	**1.78**	0.86	0.00	0.25	1.27	0.99	0.04	23
(2) 1-Chloro-3-phenylpropane	**0.79**	0.90	0.00	0.24	1.26			
Dipolarity/polarizability (*S*)						**ΔS**	**d_S**	**$\Delta S/d_S$**
(1) Pentacene	4.00	**2.71**	0.00	0.44	2.19	0.78	0.00	–
(2) Dibenz[*a*,*c*]anthracene	4.00	**1.93**	0.00	0.44	2.19			
(1) Pentacene	4.00	**2.71**	0.00	0.44	2.19	0.67	0.00	–
(2) Dibenz[*a*,*h*]anthracene	4.00	**2.04**	0.00	0.44	2.19			
(1) Pentacene	4.00	**2.71**	0.00	0.44	2.19	0.67	0.00	–
(2) Picene	4.00	**2.04**	0.00	0.44	2.19			
(1) 1,2-Dicyanobenzene	0.87	**1.96**	0.00	0.41	1.03	1.00	0.02	64
(2) 2-Methylbenzaldehyde	0.87	**0.96**	0.00	0.40	1.01			
(1) 1,4-Dicyanobenzene	0.87	**1.98**	0.00	0.42	1.03	1.02	0.02	44
(2) 2-Methylbenzaldehyde	0.87	**0.96**	0.00	0.40	1.01			
(1) 2,6-Dichlorobenzonitrile	1.10	**1.22**	0.00	0.27	1.12	0.53	0.03	21
(2) 1,2-Dihydronaphthalene	1.09	**0.69**	0.00	0.25	1.13			
Solute hydrogen bond acidity (*A*)						**ΔA**	**d_A**	**$\Delta A/d_A$**
(1) 4-Chloro-2-methylphenol	0.89	0.91	**0.63**	0.22	1.04	0.63	0.04	15
(2) 2-Chloroanisole	0.88	0.91	**0.00**	0.26	1.04			
(1) 4-Chloro-3,5-dimethylphenol	0.98	0.94	**0.61**	0.26	1.18	0.61	0.05	13
(2) 2,4-Dichloroanisole	1.00	0.94	**0.00**	0.22	1.16			
(1) 4-Chloro-3,5-dimethylphenol	0.98	0.94	**0.61**	0.26	1.18	0.61	0.05	12
(2) 3,4-Dichloroanisole	0.96	0.95	**0.00**	0.22	1.16			
(1) 3-Ethoxyphenol	0.85	1.14	**0.56**	0.48	1.12	0.56	0.05	12
(2) 2-Chloroacetophenone	0.89	1.14	**0.00**	0.47	1.14			
(1) 4-Isopropoxyphenol	0.80	1.18	**0.57**	0.49	1.26	0.57	0.05	12
(2) Methyl 4-methoxybenzoate	0.83	1.20	**0.00**	0.52	1.27			
Solute hydrogen bond basicity (*B*)						**ΔB**	**d_B**	**$\Delta B/d_B$**
(1) 2,3,5,6-Tetramethylpyrazine	0.69	0.80	0.00	**0.85**	1.20	0.51	0.03	18
(2) 2,6-Dimethylanisole	0.67	0.78	0.00	**0.34**	1.20			
(1) 2,3,5,6-Tetramethylpyrazine	0.69	0.80	0.00	**0.85**	1.20	0.55	0.03	18
(2) 3-Ethylanisole	0.72	0.80	0.00	**0.30**	1.20			
(1) 2,3,5,6-Tetramethylpyrazine	0.69	0.80	0.00	**0.85**	1.20	0.55	0.04	14
(2) 4-Ethylanisole	0.73	0.80	0.00	**0.30**	1.20			
(1) Trimethylpyrazine	0.66	0.74	0.00	**0.81**	1.06	0.51	0.05	10
(2) 4-Methylanisole	0.70	0.77	0.00	**0.30**	1.06			

other hand, the contribution to solute polarity of the two C≡N functional groups in dicyanobenzene molecules is more relevant than that of the single carbonyl group of 2-methylbenzaldehyde. The consideration applies for the cyano and chloro groups in the 2,6-dichlorobenzonitrile in relation to the 1,2-dihydronaphthalene, similar in McGowan's molecular volume, molar refraction and hydrogen acidity and basicity, but without polar substituents.

For the characterization of hydrogen bonding interactions, we selected several phenols as strong hydrogen bond donors in contrast to methoxybenzenes, aromatic ketones and esters of similar structure, atomic elements and bonds, but lacking of hydrogen atoms covalently bonded to an oxygen atom and thus $A = 0$. 4-Chloro-2-methylphenol has the same empirical formula (C_7H_7ClO) and number of bonds than 2-chloroanisole and a very similar structure. Thus, molecular volume, molar refraction, dipolarity, and hydrogen bond basicity are practically the same. Same considerations apply to 4-chloro-3,5-dimethylphenol/dichloroanisoles pairs, where a CH_3 is changed by a Cl, 3-ethoxyphenol/2-chloroacetophenone, one O and three H atoms changed by a Cl atom, and 4-isopropoxyphenol/methyl 4-methoxybenzoate pair, with two H changed by an O atom but one more bond.

Concerning solute hydrogen bond basicity, pyrazines in contrast to anisoles have been selected. The acceptor capacity of the two nitrogen atoms in the pyrazine ring leads to higher *B* values than that of the single oxygen atom of anisoles. Thus, trimethylpyrazine/methylanisole and tetramethylpirazines/dimethyl or ethylanisoles seem very adequate because they only differ in the two nitrogen atoms changed by one C and one O atoms.

As stated before, compounds of any homologous series can be used for the estimation of the cavity term because all compounds of the particular series have almost all equivalent descriptors except for the McGowan's molecular volume (*V*), as for the Tanaka's hydrophobicity test. Two consecutive members of any series differ only in one CH_2 group. We have selected *n*-alkyl ketones series for their low molecular volumes as explained in Section 3.5.

3.4. Selection of the chromatographic systems

For this study, two reversed-phase and four HILIC columns were selected as starting point to develop a characterization method suitable for different chromatographic modes. All columns share the same dimensions and have similar features in terms of particle and pore sizes. Reversed-phase columns have the same octadecyl (C18) bonded phase but differ in the support: silica for Chrom-Clone and hybrid silica for Gemini which provides to the column the advantage of a wider operational pH range. HILIC columns, having in common the silica matrix, were selected based on their different polar bonded phase chemistry: aminopropyl (Luna NH2), polyvinyl alcohol (YMC-Pack PVA-Sil), 1,2-dihydroxypropyl (YMC-Triart Diol-HILIC), and polymeric zwitterionic sulfobetaine (ZIC-HILIC).

Regarding the selection of the mobile phase, acetonitrile was chosen as organic modifier due to its eluotropic behavior, lowest system backpressure and low UV cutoff for UV/Vis detection, which makes it the most common organic solvent used in HILIC and reversed-phase chromatographic systems. Since the orthogonality features of these two modes, the significant difference must reside on the water amount in the mobile phase. The chosen eluent composition should lead to a sufficient retention of the studied compounds, allowing the accurate measurement of the retention factors. This was achieved for reversed-phase systems with a 60% acetonitrile, but for HILIC, since water is the strongest eluent, the fraction of acetonitrile was required to be increased up to 90%.

3.5. Determination of hold-up volume and system hydrophobicity (cavity term)

The method proposed so far requires an accurate determination of retention factors, which implies the trustful knowledge of the column hold-up volume (V_M). In reversed-phase, this value can be easily estimated from the elution volume of an unretained marker, such as uracil or potassium bromide (depending on the presence of salts in the eluent) [40], but in HILIC, hold-up volume determination is not that straightforward due to the complexity of the retention mechanism [41]. Therefore, we propose the determination of V_M by means of the homologous series method based on the Abraham model, discussed in previous works [42,43] and presented in Eq. (7).

$$V_R = V_M\left(1 + r^0 10^{v \cdot V}\right) \tag{7}$$

The hold-up volume (V_M), r^0 and v can be obtained after fitting to Eq. (7) the measured retention volumes (V_R), for at least four homologues, with their corresponding molecular volumes (*V* descriptor value). r^0 is a constant value depending on both the chromatographic system and the homologous series selected, and v is the Abraham's coefficient accounting for differences in the cohesivity between mobile and stationary phases. Notice that the members of a particular homologous series only differ in the molecular volume (*V*), as shown in Table S2 (supplementary material), and thus $r^0 = 10^{c + eE + sS + aA + bB}$, assuming an average value of *E*, *S*, *A*, and *B* molecular descriptors for the entire series (*c*, *e*, *s*, *a*, and *b* are constant for a particular chromatographic system, i.e. column and mobile phase). Therefore, from the injection of a few homologues it can be easily obtained the hold-up volume, necessary for the determination of retention factors, and the v system coefficient of the chromatographic system.

Three different homologous series were assayed as candidates for the measurement of hold-up volumes and v coefficients for both reversed-phase and HILIC systems: *n*-alkyl benzenes (from benzene to dodecylbenzene), *n*-alkyl phenones (from acetophenone to decanophenone) and *n*-alkyl ketones (from propanone to nonadecane-2-one). Each series was analyzed individually using Eq. (7) and also jointly as described in Refs. [35,42–44]. Although showing a lower absorbance in the UV, ketones are more convenient in the fittings to Eq. (7) due to their extended lower molecular volume range in relation to benzenes and phenones (Table S1). For instance, propanone and butanone have lower molecular volumes (*V*) than benzene (the smallest *n*-alkyl benzene member), and this range widens up to hexan-2-one when the smallest of the *n*-alkyl phenones, acetophenone, is considered. As a result, *n*-alkyl ketones allow a better estimation of hold-up volumes in reversed-phase, since extrapolation distance to zero molecular volume is shorter (Fig. 1A), and a more accurate determination of the v parameter in HILIC, because of the higher retention volume of the smallest homologue in the series (Fig. 1B). Consequently, four representative *n*-alkyl ketones were selected for each chromatographic mode: propanone, heptan-2-one, decan-2-one, and dodecan-2-one for reversed-phase, and propanone, heptan-2-one, dodecan-2-one, and nonadecan-2-one for HILIC. As example, the chromatograms obtained for the Chrom-Clone column for reversed-phase and on the ZIC-HILIC column for HILIC are shown in Fig. 2.

The fitted values of V_M, r^0, and v for each of the studied chromatographic systems are presented in Table 4. The main difference between both retention modes is the sign of the v coefficient, positive for reversed-phase and negative for HILIC. In reversed-phase, the C18 bonded phase acting as stationary phase is less cohesive than the hydroorganic mobile phase used as eluent, and thus creating a cavity for the solute in the bonded phase is less energy consuming. Consequently, larger solutes are more prone to partition into the bonded phase, increasing their retention (Fig. 1A). However, in HILIC, the stationary phase is believed to be mainly a water layer [45–49], which is more cohesive than the hydroorganic mobile phase, and thus larger molecules partition more favorably into the mobile phase, which in turn leads to a reduction in their retention (Fig. 1B).

V_M and v values obtained using the four selected ketones are consistent with the fitted values from the joint analysis of the three

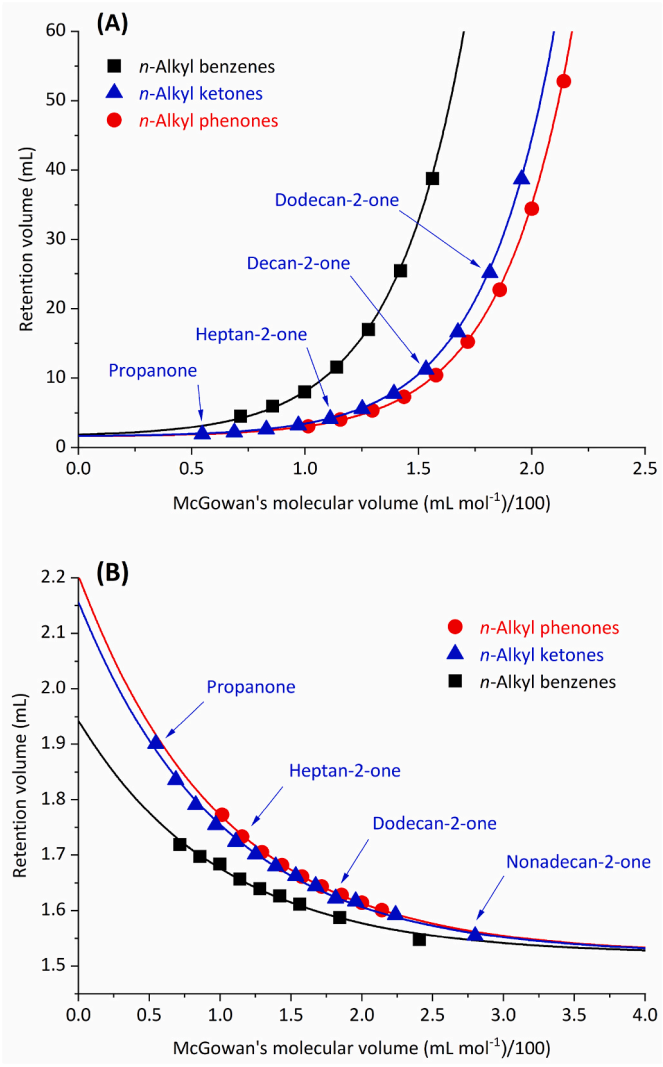


Fig. 1. Representative examples of retention volumes of *n*-alkyl benzenes, *n*-alkyl phenones and *n*-alkyl ketones homologous series in a (A) reversed-phase Gemini C18 column (60% acetonitrile/40% water) and a (B) HILIC PVA-Sil column (90% acetonitrile/10% water). The ketones selected for the fittings to Eq. (7) are explicitly indicated for (A) reversed-phase and (B) HILIC.

complete homologous series. In fact, fitted hold-up volumes match the elution volume of uracil in reversed-phase (unbuffered mobile phase) and dodecylbenzene in HILIC, which can be considered as hold-up volume markers [40,41]. Furthermore, fitted cavity coefficients were very similar to the average *v* values obtained for all possible pairs of homologues through the analogous version of equation Eq. (4), with differences between fitted and mean values not higher than 0.05 for all the studied chromatographic systems.

3.6. Determination of solute-solvent interactions

The estimated *e*, *s*, *a*, and *b* Abraham's system coefficients from Eq. (4) for all the pairs of compounds and chromatographic systems studied in this work are shown in Table 5. The retention factors needed for the estimation of the system coefficients in reversed-phase and HILIC are shown in Table S3 and Table S4, respectively. Relatively similar system coefficients were obtained from the different pairs of solute candidates selected to evaluate a specific interaction. Hence, mean values for each coefficient have been obtained and are also presented in Table 5. The sign and magnitude of the coefficients are in agreement with those obtained for other reversed-phase and HILIC systems by means of conventional multiple linear regression analysis to Abraham's solvation parameter model (Eq. (1)) [36,50].

For the studied columns (except Luna NH2), the mean *e* coefficient is close to zero indicating that excess polarizability contributions from *n*- and π-electrons do not play a relevant role in chromatographic retention since this type of interactions between the solutes and the two chromatographic phases (stationary and mobile) are of similar magnitude. In the case of the amino bonded phase, *e* takes greater positive values showing that these particular solute-solvent interactions favor partition into the stationary phase.

The averaged *s* coefficient shows the effect of the solute-solvent dipolarity/polarizability on the chromatographic retention. For reversed-phase columns, the value is large and negative, denoting that dipolar-type interactions favor solute partitioning in the mobile phase rather than in the stationary phase. However, in HILIC systems, *s* is slightly negative for the amino and polyvinyl alcohol bonded phases and somewhat positive for the diol and zwitterionic ones. In any case, these interactions are close to zero and they have practically no impact on retention.

The *a* and *b* coefficients measure the difference in the hydrogen bond acceptor and donor capabilities, respectively, between stationary and mobile phases. In reversed-phase, mean values of these coefficients exhibit a negative sign, indicating that the interactions between the solute and the hydroorganic mobile phase are stronger than the ones with the non-polar C18 stationary phase. The opposite occurs in HILIC, where positive coefficients denote that the solute tends to interact by hydrogen bonding with the water-rich layer acting as stationary phase, greatly increasing the solutes retention. Nevertheless, the magnitude of *a* and *b* coefficients depends on the nature of the bonded phases, pointing out that the ligand is playing a direct role in the hydrogen bonding interactions and/or in the composition and properties of the stationary phase water-rich layers. The largest *b* values, negative in reversed-phase and positive in HILIC, appear to be of paramount importance in explaining retention in both chromatographic modes.

3.7. Selection of the best solute-solvent interactions indicator pairs

In the fast method we propose, it is assumed that each pair of solutes suggested for the estimation of a system coefficient differs only in one specific molecular descriptor, being the rest of descriptors virtually the same and thus their contribution can be neglected (Eq. (4)). Nevertheless, even small differences between descriptors might be responsible for changes in the chromatographic retention, particularly for interactions represented by large system coefficients. In the following part of the study, we evaluated the importance of these contributions on the estimation of system coefficients, and thus the error we might incur if they are neglected in the selection of the most appropriate pairs of compounds. Reorganizing Eq. (3), it is possible to obtain the expression presented in Eq. (8) which allows to estimate the overall value of a system coefficient ($x_{i,\mathrm{overall}}$) taking into account the contribution of all solute-solvent interactions. The contribution to residual mismatches between solute descriptors for the four other specific interactions ($\Sigma\, x_j \cdot (X_{j,1}–X_{j,2})$) is subtracted to the experimentally determined selectivity factor ($\log\, \alpha_{1/2}$, Eq. (3)).

$$x_{i,\mathrm{overall}} = \frac{\log\ \alpha_{1/2} - \sum_{\substack{i=4\\ i\neq j=1}} x_j \cdot \left(X_{j,1} - X_{j,2}\right)}{X_{i,1} - X_{i,2}} \tag{8}$$

As example, the application of Eq. (8) for the estimation the overall hydrogen bond basicity behavior of the chromatographic system to a particular pair of solute data is shown in Eq. (8a).

$$a_{\mathrm{overall}} = \frac{\log\ \alpha_{1/2} - [e\cdot(E_1 - E_2) + s\cdot(S_1 - S_2) + b\cdot(B_1 - B_2) + v\cdot(V_1 - V_2)]}{A_1 - A_2} \tag{8a}$$

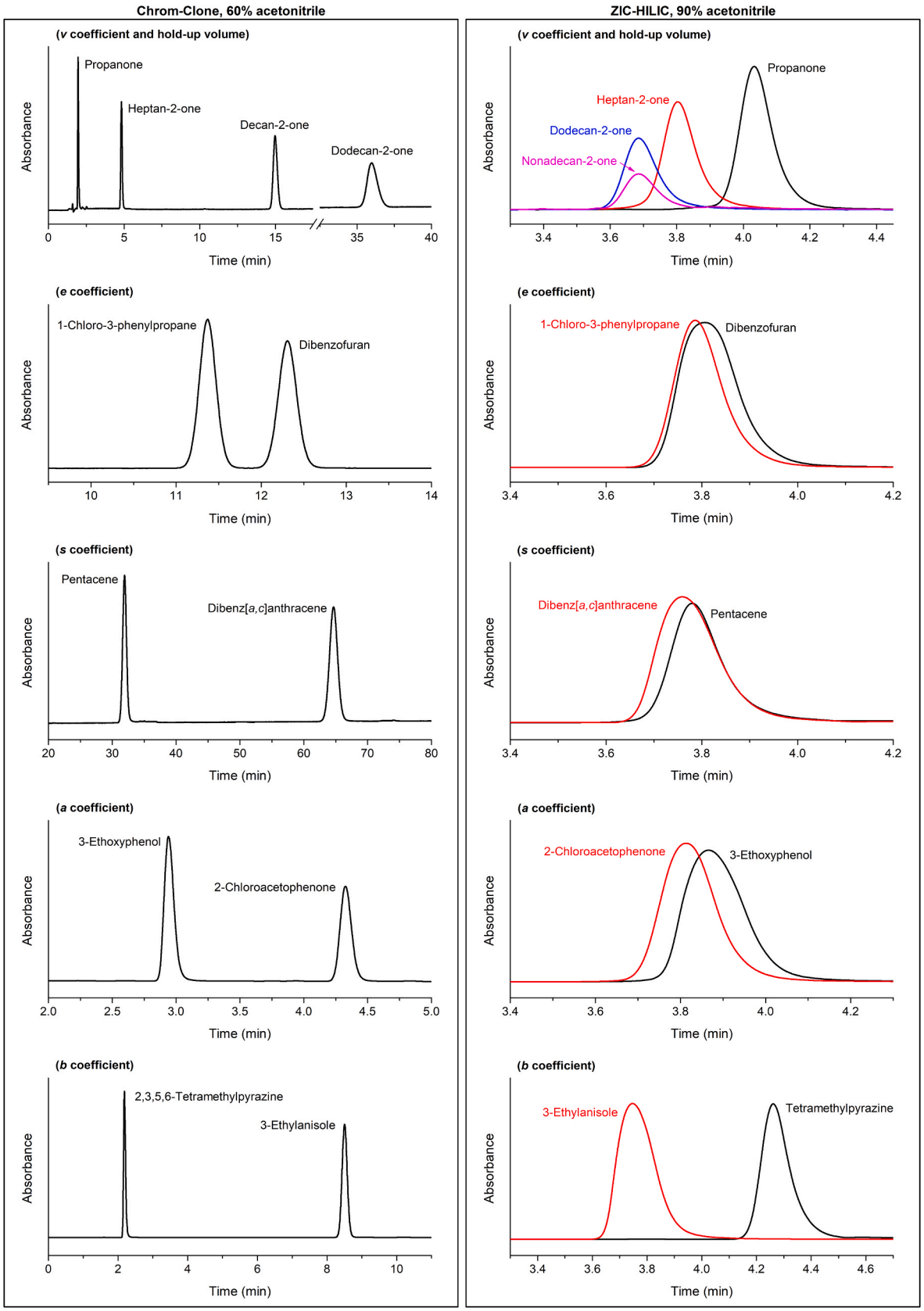


Fig. 2. Chromatograms obtained on Chrom-Clone column (60% acetonitrile/40% water) and the ZIC-HILIC column (90% acetonitrile/10% water) for the finally proposed individual pairs of test compounds (*e*, *s*, *a*, and *b*) and homologous series (*v* and hold-up volume).

Table 4
Hold-up volumes (V_M), r^0, and volume coefficient (v) (± standard deviation) for each column obtained from the fittings to Eq. (7) for the selected four *n*-alkyl ketones. The adjusted determination coefficients (R^2_{adj}), and the root-mean-square error (*RMSE*) of the fittings are also given.

	Column	V_M (mL)	r^0	v	R^2_{adj}	*RMSE*
RPLC	**Chrom-Clone**	1.364 ± 0.045	0.060 ± 0.004	1.442 ± 0.007	1.000	0.043
	Gemini	1.498 ± 0.060	0.054 ± 0.005	1.359 ± 0.012	1.000	0.053
HILIC	**Luna NH2**	1.600 ± 0.004	0.278 ± 0.002	−0.373 ± 0.011	1.000	0.001
	PVA-Sil	1.672 ± 0.006	0.367 ± 0.006	−0.472 ± 0.021	1.000	0.003
	Diol-HILIC	1.525 ± 0.010	0.448 ± 0.012	−0.474 ± 0.033	0.999	0.005
	ZIC-HILIC	1.734 ± 0.002	0.284 ± 0.013	−0.828 ± 0.043	0.999	0.002

Acetonitrile/water mobile phases: reversed-phase (RPLC) 60/40, HILIC 90/10.

In this work, the x_j values required in Eq. (8) were the average of the system coefficients obtained from each group of pair of compounds proposed for the estimation of *a*, *b*, *s*, and *e* (Table 5), and *v* was the value fitted from the homologous series approach (Table 4). The closer the x_i and $x_{i,overall}$ values, the lower the significance of side contributions to differences in retention for a particular pair of compounds. Additionally, if there were a significant bias in any of the solute molecular descriptors, this would be reflected in the differences between x_i and $x_{i,overall}$.

System coefficients obtained from Eq. (8) ($x_{i,overall}$) and Eq. (4) (x_i) were compared ($\Delta x_i = x_{i,overall} - x_i$) for every pair of solute candidates and chromatographic system, and they are reported in Table 6. In general, the differences are minimal, leading to the conclusion that the selection criteria handled was an appropriate approach, and the molecular descriptors used for the selection process were well identified. However, the differences in *e* determination by dibenzofuran/1-chloro-3-phenylpropane seems slightly better than by 1,8-dihydroxyanthraquinone/1-chloroanthraquinone. Differences in *s* determination by 2,6-dichlorobenzonitrile/1,2-dihydronaphthalene are clearly larger than by the other indicator pairs, particularly those of pentacene and dibenzoanthracenes or picene that are practically null. In the same way 4-chloro-2-methylphenol/2-chloroanisole performs worse than the other pairs for *a* determination, being 3-ethoxyphenol/2-chloroacetophenone and 4-isopropoxyphenol/methyl 4-methoxybenzoate the most accurate ones. Finally, the pairs of anisoles with tetramethylpyrazine give better results for *b* that with trimethylpyrazine. For this system descriptor, 2,3,5,6-tetramethylpyrazine/3-ethylanisole give the smallest deviations. Thus, the first pair of each group indicated in Table 6 is proposed: dibenzofuran and 1-chloro-3-phenylpropane for excess polarizability interactions (*e*); pentacene and dibenz[*a*,*c*]anthracene for dipolarity/polarizability interactions (*s*); 3-ethoxyphenol and 2-chloroacetophenone for hydrogen bonding donation from solute to solvent phases (*a*); and 2,3,5,6-tetramethylpyrazine and 3-ethylanisole for hydrogen bonding donation from solvent phases to solute (*b*).

The orthogonality of these pairs of compounds used for the estimation of *e*, *s*, *a*, and *b* system coefficients was assessed by a correlation matrix of the differences in their *E*, *S*, *A*, *B* and *V* molecular descriptors (ΔX_i, Eq. (6)). Heptan-2-one and dodecan-2-one, the two common ketones used for the estimation of *v* coefficient for both HILIC and reversed-phase chromatographic modes (Section 3.5), were also introduced in the matrix accounting for the system hydrophobicity (cavity term). Table 7 shows correlation coefficients in the range between −0.28 and 0.27, confirming the orthogonality of the selected pairs of test solutes.

Fig. 2 shows representative chromatograms of the finally proposed pairs of test compounds and homologous series for reversed-phase and HILIC chromatographic systems.

Table 5
Estimated *e*, *s*, *a*, and *b* Abraham's system coefficients from Eq. (4) for each pair of solute candidates and chromatographic system studied in this work.

Compounds	Chrom-Clone	Gemini	Luna NH2	PVA-Sil	Diol-HILIC	ZIC-HILIC
	60% MeCN	60% MeCN	90% MeCN	90% MeCN	90% MeCN	90% MeCN
e						
1,8-Dihydroxyanthraquinone/1-Chloroanthraquinone	0.02	0.01	0.38	0.05	0.02	0.00
Dibenzofuran/1-Chloro-3-phenylpropane	0.04	0.08	0.14	0.08	0.11	0.03
Mean	*0.03*	*0.04*	*0.26*	*0.06*	*0.06*	*0.01*
s						
Pentacene/Dibenz[*a*,*c*]anthracene	−0.41	−0.36	−0.07	−0.03	0.13	0.14
Pentacene/Dibenz[*a*,*h*]anthracene	−0.53	−0.48	−0.05	−0.01	0.15	0.16
Pentacene/Picene	−0.53	−0.47	−0.09	−0.05	0.13	0.15
1,2-Dicyanobenzene/2-Methylbenzaldehyde	−0.26	−0.08	−0.01	−0.02	−0.04	0.02
1,4-Dicyanobenzene/2-Methylbenzaldehyde	−0.23	−0.07	−0.06	−0.05	−0.08	−0.02
2,6-Dichlorobenzonitrile/1,2-Dihydronaphthalene	−0.73	−0.66	0.07	0.06	0.05	0.11
Mean	*−0.45*	*−0.36*	*−0.03*	*−0.02*	*0.05*	*0.09*
a						
4-Chloro-2-methylphenol/2-Chloroanisole	−0.30	−0.30	0.36	0.15	0.14	0.28
4-Chloro-3,5-dimethylphenol/2,4-Dichloroanisole	−0.57	−0.56	0.67	0.22	0.22	0.46
4-Chloro-3,5-dimethylphenol/3,4-Dichloroanisole	−0.66	−0.63	0.68	0.22	0.23	0.49
3-Ethoxyphenol/2-Chloroacetophenone	−0.50	−0.48	0.34	0.18	0.16	0.32
4-Isopropoxyphenol/Methyl 4-methoxybenzoate	−0.40	−0.38	0.72	0.15	0.16	0.29
Mean	*−0.49*	*−0.47*	*0.55*	*0.18*	*0.18*	*0.37*
b						
2,3,5,6-Tetramethylpyrazine/2,6-Dimethylanisole	−1.90	−1.19	0.82	1.17	1.35	1.59
2,3,5,6-Tetramethylpyrazine/3-Ethylanisole	−1.82	−1.38	0.81	1.14	1.34	1.57
2,3,5,6-Tetramethylpyrazine/4-Ethylanisole	−1.85	−1.39	0.81	1.15	1.35	1.59
Trimethylpyrazine/4-Methylanisole	−1.85	−1.31	0.82	1.17	1.48	1.62
Mean	*−1.85*	*−1.32*	*0.81*	*1.16*	*1.38*	*1.59*

Table 6
Differences between system coefficients obtained from Eq. (8) and Eq. (4) ($\Delta x_i = x_{i,\text{overall}} - x_i$) for every pair of solute candidates and chromatographic system.

Compounds	Chrom-Clone	Gemini	Luna NH2	PVA-Sil	Diol-HILIC	ZIC-HILIC
	60% MeCN	60% MeCN	90% MeCN	90% MeCN	90% MeCN	90% MeCN
e	**Δ*e***					
Dibenzofuran/1-Chloro-3-phenylpropane	−0.018	−0.019	−0.005	−0.006	−0.006	−0.002
1,8-Dihydroxyanthraquinone/1-Chloroanthraquinone	−0.030	−0.019	0.014	0.021	0.026	0.028
s	**Δ*s***					
Pentacene/Dibenz[*a*,*c*]anthracene	0.000	0.000	0.000	0.000	0.000	0.000
Pentacene/Dibenz[*a*,*h*]anthracene	0.000	0.000	0.000	0.000	0.000	0.000
Pentacene/Picene	0.000	0.000	0.000	0.000	0.000	0.000
1,2-Dicyanobenzene/2-Methylbenzaldehyde	0.001	−0.003	−0.004	−0.006	−0.008	−0.006
1,4-Dicyanobenzene/2-Methylbenzaldehyde	0.020	0.010	−0.012	−0.017	−0.022	−0.022
2,6-Dichlorobenzonitrile/1,2-Dihydronaphthalene	0.103	0.081	−0.044	−0.056	−0.065	−0.080
a	**Δ*a***					
3-Ethoxyphenol/2-Chloroacetophenone	0.088	0.077	−0.010	−0.034	−0.038	−0.058
4-Isopropoxyphenol/Methyl 4-methoxybenzoate	−0.072	−0.042	0.045	0.051	0.065	0.065
4-Chloro-3,5-dimethylphenol/2,4-Dichloroanisole	0.079	0.047	−0.034	−0.060	−0.074	−0.079
4-Chloro-3,5-dimethylphenol/3,4-Dichloroanisole	0.070	0.038	−0.051	−0.064	−0.077	−0.078
4-Chloro-2-methylphenol/2-Chloroanisole	−0.118	−0.084	0.048	0.073	0.087	0.101
b	**Δ*b***					
2,3,5,6-Tetramethylpyrazine/3-Ethylanisole	0.001	0.002	0.014	0.003	0.004	0.001
2,3,5,6-Tetramethylpyrazine/4-Ethylanisole	0.002	0.003	0.019	0.004	0.005	0.001
2,3,5,6-Tetramethylpyrazine/2,6-Dimethylanisole	0.017	0.012	−0.009	−0.002	−0.005	−0.004
Trimethylpyrazine/4-Methylanisole	−0.024	−0.017	0.018	0.004	0.008	0.007

Table 7
Correlation matrix of the differences (ΔX_i, Eq. (6)) between the molecular descriptors (*E*, *S*, *A*, *B*, *V*) of the pairs of compounds selected for the estimation of system coefficients (*e*, *s*, *a*, *b*) and heptan-2-one/dodecan-2-one (*v*).

	Δ*E*	Δ*S*	Δ*A*	Δ*B*	Δ*V*
Δ*E*	1				
Δ*S*	−0.28	1			
Δ*A*	−0.28	−0.23	1		
Δ*B*	−0.26	−0.25	−0.24	1	
Δ*V*	0.23	0.24	0.22	0.27	1

4. Conclusions

The characterization by means of the Abraham's linear solvation energy relationships model provides accurate information about the main interactions between the solute and the solvents constituting the chromatographic phases (polarizability, dipolarity, hydrogen bond acidity and basicity) and differences in cohesion between the mobile and stationary phases. However, the application of the model is significantly time consuming since it requires the measurement of the retention of a relatively large amount of carefully selected test solutes. In order to overcome this drawback, we propose here a fast method based on the Abraham's solvation parameter model but inspired by the Tanaka's scheme developed for the characterization of reversed-phase columns based on the selectivity factors between pairs of test compounds to model different features relevant for chromatographic retention.

The screening of Abraham's molecular descriptors databases allows us to find pairs of test substances with similar descriptors except for one. The difference in the dissimilar descriptors values allows a direct characterization of the corresponding interactions. The selected pairs of solute candidates can be used as test compounds to characterize the selectivities of chromatographic systems: selectivities for polarizability contributions from *n*- and *π*-electrons and dipolarity/polarizability (*s* and *e*) and selectivities for hydrogen bonding from solute to solvent and from solvent to solute (*a* and *b*). The recommended pairs of indicators are: dibenzofuran and 1-chloro-3-phenylpropane reflecting the polarizability contributions from *n*- and *π*-electrons, pentacene and dibenz[*a*,*c*] anthracene are proposed for dipolarity/polarizability interactions, 3-ethoxyphenol and 2-chloroacetophenone to characterize solute hydrogen bond acidity selectivity, and 2,3,5,6-tetramethylpyrazine and 3-ethylanisole solute hydrogen bond basicity selectivity. Since the calculation of the selectivity factor requires an accurate measurement of retention factors, we propose the determination of hold-up volumes using a homologous series approach consisting of four representative alkyl ketones: propanone, heptan-2-one, decan-2-one, and dodecan-2-one for reversed-phase, and propanone, heptan-2-one, dodecan-2-one, and nonadecane-2-one for HILIC. From the injection of these four homologues, besides hold-up volume, the chromatographic selectivity derived from the solute molecular volume is obtained.

The fast method proposed in this work allows the characterization of not only reversed-phase chromatographic systems, as in Tanaka's scheme, but also HILIC systems. In this work, we propose acetonitrile/water eluents containing 60% and 90% of organic modifier for reversed-phase and HILIC, respectively, but this characterization model can be in principle applied to mobile phases of different compositions.

The developed fast method is intended to be potentially applicable to any liquid chromatographic mode, independently of the considered bonded phase. However, some other solute-solvent interactions, such as those of ionic nature or based on steric selectivity, are not included in the Abraham model used in the present work. Modeling of additional complex interactions are indeed current challenges that will need to be addressed in the future.

CRediT authorship contribution statement

Lídia Redón: Investigation, Writing – original draft, Visualization. **Mahmoud Safar Beiranvand:** Software, Investigation. **Xavier Subirats:** Methodology, Validation, Supervision, Writing – review & editing. **Martí Rosés:** Conceptualization, Methodology, Writing – review & editing, Project administration, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

Acknowledgements

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.aca.2023.341672.

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SUPPLEMENTARY MATERIAL

Characterization of Solute-Solvent Interactions in Liquid Chromatography Systems: a Fast Method Based on Abraham's Linear Solvation Energy Relationships

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Table S1

Structure of the pairs of solute candidates considered in the study.

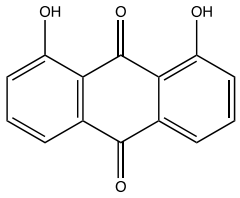
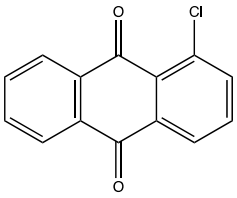
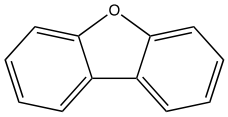
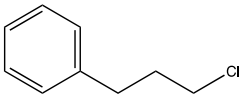
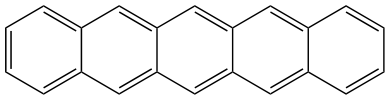
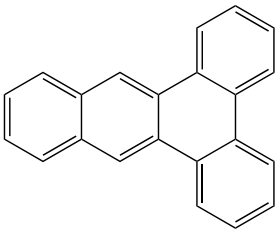
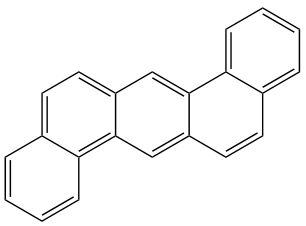
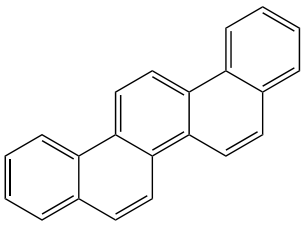
Solute excess polarizability estimation (*e*)	
	
1,8-Dihydroxyanthraquinone	1-Chloroanthraquinone
	
Dibenzofuran	1-Chloro-3-phenylpropane
Solute dipolarity/polarizability selectivity estimation (*s*)	
	
Pentacene	Dibenz[*a,c*]anthracene
	
	Dibenz[*a,h*]anthracene
	
	Picene

Table S2 (Continued)

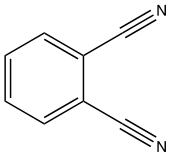
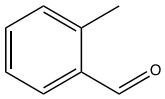
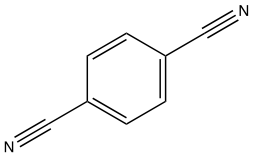
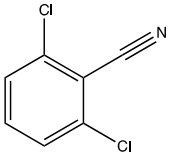
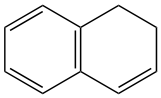
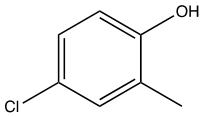
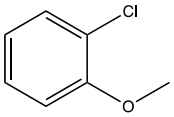
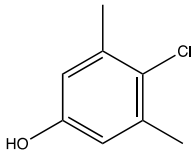
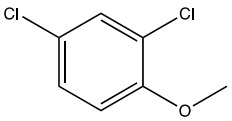
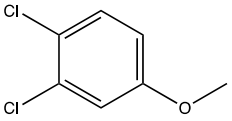
Solute dipolarity/polarizability selectivity estimation (*s*)	
	
1,2-Dicyanobenzene	2-Methylbenzaldehyde
	
1,4-Dicyanobenzene	
	
2,6-Dichlorobenzonitrile	1,2-Dihydronaphthalene
Solute hydrogen bond acidity estimation (*a*)	
	
4-Chloro-2-methylphenol	2-Chloroanisole
	
4-Chloro-3,5-dimethylphenol	2,4-Dichloroanisole
	
	3,4-Dichloroanisole

Table S2 (Continued)

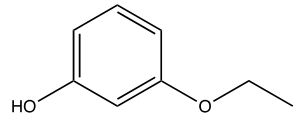
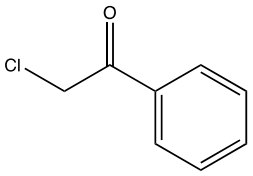
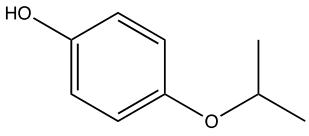
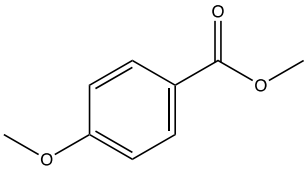
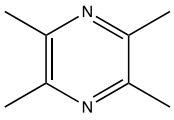
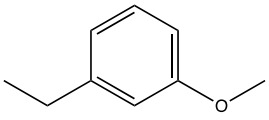
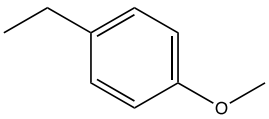
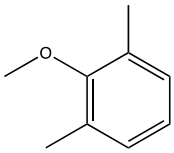
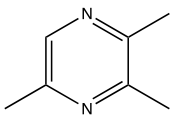
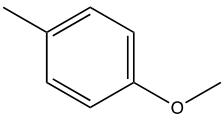
Solute hydrogen bond acidity estimation (*a*)	
	
3-Ethoxyphenol	2-Chloroacetophenone
	
4-Isopropoxyphenol	Methyl 4-methoxybenzoate
Solute hydrogen bond basicity estimation (*b*)	
	
2,3,5,6-Tetramethylpyrazine	3-Ethylanisole
	
	4-Ethylanisole
	
	2,6-Dimethylanisole
	
Trimethylpyrazine	4-Methylanisole

Table S2 (Continued)

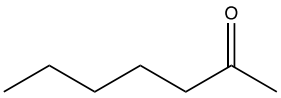
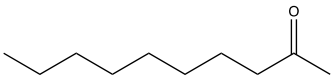
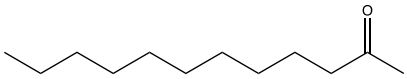
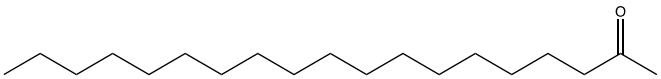
V_M and solute volume selectivity estimation (v)
 Propanone
 Heptan-2-one
 Decan-2-one
 Dodecan-2-one
 Nonadecan-2-one

Table S2

Molecular descriptors of the homologues considered in this work [1].

Homologous series	*E*	*S*	*A*	*B*	*V*
***n*-Alkyl benzenes**					
Benzene	0.61	0.52	0.00	0.14	0.716
Toluene	0.60	0.52	0.00	0.14	0.857
Ethylbenzene	0.61	0.51	0.00	0.15	0.998
Propylbenzene	0.60	0.50	0.00	0.15	1.139
Butylbenzene	0.60	0.51	0.00	0.15	1.280
Pentylbenzene	0.59	0.51	0.00	0.15	1.421
Hexylbenzene	0.59	0.50	0.00	0.15	1.562
Octylbenzene	0.58	0.48	0.00	0.15	1.844
Dodecylbenzene	0.57	0.47	0.00	0.15	2.407
***n*-Alkyl phenones**					
Acetophenone	0.82	1.01	0.00	0.48	1.014
Propiophenone	0.80	0.95	0.00	0.51	1.155
Butyrophenone	0.80	0.95	0.00	0.51	1.296
Valerophenone	0.80	0.95	0.00	0.50	1.437
Hexanophenone	0.78	0.95	0.00	0.51	1.578
Heptanophenone	0.77	0.95	0.00	0.50	1.718
Octanophenone	0.77	0.95	0.00	0.50	1.859
Nonanophenone	0.76	0.95	0.00	0.50	2.000
Decanophenone	0.75	0.95	0.00	0.50	2.141
***n*-Alkyl ketones**					
Propanone	0.18	0.70	0.04	0.49	0.547
Butanone	0.17	0.70	0.00	0.51	0.688
Pentan-2-one	0.14	0.68	0.00	0.51	0.829
Hexan-2-one	0.14	0.68	0.00	0.51	0.970
Heptan-2-one	0.12	0.68	0.00	0.51	1.111
Octan-2-one	0.11	0.68	0.00	0.51	1.252
Nonan-2-one	0.11	0.68	0.00	0.51	1.392
Decan-2-one	0.11	0.68	0.00	0.51	1.533
Undecan-2-one	0.10	0.68	0.00	0.51	1.674
Dodecan-2-one	0.10	0.68	0.00	0.51	1.815
Tridecan-2-one	0.10	0.68	0.00	0.51	1.956
Pentadecan-2-one	0.10	0.68	0.00	0.51	2.238
Nonadecan-2-one	0.09	0.68	0.00	0.51	2.801

[1] N. Ulrich, S. Endo, T.N. Brown, N. Watanabe, G. Bronner, M.H. Abraham, K.-U. Goss, UFZ-LSER database v 3.2 [Internet], (2017). http://www.ufz.de/lserd.

Table S3

Retention (*k*) and selectivity factors ($\alpha_{1/2}$) for the studied reversed-phase columns for each pair of solute candidates and reversed-phase chromatographic system studied in this work.

Compounds	Chrom-Clone 60% MeCN			Gemini 60% MeCN		
	k_1	k_2	$\alpha_{1/2}$	k_1	k_2	$\alpha_{1/2}$
e						
1,8-Dihydroxyanthraquinone / 1-Chloroanthraquinone	5.49	5.38	1.02	4.14	4.07	1.02
Dibenzofuran / 1-Chloro-3-phenylpropane	7.63	7.02	1.09	5.63	4.73	1.19
s						
Pentacene / Dibenz[*a,c*]anthracene	21.52	44.90	0.48	17.35	33.25	0.52
Pentacene / Dibenz[*a,h*]anthracene	21.52	49.03	0.44	17.35	36.49	0.48
Pentacene / Picene	21.52	48.97	0.44	17.35	36.04	0.48
1,2-Dicyanobenzene / 2-Methylbenzaldehyde	1.03	1.86	0.56	0.86	1.05	0.82
1,4-Dicyanobenzene / 2-Methylbenzaldehyde	1.07	1.86	0.58	0.89	1.05	0.85
2,6-Dichlorobenzonitrile / 1,2-Dihydronaphthalene	2.94	7.16	0.41	2.29	5.15	0.44
a						
4-Chloro-2-methylphenol / 2-Chloroanisole	2.01	3.11	0.65	1.48	2.28	0.65
4-Chloro-3,5-dimethylphenol / 2,4-Dichloroanisole	2.49	5.52	0.45	1.80	3.98	0.45
4-Chloro-3,5-dimethylphenol / 3,4-Dichloroanisole	2.49	6.32	0.39	1.80	4.34	0.41
3-Ethoxyphenol / 2-Chloroacetophenone	1.08	2.05	0.53	0.83	1.53	0.54
4-Isopropoxyphenol / Methyl 4-methoxybenzoate	1.18	1.99	0.59	0.92	1.51	0.61
b						
2,3,5,6-Tetramethylpyrazine / 2,6-Dimethylanisole	0.51	4.75	0.11	0.60	2.43	0.25
2,3,5,6-Tetramethylpyrazine / 3-Ethylanisole	0.51	5.09	0.10	0.60	3.47	0.17
2,3,5,6-Tetramethylpyrazine / 4-Ethylanisole	0.51	5.25	0.10	0.60	3.52	0.17
Trimethylpyrazine / 4-Methylanisole	0.41	3.54	0.11	0.53	2.46	0.21

Table S4

Retention (k) and selectivity factors ($\alpha_{1/2}$) for the studied HILIC columns for each pair of solute candidates and HILIC chromatographic system studied in this work.

Compounds	Luna NH2 90% MeCN			PVA-Sil 90% MeCN			Diol-HILIC 90% MeCN			ZIC-HILIC 90% MeCN		
	k_1	k_2	$\alpha_{1/2}$	k_1	k_2	$\alpha_{1/2}$	k_1	k_2	$\alpha_{1/2}$	k_1	k_2	$\alpha_{1/2}$
e												
1,8-Dihydroxyanthraquinone / 1-Chloroanthraquinone	0.21	0.13	1.62	0.11	0.10	1.06	0.12	0.12	1.02	0.04	0.04	1.00
Dibenzofuran / 1-Chloro-3-phenylpropane	0.11	0.08	1.37	0.09	0.08	1.19	0.10	0.08	1.29	0.03	0.03	1.06
s												
Pentacene / Dibenz[*a,c*]anthracene	0.14	0.16	0.88	0.07	0.07	0.96	0.11	0.09	1.26	0.03	0.02	1.29
Pentacene / Dibenz[*a,h*]anthracene	0.14	0.15	0.93	0.07	0.07	0.98	0.11	0.09	1.26	0.03	0.02	1.28
Pentacene / Picene	0.14	0.16	0.87	0.07	0.08	0.93	0.11	0.09	1.22	0.03	0.02	1.26
1,2-Dicyanobenzene / 2-Methylbenzaldehyde	0.12	0.12	0.98	0.11	0.12	0.95	0.13	0.14	0.91	0.05	0.05	1.06
1,4-Dicyanobenzene / 2-Methylbenzaldehyde	0.11	0.12	0.86	0.11	0.12	0.88	0.12	0.14	0.82	0.04	0.05	0.95
2,6-Dichlorobenzonitrile / 1,2-Dihydronaphthalene	0.11	0.10	1.09	0.10	0.09	1.07	0.11	0.10	1.06	0.04	0.03	1.14
a												
4-Chloro-2-methylphenol / 2-Chloroanisole	0.19	0.11	1.67	0.12	0.10	1.24	0.14	0.11	1.23	0.04	0.03	1.51
4-Chloro-3,5-dimethylphenol / 2,4-Dichloroanisole	0.25	0.10	2.55	0.12	0.09	1.35	0.13	0.10	1.36	0.04	0.02	1.92
4-Chloro-3,5-dimethylphenol / 3,4-Dichloroanisole	0.25	0.10	2.59	0.12	0.09	1.37	0.13	0.10	1.38	0.04	0.02	1.98
3-Ethoxyphenol / 2-Chloroacetophenone	0.20	0.13	1.55	0.14	0.11	1.26	0.16	0.13	1.23	0.05	0.03	1.51
4-Isopropoxyphenol / Methyl 4-methoxybenzoate	0.19	0.08	2.56	0.14	0.11	1.22	0.16	0.13	1.23	0.05	0.03	1.47
b												
2,3,5,6-Tetramethylpyrazine / 2,6-Dimethylanisole	0.26	0.10	2.61	0.35	0.09	3.96	0.52	0.11	4.88	0.16	0.03	6.46
2,3,5,6-Tetramethylpyrazine / 3-Ethylanisole	0.26	0.09	2.78	0.35	0.08	4.23	0.52	0.10	5.49	0.16	0.02	7.30
2,3,5,6-Tetramethylpyrazine / 4-Ethylanisole	0.26	0.09	2.79	0.35	0.08	4.29	0.52	0.09	5.56	0.16	0.02	7.44
Trimethylpyrazine / 4-Methylanisole	0.27	0.10	2.63	0.37	0.09	3.95	0.60	0.11	5.65	0.18	0.03	6.73