



Solvation parameters. Part 5: Physicochemical interpretation of experimental solvent values for stationary phases of gas–liquid chromatography

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ABSTRACT

It has been demonstrated for a long time that in the particular case of gas–liquid chromatography (GLC), a linear free energy relationship (LFER) of five terms can be established, each term including a parameter of solute and a parameter of solvent. The nature of some of these parameters has been quite clearly identified, even if not always well predicted from the molecular structure. First of all, the five solute parameters: two involved in the hydrogen bonding and three in the Van der Waals forces; secondly, the two solvent parameters involved in hydrogen bonding. It was remaining an uncertainty concerning the nature of the solvent parameters named D , W and E , respectively associated with the solute parameters of dispersion, orientation and induction/polarizability. This uncertainty has been solved using experimental chromatographic data of McReynolds (56 phases) and of the Kováts group (11 phases). The parameter W appears as of polar nature strictly speaking. The parameters D and E can be expressed by two opposite bilinear functions of $1/V$ (inverse of molecular volume) and PSA/V (ratio of the polar surface area over the molecular volume). These results are in agreement with previous studies limited to alkanes by the Kováts group.

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1. Introduction

In a series of four articles recently published [1–4], we have developed several aspects of the solvation parameters (also named solvation descriptors or solubility factors). Applied to GLC (gas–liquid chromatography), the following equation can be written:

$$RI - RI_{CH_4} = \delta D + \omega W + \varepsilon E + \alpha A + \beta B \quad (1)$$

in which RI stands for the Kováts retention index of the solute on the stationary phase under study, and RI_{CH_4} stands for the retention index of methane (always equals to 100). The lower case Greek letters stand for the parameters of solutes, and the Latin upper case letters for the solvent parameters of stationary phases.

Even oversimplified, Fig. 1 shows the elements presently clarified and those needing improvements.

First of all, let us specify that our previous studies as well as the present one are not at all of theoretical nature. If we mention the forces of Van der Waals, London, Keesom and Debye, it is just in order to roughly understand the nature of the results obtained via a purely experimental approach. Otherwise, it should be underlined that there is a general agreement of the authors involved in this field to consider that five independent terms in Eq. (1) are needed

and sufficient for a complete characterization of the solutions. By contrast, the characterization of parameters differs according to the authors [1,5]. The presentation in Fig. 1 corresponds to our point of view.

Presently, we have handled two sets of experimental solute solvation parameters: (i) an accurate one for 127 compounds [1,4], established using solely gas/liquid partition data by GLC from the Kováts group [6–11]; (ii) a data pool for 456 compounds [3], which includes the above data and additional ones based on published values by Abraham and co-authors [12,13]. Rules of selection and transformation of Abraham data are specified elsewhere [1–3]. The pooled set, less accurate, has the advantage of including a larger variety of molecular structures and more compounds with multiple functional groups of the same type.

A simplified molecular topology (SMT) has been developed and applied to these two above data sets, as learning material for predicting rules of solute solvation parameters determination. The results are only satisfactory for the parameters δ (dispersion) and ε (polarizability/induction) [2,3]. Therefore, a further determination of solute parameters entirely from GLC experimentation has been suggested, following a specified procedure [4].

1.1. Physicochemical meaning of solute parameters

There are clearly two groups of parameters: the two involved in hydrogen bonding and the three involved in the Van der Waals forces.

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forces		Van der Waals			hydrogen bonding	
		London	Keesom	Debye	proton donor	proton acceptor
SOLUTES	parameters	dispersion	orientation	induction	acidity	basicity
	acronyms	δ	ω	ε	α	β
SOLVENTS	acronyms	D	W	E	A	B
	identification	only partial at the beginning of the present study			proton acceptor	proton donor

Fig. 1. Summary of the state-of-art, at the beginning of the present study, on the solvation parameters of solutes and GLC stationary phases, focused on their physicochemical meaning. See text for details.

- The hydrogen bonding parameters α and β
These parameters are strongly correlated with the values obtained since the 70s by various authors who have combined via spectroscopic measurements:
(i) the heat of hydrogen bonding for *n*-alcohols
(ii) the heat of hydrogen bonding between non-associated compounds and suitable solvents acceptors and donors of hydrogen bonds.
A history of this experimentation is specified in [1].
- The dispersion parameter δ
Among the five solute parameters, four are constant along homologous series and one is proportional to the size of the molecule, which has sometimes been named the apolar parameter. Of course, many properties are proportional to the molecular size, but rather than the molar volume or $\log L16$ (the Ostwald solubility coefficient of the solute on *n*-hexadecane at 298 K) applied by Abraham and co-authors [12,13], we have chosen the molar refraction as best reflecting this experimental *apolar* factor, which we therefore name of *dispersion* [1].
- The orientation parameter ω
It is strictly speaking the polar parameter, strongly correlated with the dipole moment for compounds having a single polar function. For compounds with various polar functions and without dipole moment (e.g. 1,4-dioxane), the orientation parameter presents, however, positive values. We have found this property more suitable than π_2^H (or *S*) proposed by Abraham and co-authors [12,13]. Arguments can be seen in [1].
- The polarizability/induction parameter ε

The identification of this experimental parameter to molecular characteristics is a long story. A molecular property related to the molar volume plus the molar refraction was first defined in 1969 and applied in QSAR (quantitative structure–activity relationship) of olfactory studies [14]. It was later named ε (as electron factor) [15]. Its first definition was based on the highest ratio r/ν of the atoms of a given molecule, r and ν standing respectively for the additive increments of the molar refraction and for the molar volume at boiling point. This first definition was later discarded and replaced by a value derived from GLC experimentation [16], which in turn was identified to the expression $f_n \times V_{20}/V_b$ (f_n standing for the Lorentz and Lorenz function of the refractive index n at 20 °C, V_{20} for the molar volume at 20 °C, and V_b for the molar volume at boiling point) [17]. The evolution of the determination of this polarizability/induction parameter called ε was largely ignored in

the physicochemical literature until the study of Abraham et al. [18]. In the meantime, the induction parameter was more often wrongly defined; more details can be seen in [1]. Rather than the expression $f_n \times V_{20}/V_b$, we have proposed in 1997 [19], a bilinear equation of ($f_n \times V_b$) and V_b , similar to that suggested by Abraham et al. [18]. We have recently shown that one or another of these two later bilinear equations are slightly more in agreement with the experimental GLC data than $f_n \times V_{20}/V_b$ [1].

1.2. Physicochemical meaning of solvent parameters

At first sight, the solvent parameters associated to the solute parameters α and β reflect respectively proton acceptor and proton donor properties. We will here verify this preliminary feeling. Nevertheless, the aim of the present study is mainly to identify the nature of the experimental parameters we have called *W* and *E*, i.e. respectively associated in Eq. (1) to the solute parameters of orientation and induction/polarizability. Let us remember that the *D* parameter associated to δ , the solute parameter of dispersion, is supposed to be a constant.

We have also considered the parameter called *b* by McReynolds [20], and defined as the slope of the line obtained when the logarithm of the net retention times of the *n*-alkanes are plotted as a function of their number of carbon atoms. In practice, the McReynolds *b* parameter plus the solvent parameters derived from retention indices provide the same information as the solvent parameters derived from retention volumes ($\log V_g$), but differently presented. The latter can almost be considered as directly proportional to the product of the former and *b*.

Shortly after the beginning of the GLC, in 1952, by James and Martin [21], two important phenomena were observed:

- The five types of *polarity*

In GLC, a stationary phase is called polar when a solute other than *n*-paraffin has a retention index greater than on a paraffin phase chosen as reference (e.g. squalane). Rohrschneider proposed in 1966 [22] the retention indices of benzene, ethanol, 2-butanone, nitromethane and pyridine to characterize stationary phases. McReynolds [20] substituted 1-butanol, 2-pentanone and 1-nitropropane, respectively for ethanol, 2-butanone and nitromethane in order to overcome their low volatility, and added five supplementary compounds for a slightly better prediction of retention indices. The classification of McReynolds (particularly using the first five solutes) remains presently the most popular,

even in commercial compilations (e.g. the current Supelco catalog [23]). The solvent parameters classification can be considered as an improvement in the characterization of stationary phases: these parameters are, in some way, the orthogonal values of the McReynolds constants.

Various studies have been published in order to predict the characteristics of stationary phases. Recently, Hoffmann et al. obtained good results using respectively nine and five quantum chemical descriptors in the prediction of McReynolds constants [24] and solvent solvation parameters [25]. These results, useful for a predictive purpose, are however difficult to be interpreted in terms of physicochemical interpretation, because of the involvement of three or four descriptors in the prediction of each solvation parameter.

- The *polarity* of heavy alkanes

The seemingly surprising *polar* behavior of paraffinic stationary phases of high molar mass, compared with an *apolar* reference such as squalane, has mainly been studied by the Kováts group since 1973 [26–29], experimentally and theoretically as well. These authors demonstrated (among other things) that the retention indices of *polar* solutes on various paraffinic stationary phases of different molar mass M_L strongly depend on this value of M_L , as shown in Fig. 2. It should be underlined that this dependence of the *polarity* of stationary phases on their molar mass is limited to alkanes and cannot be extended to classical polar phases. For example, as we will see later, the polarities of polyethylene glycols (PEG) are very similar whatever is their molar mass.

The five selected compounds in Fig. 2 are those chosen by McReynolds [20] as better reflecting the various types of *polarity* of solutes. The slopes observed in this figure are strongly correlated (rank correlation coefficient = 1.00) with indices of polarizability ε established using bilinear equations of $f_n V_b$ and V_b , as reported above [1,19].

This important fact results from a fruitful discussion with Ervin Kováts in 1977 (pers. commun.) and has been confirmed for larger samples of solutes [30,31]. An attempt of extending it to truly polar phases has been tried via the concept of density, which is inversely proportional to the molar mass for *n*-alkanes [31], but the results have not really been convincing. One of the purposes of the present study is to reach this extension more satisfactorily.

2. Experimental and data processing

2.1. Statistical tools

In addition to the Microsoft Excel Windows facilities for drawing diagrams and handling data sets, the SYSTAT® 10.2 for Windows has been applied for stepwise MLRA (Multidimensional Linear Regression Analysis).

2.2. Experimental solvent parameters of stationary phases

As in our recent studies on solutes [1–4], we have selected, in the present one on stationary phases, two data sets of experimental solvent parameters.

2.2.1. An accurate set for 11 stationary phases

This set of data has been established using GLC retention indices from the Kováts group for 127 solutes [6–11] and an original statistical tool called MMA (multiplicative matrix analysis) described in Ref. [1]. The values of solvent parameters D , W , E , A and B are from Table 4 of Ref. [4] and are reported in Table SI-1 of the present study

Table 1

Solute solvation parameters according to Ref. [4] for the 11 compounds serving as basis of MLRA in order to establish the solvent parameters of the 207 stationary phases (226 columns) studied by McReynolds [20]. Data for bold compounds have been extrapolated.

Compounds	δ	ω	ε	α	β
Octane	3.430	0.000	0.000	0.000	0.000
Benzene	2.004	0.247	0.518	−0.032	0.080
1-Butanol	1.825	0.154	0.304	0.999	0.382
2-Pentanone	2.193	0.687	0.064	−0.062	0.339
1-Nitropropane	1.922	1.151	0.290	0.137	0.173
Pyridine	1.979	0.294	0.609	0.014	0.525
2-Methyl-2-pentanol	2.515	0.204	0.144	0.632	0.358
1-Iodobutane	2.739	0.006	0.628	0.000	0.109
2-Octyne	3.374	0.217	0.225	0.000	0.073
1,4-Dioxane	2.105	0.299	0.354	0.049	0.383
cis-Hydrindane	3.716	−0.146	0.652	−0.061	0.047

(Supplementary information). The b values for these 11 stationary phases are also reported in Table SI-1, from Table 2 of Ref. [1].

2.2.2. A less precise set for 56 stationary phases

McReynolds published two important collections of retention indices: one in 1966 for 77 stationary phases and more than 300 solutes [32], and the other one in 1970 for 207 phases and 10 solutes [20]. There are numerous occurrences of a given solute on a given phase in both data sets, but their cross-checking is not always excellent. For several reasons, it is usually admitted that the latter set is more accurate than the former, and we have limited our McReynolds sources to it.

We suggested (Table 5 of Ref. [4]) an updated determination of solvent parameters of stationary phases using only the retention indices of six selected solutes: *n*-octane, 2-hexanone, 1-nitropropane, azulene, 1-butanol and 3,4-lutidine (the retention index of *n*-octane is in lieu of a constant). This set of six solutes provides an excellent reproducibility of solvent parameters obtained using 127 solutes ($r=0.999$), contrary to what happens with a similar model including the five principal solutes proposed by McReynolds (plus the *n*-octane or a constant). Therefore, because solutes such as azulene and 3,4-lutidine have not been studied by McReynolds, we decided to apply an MLRA (multiple linear regression analysis) to all of the retention indices of Ref. [20], the parameters for the 11 solutes studied by McReynolds being fixed as in Table 1, according to Table SI-3 of Ref. [4].

Among the 207 phases (226 columns) studied by McReynolds [20], we identified the molecular structure for 56 phases (64 columns), including six polyethylene glycols (assuming a mean molar mass for each one). Table SI-2 of Supplementary information includes the solvent parameters D , W , E , A and B , as well as the original retention indices from which they are derived using a MLRA and the solute parameters of Table 1. It also includes the McReynolds b parameter from Ref. [20].

2.2.3. A pooled set of the two previous ones

Table SI-3 summarizes the principal results of the two previous steps, i.e. mainly the solvent parameters themselves and the b values for 67 stationary phases (75 columns). In fact, the less precise set of 56 phases has never been tested alone: only the accurate set of 11 phases and the pooled one of 67 phases.

Are also included in Table SI-3 the above solvent parameters multiplied by the relative slope (RSL), according to West [33]:

$$RSL = \frac{b}{b_{\text{reference}}} \quad (2)$$

In the present study squalane has been chosen as reference.

According to the definition of the Kováts retention indices RI , multiplication of all the terms of Eq. (1) by RSL leads to a prediction

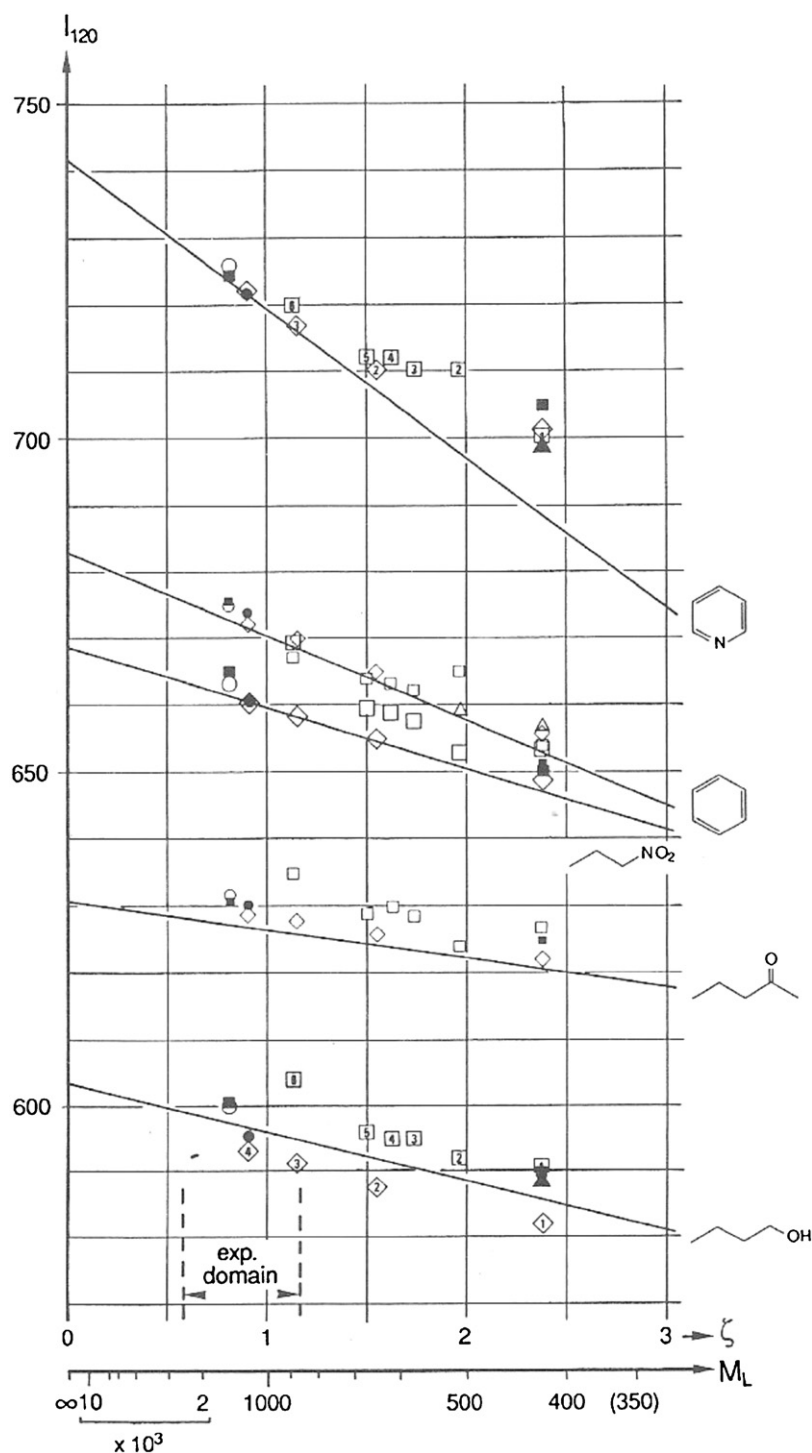


Fig. 2. Retention indices of five solutes at 120 °C on various paraffin stationary phases as a function of the ζ values of the latter ($\zeta = 1000/M_L$) (from Reddy and Kováts [29]). The different patterns of experimental points allow the identification of sources, specified in the original publication.

of retention indices which can be considered as *absolute* because directly related to $\log V_g$, in contrast to the *relative* retention indices strictly speaking:

$$RI_{\text{abs}} = RI \times RSL \quad (3)$$

2.3. Molecular properties of stationary phases

All the properties to be tested as possibly involved in the experimental solvent parameters of stationary phases are, in the present study, derived from their molecular structure. The most evident is

the molar mass, but it is not sufficient. As already mentioned in the introduction, we have developed a simplified molecular topology (SMT) in order to derive more information from the molecular structure.

2.3.1. Characteristics of SMT

This tool takes into account, for each atom of a molecule, its nature, the nature of its bonds, and in some cases the nature of its first neighbors. Each atom is provided with an index, comprised of a series of digits. Their sum is at most equal to its valence. The

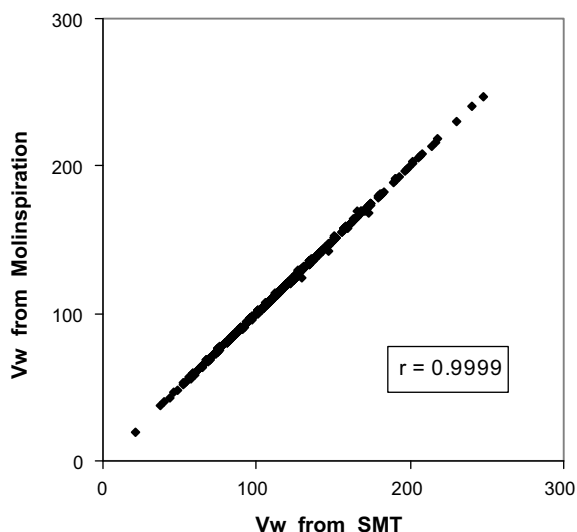


Fig. 3. Correlogram for molecular volumes of 456 compounds calculated using two methods. See text for details.

value of the digits defines the type of bonds (1 for a single, 2 for a double bond, etc.), but the bonds with hydrogen are excluded. In addition, the immediate neighboring is taken into account for oxygen, nitrogen and halogens. So, the possibilities for oxygen, for example, are the following: O0, O1, O11, O2, with six subcategories for O1 (linked to C1, C11, C111, C1111, C12 and C112).

In addition to the about 50 atom characteristics with their immediate environment finally kept, we also consider two additional topological features trying to account for spatial proximities between proton donors and proton acceptors existing in some ortho derivatives of phenols and in some amides, which we respectively call POSPA (phenol ortho substituted with proton acceptor) and NCO (amines linked to [a carbon linked to O2]). We also consider a connectivity parameter due to Zamora [34] called the “smallest set of smallest rings” (SSSR). According to this concept, for the naphthalene for example, which contains two individual C-6 rings and one C-10 ring embracing them, only the two six numbered rings are considered. Two six numbered rings corresponding to 12 carbon atoms, the SSSR value of naphthalene is therefore be taken equal to 12.

The SMT profiles of molecules under study can be established using our SMT applet, which will be soon updated on our freely available website [35]. In the present study we have made the calculations manually.

2.3.2. Solute parameters of stationary phases

Even if experimental parameters of stationary phases under study are known as solvents, we have applied to them the rules developed for solutes, just to see. Two predicting rules of solute parameters have been published which we call respectively 2006 and 2008 versions [2,3]. The 2008 version is reproduced in Fig. 3 for the parameters δ , ω , ϵ , and α . The parameter β has been replaced by an unpublished 2011 version, supposed to be more suitable.

2.3.3. Molar and molecular volumes

It is well known that the molar volume V_{20} of a given compound in liquid state at 20 °C, i.e. obtained dividing its molar mass by its density at 20 °C, is not an additive property, unlike the molar volume at boiling point V_b . Because at boiling point the intermolecular forces of cohesion in condensed phases are exactly equilibrated by those of thermal motion, the V_b expression has been often considered as reflecting the intrinsic molecular volume. Few experimental values are available and several expressions have been proposed

since the XIXth century to evaluate them by means of molecular increments [14,15,19,36–38]. Another popular expression using molecular fragments is that proposed by Abraham and McGowan [39], called V_x . The justification of this parameter leads on a good fitting with computer-calculated intrinsic volumes derived from X-ray structures by Leahy [40]. Both, V_b and V_x are expressed in ml.

Finally, we have preferred, in the present study, the values of molecular volumes (expressed in cubic angstroms) proposed by the freely interactive calculator of Molinspiration [41]. The authors of this calculator have used, in a first step, a semi-empirical quantum chemistry method to build 3D molecular geometries for a training set of about 12,000 molecules. In a second step, they have fitted sum of fragment contributions to the supposed real volumes of the training set. Let us name this expression V_w (as Van der Waals volume). Our simplified molecular topology (SMT) provides, as shown in Fig. 3, practically identical molecular volumes than that provided by Molinspiration. The SMT way can therefore be considered as an alternative method to get V_w values.

It should be noted that in order of an optimal fitting with the molecular volume values from Molinspiration, the SMT equation establishing V_w has a constant (see Fig. 4). This fact implies that, on the contrary to other predictive models such as V_b , for example, the V_w model is not valid at the lower limit, i.e. in the absence of any atom.

For a limited but significant set of 456 compounds, we have found an excellent mutual fitting of V_x , V_b and V_w ($r=0.996$ for the three comparisons). Nevertheless, we consider that the more modern V_w expression, finally kept in the present study, includes refined values of the atomic contributions of the two others, as well as the SSSR Zamora connectivity parameter also applied in the definition of V_b [19].

2.3.4. Polar surface area (PSA)

The polar surface area is a quite fascinating concept on various aspects. On one hand its definition is chemically very simple and precise, according to Palm et al. [42]: “the area occupied by nitrogen and oxygen atoms, and hydrogen atoms attached to these heteroatoms”. On the other hand its justification seems strictly pharmacological, in the sense that it reflects very well the molecular transport properties of drugs, particularly intestinal absorption and blood–brain barrier penetration [42–47]. Even if slightly polar atoms as sulfur and phosphor have sometimes been taken into consideration [44,47], the contributions of strongly polar elements such as halogens, particularly fluorine, have never been included. The discarding of halogens, and more often of sulfur and phosphor, could be due to their lack of contribution in molecular transport properties. In spite of the ambivalent characteristics of PSA, we have decided to test it as possibly involved in the solubility properties of GLC stationary phases.

PSA values have been established using sophisticated programs, taking into account the molecular three-dimensional shape and its flexibility [42,43]. However, a very simple topological method using summation of surface contributions of polar fragments (termed TPSA) has been applied by Ertl et al. [44], exhibiting an excellent correlation with theoretical PSA values ($r=0.991$, $N=34,810$ substances). Our simplified molecular topology (SMT) provides, using about three times less molecular features, identical TPSA values than those of Ertl et al., except for 5-ring aromatic molecules ($r=0.9995$ with a set of 456 molecules including five outliers of this type). The observed differences for the 5-ring aromatic molecules can be easily explained: two single bonds for the heteroatom in one case and two “aromatic bonds” in the other case. This difficulty does not appear for 6-ring molecules (one single bond and one double bond in one case and two “aromatic” bonds in the other case).

The SMT predictive equations for the seven molecular properties summarized above, i.e. the five solvation parameters of solutes (δ ,

Features	Coefficients	Features	Coefficients	Features	Coefficients	Features	Coefficients
C	10.717	Constant	-0.612	C2+C12+C13	0.073	C13	0.139
H	3.032	C total	0.413	O1	0.180	O0	2.317
O	8.481	O - (O0+O1)	0.250	O2	0.096	sqrt [O1 x (C1+C11)]	1.091
N	9.344	O0+O1	0.449	N1	0.250	O1 x C111	0.932
F	7.973	N-N1	0.420	F1	-0.084	O1 x C1111	0.655
Cl	16.637	N1	0.698	Cl1	0.149	O1 x C12	2.034
Br	21.039	Cl1	0.628	Br1	0.315	O1 x C112	1.705
I	27.186	Br1	0.942	I1	0.657	N1 x C12	1.751
S	17.901	I1	1.264	S1	0.365	N11 x C12	1.144
P	18.021	S1+S11+S2	0.958	S11	0.299	(N1+N11) x C112	0.631
Si	23.122	Si1111	0.492	S2	0.426	sqrt[(N1+N11) nlk C12, nlk C1	0.314
Sn	32.549	Sn1111	1.204	Si1111	-0.420	F x C1111	0.121
SSSR	-0.811	H1	0.044	SSSR	0.053	Cl x C111	0.139
Constant	6.239					POSPA	-0.795
Molec. Vol. (V_w) 2011		DISPERSION (δ) 2008		POLARIZABILITY (ε) 2008		ACIDITY (α) acidity 2008	

Features	Coefficients	Features	Coefficients	Features	Coefficients
C12	0.037	O0+O1	0.338	O0	29.270
O11	0.115	O1xC112	-0.244	O1	20.227
O0+O1	0.167	O11	0.122	O11	9.386
O2	0.503	O2	0.248	O2	17.017
N3	0.944	N1+N111	0.431	N1	26.027
F1	0.133	N11	0.379	N11	12.351
Cl1 nlk C111'	0.173	N12	0.358	N111	3.366
Br1	0.146	N3	0.266	N12	13.109
NCO	0.405	N122	-0.325	N122	11.789
		NCO	-0.192	N3	23.792
		SSSR	0.0156	N13+	4.362
ORIENTATION (ω) 2008		BASICITY (β) 2011		TPSA 2011 (NO)	

Fig. 4. Molecular features and their corresponding coefficients involved in predicting values using a simplified molecular topology (SMT), for molecular volume V_w , the five solvation parameters δ , ω , ϵ , α and β , and the polar surface area TPSA (limited to nitrogen and oxygen). The mentioned years stand for the published versions (Ref. [3] and the present study, respectively). See text for details.

ω , ϵ , α and β), the molecular volume V_w , and the polar surface area PSA, are summarized in Fig. 4. Numerical values of these molecular properties for the 67 stationary phases under study are reported in Table SI-4.

The Supplementary information also includes the 2D representation of the 67 phases molecular structures (SI-5).

3. Results

3.1. Simple statistics on the data sets

Before starting regressive equations between the experimental phases parameters and other properties, we have checked the mutual degree of independence of the two data sets under study, as shown in Fig. 5 (a correlation matrix of the parameters D_{abs} , W_{abs} , E_{abs} , A_{abs} and B_{abs} of the pool set is very similar to that of the bottom of Fig. 5).

Obviously, the independence of parameters is greater for the Kováts set ($N = 11$) than for the pool set ($N = 75$). That could be partially due to a narrow similarity of molecules in the pool set, on the contrary to the Kováts set one.

3.2. General trends

Because of the observed phenomenon in Fig. 5 and due to the lack of accuracy of the parameters ω , α and β , mentioned in the introduction, we have firstly looked for general trends, without predicting purposes. This first enquiry has been done separately: (i) in the Kováts set, (ii) in the pool set expressed in classical retention indices, (iii) in the pool set expressed in absolute retention indices. The results obtained at this stage had been summarized in Fig. 6.

Various facts can be attested from the figure:

- The characterization of the McReynolds b parameter is necessarily made via the pool set (reduced to 74 observations, diglycerol

appearing an outlier as it will be later specified). By contrast, the solvent solvation parameters W , E , A and B appear as better characterized using the Kováts set. These observations are in agreement with Fig. 5.

- More often, the explanatory properties of the solvent parameters appear as divided by V , in other words, as specific properties (in the sense of specific gravity or specific heat). One of them, the term PSA/V (which could be named the density of polar surface area), is dominating. This surprising result observed in a purely physicochemical phenomenon seems to clearly indicate that PSA is not only a pharmacological property, as set out in Section 2. Its real molecular nature should be better understood on a theoretical point of view.
- As a general trend (not always verified), the regression equations include a constant, the term PSA/V and a third term characteristic of the solvent parameter. The constants and the multiplicative coefficients of PSA/V differ from each solvent parameter to each other.
- The terms including molar mass and the δ solvation parameter have never been preferred by the MLRA. The ϵ solvation parameter is very rarely selected.

Once made these general observations, and in spite of the diversity of the regression equations obtained in the three data subsets, the physicochemical nature of the solvent parameters W , A and B can be quite clearly established as follows:

- The A and B parameters, involved in the hydrogen bonding, are respectively identified as proton acceptor and proton donor properties, as expected.
- The strictly speaking polar parameters W and ω , associated in Eq. (1), are of the same nature. In other words, and in contrast to the hydrogen bonding parameters, the rule “birds of a feather flock together” can be applied to the couple W and ω .

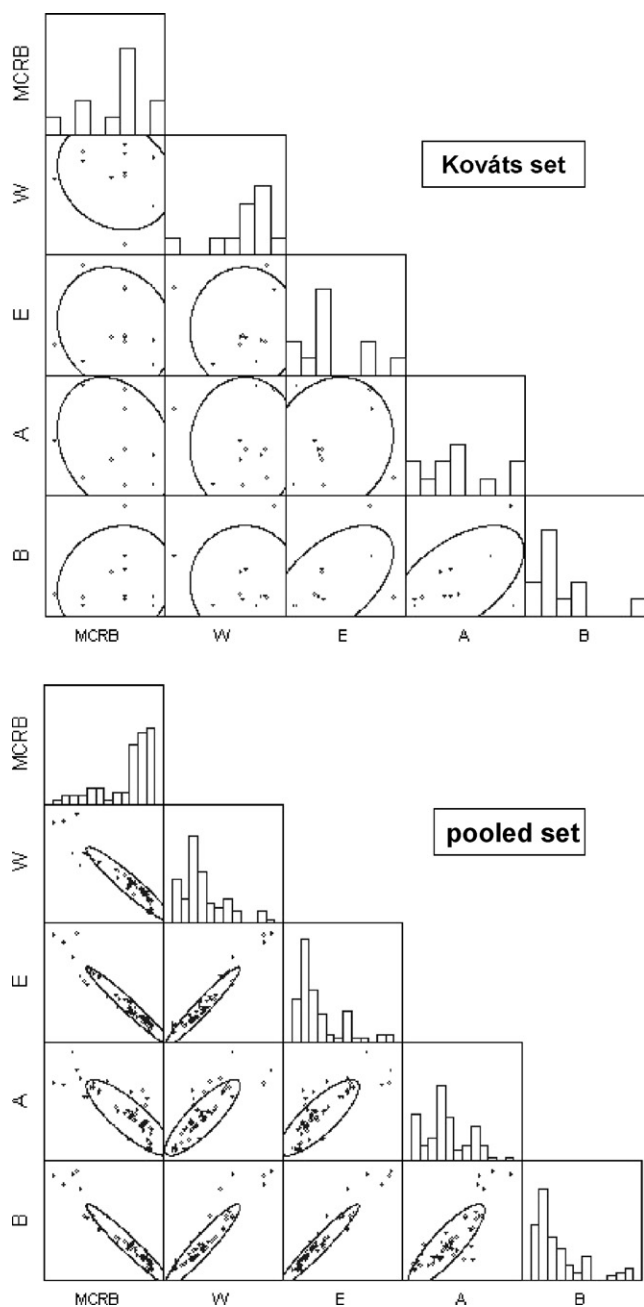


Fig. 5. Visualized correlation matrices between the McReynolds b parameter and the solvation parameters W , E , A and B , for the two data sets under study (D parameter is supposed to be a constant in all cases and had not therefore been checked).

On the other hand, as the parameters nature of b and E can be explained using only the properties PSA and V , easily obtainable with accuracy, we detail hereafter the study of these two solvent parameters in a predicting purpose.

3.3. McReynolds b parameter

The predicting equation of the McReynolds b parameter, summarized in Fig. 6, is as follows:

$$b = 0.29 - 0.26 \frac{PSA}{V} + \frac{6.22}{V} \quad (4)$$

in which PSA and V , respectively polar surface area and molecular volume, are established using the equations of Fig. 4.

The correlation with experimental values is shown in Fig. 7.

Training set	Dependent variable	Selected independent variables (partial F ratios ≥ 10)	r	SEE
"Kováts" ($N = 11$)	McR b param	none (*)	—	—
	W	ω / V (119) ; PSA / V (16)	0.98	6
	E	PSA / V (13) ; $1 / V$ (13)	0.85	5
	A	PSA / V (177)	0.96	6
	B	α / V (35) ; PSA / V (18)	0.94	12
"pool" ($N = 74$)	D_{abs}	PSA / V (312) ; $1 / V$ (13)	0.91	9
	W_{abs}	PSA / V (308)	0.90	40
	E_{abs}	PSA / V (130) ; β (11)	0.83	39
	A_{abs}	β / V (89)	0.74	42
	B_{abs}	PSA / V (211) ; α (14)	0.90	68
	McR b param	PSA / V (306) ; $1 / V$ (13)	0.91	0.01
	W	PSA / V (74) ; ω / V (12)	0.93	57
	E	PSA / V (180)	0.85	81
	A	β / V (215) ; ε / V (15)	0.87	43
	B	PSA / V (197) ; α (10)	0.89	114

(*) Predicted values are almost a constant, as well as experimental values. The correlation is therefore near of zero.

Fig. 6. General trends of stepwise MLRA of the McReynolds b parameter and of solvent solvation parameters vs. many combinations of the seven selected molecular properties (plus molar mass), on the two experimental data sets under study. Data between parentheses indicate partial F ratios in the regressions. r and SEE respectively stand for correlation coefficient and for standard error of estimate. See text for details.

It clearly appears in this figure that diglycerol is an outlier. The observation of an abnormal chromatographic behavior of this phase, due to its high surface adsorption, has already been pointed out in other studies [23,24,48,49]. Diglycerol has therefore been discarded in all the regressions summarized in Fig. 6, as already seen.

Eq. (4) applied to the Kováts set provides an almost constant value of b (0.29) for the 11 phases under study, nearly identical to the experimental values.

As far as we know, an analogous physicochemical meaning of the McReynolds b parameter has never been previously shown.

Multiplying all the terms of Eq. (4) by 700 provides a nearly predictive equation of D_{abs} . This it is not surprising since D_{abs} is

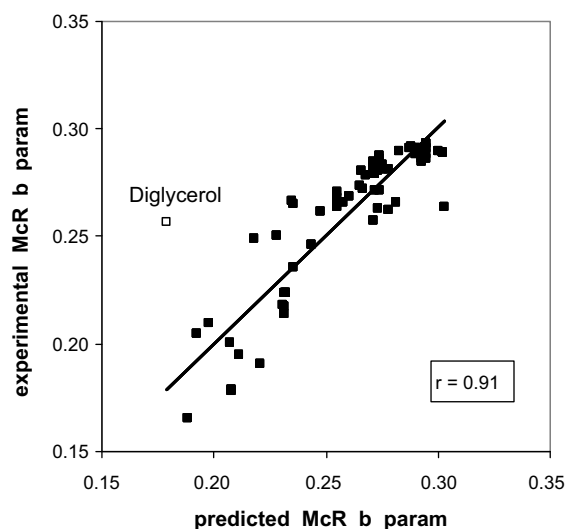


Fig. 7. McReynolds b parameters vs. PSA/V for 66 GLC stationary phases (74 columns). Diglycerol, an outlier, has not been included in the correlation.

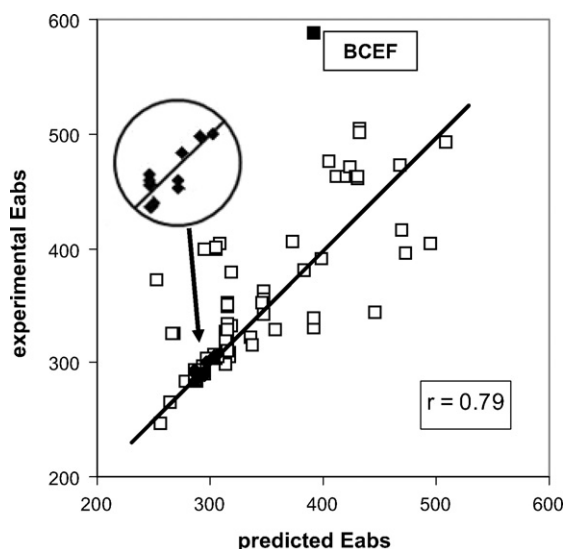


Fig. 8. Comparison between experimental E_{abs} values and predicted values using Eq. (6), for 66 phases under study (74 columns). BCEF, an outlier, has not been included in the correlation. For the 11 phases of the Kováts set (full diamonds and magnified view), the correlation coefficient is equal to 0.85.

obtained multiplying the McReynolds b parameter by an almost constant D . The predictive equation of D_{abs} obtained by regression with the pool set is as follows:

$$D_{\text{abs}} = 204.3 - 177.2 \frac{\text{PSA}}{V} + \frac{3814}{V} \quad (5)$$

3.4. The E_{abs} solvent solvation parameter

We have chosen the Kováts set to establish the predictive equation of E and E_{abs} , identical in this particular case:

$$E = E_{\text{abs}} = 306.4 + 561 \frac{\text{PSA}}{V} - \frac{25,700}{V} \quad (6)$$

Eq. (6) has been applied to the experimental pool set (E_{abs} only). Results are shown in Fig. 8.

BCEF clearly appears in this figure as an outlier among the 75 columns (67 phases) under study. This phase has therefore been excluded of the correlation (and diglycerol kept). However, because we did not find in recent publications an objection against BCEF, we have kept it in the general systematic enquiry summarized in Fig. 6. The only comment we can make about BCEF on the basis of the seven molecular characteristics considered in the present study (plus molar mass) is that this phase presents a very high value of ω/V (the highest value of the 67 studied phases). This fact could be a trail for a possible updating of Eq. (6), presently out of reach with the available values, not accurate enough, of E and ω for the phases studied by McReynolds [20].

As the range of experimental E_{abs} values in the Kováts set is small, compared to the pool set, we have inserted a magnified view of the former in Fig. 8. This highlights that Eq. (6) is consistent in the two data sets, with the exception of BCEF.

Are of particular interest the cases where PSA values are equal to zero, and therefore when Eq. (6) is limited to the variable $1/V$. These cases are in agreement with the observations of Kováts et al. [25–28] for paraffinic phases, partially shown in Fig. 2.

It should be underlined that as within all the properties proportional to the molecular size tested in the present study, the molecular volume has always been selected by the stepwise MLRA program, never the molar mass nor the δ solvation parameter.

4. Discussion – conclusion

The observations of various authors confirmed by the present study, of an abnormal chromatographic behavior of diglycerol, invalidate one of our previous suggestions to consider this phase as a possible reference for a proton donor property [1,4]. An alternative phase could be Hyprose–SP 80, as suggested by McReynolds himself (pers. commun., 1970).

The considered solvent parameters in the present study, named absolute, have been obtained from classical retention indices corrected by the “McReynolds b parameter” in order to be directly related to $\log V_g$. A simple predictive equation of the b McReynolds parameter has been proposed, seemingly for the first time.

The physicochemical meaning of the solvation parameters of GC stationary phases has now been elucidated, as described in Section 3. The expected nature of the parameters involved in hydrogen bonding has been verified, and the strictly speaking polar nature of the solvent parameter W , associated with the solute polar parameter ω in Eq. (1), has been observed.

Two predictive equations of the solvent parameters associated with the solute parameters of dispersion and induction/polarizability have been proposed. Both include $1/V$ (the inverse of the molecular volume) and PSA/V (the ratio of the polar surface area over the molecular volume) but in opposite side and with different coefficients. The reference value, represented by a constant, corresponds to a hypothetical paraffin of infinite molecular volume. This stage confirms and completes previous observations made by the Kováts group on paraffinic phases of various molecular sizes.

The explanatory properties of the solvent parameters of GC phases trends to be proportional to $1/V$. The density (i.e. M/V) has been however always discarded by the stepwise MLRA, contrary to one of our previous suggestions [31]. The ratio δ/V , close to the solute ε parameter, has not been selected, either.

By contrast, the ratio PSA/V has often been selected. This fact, as the general nature of PSA, probably deserves to be better understood from a theoretical point of view.

Results presented here have been obtained using experimental chromatographic data of the seventies, as in other recent similar studies, but enriched by more recent data from the Kováts group. Our study has also been extended to some polymers, overcoming a previous limitation.

As a general conclusion, we would underline that the interesting results presented here have been obtained using very simple tools. Our hope would be that other authors improve again the stage here exposed, using the sophisticated tools of quantum chemical descriptors applied to experimental chromatographic data as those of our [Supplementary information tables](#) (more extended and less “mixed” than in some recent publications).

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at [doi:10.1016/j.chroma.2011.04.068](https://doi.org/10.1016/j.chroma.2011.04.068).

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