
INTERPRETATION OF PARTITION BETWEEN PHASES AND CHROMATOGRAPHIC RETENTION FOR A SERIES OF OXYGEN COMPOUNDS

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The Gibbs free energies of solvation in water and in 1-octanol were calculated for a series of 13 oxygen compounds using the polarizable continuum approach. The values obtained were correlated with the experimental distribution constants in the water–1-octanol system and with the capacity factors related to HPLC retention. Statistically significant correlations were found between the calculated and experimental data, indicating that the model used and the methods applied describe the physical nature of the studied properties of substances in a qualitatively correct manner.

Among the most important physico-chemical properties of substances is their partition between phases, which affects significantly their behaviour in multiphase systems (e.g. biological systems) and so co-determines other properties. Recognition of how a substance is distributed between polar and nonpolar phases (hydrophilic or lipophilic nature) allows us to assess the possibilities of its separation by extraction; it is also of assistance when considering the structure–biological activity relationships (QSAR) and enables the behaviour of the substance in a chromatographic system to be predicted.

Partition between phases, or lipophilicity, is largely expressed in terms of the logarithm of the distribution constant ($\log K_D$) in the 1-octanol–water system. This partition is also the underlying principle of partition chromatography, chromatographic properties of substances being conventionally quantified by the capacity factor k .

A linear dependence has been found^{1,2} between the distribution constant in the 1-octanol–water system and that in a stationary phase–mobile phase system during chromatographic separation.

At present, several experimental and theoretical approaches exist attempting to express the structure–distribution relationship. In the Hansch's empirical approach, the lipophilic parameter π is defined based on the difference between the distribution constants of the unsubstituted and substituted molecules. The $\log K_D$ values then are

calculated as

$$\log K_D \equiv \sum_i^n \pi_i, \quad (1)$$

where n is the number of fragments into which the molecule is divided³⁻⁵.

Rekker and Nyss^{5,6} introduced the fragment method where the $\log K_D$ value of a molecule is calculated as the sum of fragment constants expressing the lipophilicity of the structural fragments.

In both approaches, problems are encountered arising from the fact that the molecule can be separated into fragments in several ways, and the fragment constants are not accurate enough, various intramolecular interactions, in particular the electron redistribution, being disregarded. Klopman and coworkers^{7,8} suggested a different empirical approximation, where the electron distribution in the molecules is taken into account, although in a simplified manner; on the other hand, the fact that in this method some empirical parameters are used in order to improve the correlation detracts from the physical sense of the approach.

Moriguchi⁹ parametrized the lipophilicity by means of quantities associated with the volume of the molecule, molar refraction, etc. High correlations of the distribution constants with the connectivity indices have been thus obtained particularly for homologous series of substances¹⁰.

Rogers and Cammarata^{11,12} applied the quantum chemical perturbation approximation to the calculation of the Gibbs free energy of partition by means of the difference in the electrostatic contribution to the solvation energy, ignoring the dispersion, repulsion and cavitation contributions. The calculation of the electrostatic contribution itself was rather crude.

The approach by Hopfinger and Battershell¹³ is similar; these authors estimated the solvation energy by using the procedure of the conformation analysis in solvent.

Zahradník and coworkers¹⁴ calculated the $\log K_D$ value directly by means of a discrete model where the energy changes are expressed as the interaction energy and statistical thermodynamics is employed for determining the entropy changes. The number of solvent molecules to be included in the calculation of the solvation, and their location, pose a problem that must be solved in discrete models. In the case of large solvent molecules, such as octanol, this model imposes enormous computation demands.

A number of methods have been suggested for accounting for the relation between the structure and chromatographic retention of substances (QSRR)¹⁵. They can be divided into three classes. The first class comprises correlations between retention and various physico-chemical experimental and empirical quantities or topological or quantum chemical parameters such as the number of carbon atoms¹⁶, the distribution constant¹⁷, dipole moment¹⁸, the solubility parameter¹⁹, van der Waals volume²⁰, charge densities²¹, etc.

The second class includes correlations of the retention data with structural group contributions; the Gibbs free energy is fragmented as a linear combination of retention energies of the individual fragments of the molecule²².

While in the above two classes the physical sense of the method is only implicitly included, procedures of the third class aim to explicitly express the dependence of retention on the Gibbs free energy of partition, or to calculate this value as exactly as possible. For the conditions of high performance liquid chromatography, this approach has been applied by Jinno and Kawasaki²³ and by Kamlet, Carr, Taft and others²⁴⁻²⁸.

A most detailed way of expressing the log k value has been elaborated by Horváth and coworkers²⁹, who applied Sinanoglu's solvophobic theory³⁰ to the calculation of the cavitation and interaction energy and compared this energy with the retention parameters. Solvation in the stationary phase, however, was ignored.

The various approaches to the calculation of the log K_D and log k values have been discussed in detail by Kaliszan¹⁵.

The aim of the present work was, for seeking the relationship between the structure and partition between phases, to express the total Gibbs free energy of solvation in the two phases as completely as possible based on the calculation of the energy contributions. The quantities so obtained are used to describe the partition in the 1-octanol-water system, and the agreement between the experimental and calculated values is discussed.

This paper is linked up with our previous work³¹ where a series of polychlorinated biphenyls has been examined. The objective of the present work was to verify the theoretical model, which enables the Gibbs free energies of partition and retention to be calculated, on a series of alcohols and ethers, for which experimental data of log K_D and log k are available³². Efforts are made for the calculation of the Gibbs free energy of solvation to be based on the electrostatic, dispersion, repulsion and cavitation contributions calculated as exactly as possible. Furthermore, we want to verify the possibility of predicting the lipophilic and retention properties of additional members of the above group of substances, for which the data are unknown, based on the obtained correlations between theoretical (ΔG) and experimental quantities (log K_D , log k).

THEORETICAL

The expressing of lipophilicity in terms of the Gibbs free energy of partition in the 1-octanol-water system is based on the relation

$$\log K_D = -\Delta G_{\text{part}}^{o/w}/(2.3RT), \quad (2)$$

where the superscript o/w refers to the octanol–water system, R is the gas constant and T is absolute temperature.

For modelling the process of chromatographic retention in a reversed phase high performance liquid chromatographic system, the equation

$$\log k = \log K_D^{s/m} + \log (V_s/V_m) \quad (3)$$

was used; here V_s/V_m is the stationary phase-to-mobile phase volume ratio and $K_D^{s/m}$ characterizes the distribution of the substance between the stationary (s) and mobile (m) phases.

The quantum chemical model of the two solvents was used when studying the distribution in the 1-octanol–water system.

When modelling the chromatographic separation in the RP HPLC system, the polar mobile phase, which was mostly a methanol–water mixture, was also modelled as water for simplicity; attempts to set up a model for the mixed mobile phase did not result in a marked improvement in the correlations of the Gibbs free energy of partition with the retention data. The modelling of the stationary phase is more complicated. RPLC systems involve chemically bonded stationary phases with C_{18} alkyl chains, which are highly nonpolar. However, some unreacted OH groups remain on the support surface after its alkylation, and these polar groups play a role in the separation of substances. Because of this, modelling of the RPLC stationary phase by 1-octanol, involving a nonpolar carbon chain and a polar OH group, was successful. Thus, the partition in the 1-octanol–water system (correlations of the $\log K_D = f(\Delta G_{\text{part}}^{o/w})$ type) and the chromatographic separation (correlations of the $\log k = f(\Delta G^{s/m})$ type) are modelled in the same manner; this approach is warranted, as Eq. (3) demonstrates.

So, by combining Eqs (2) and (3) we obtain a relation for the chromatographic separation,

$$\log k = -\Delta G^{s/m}/(2 \cdot 3RT) + \log (V_s/V_m), \quad (4)$$

where $\Delta G^{s/m}$ is the Gibbs free energy of retention.

Eqs (2) and (4) enable the relation between $\log K_D$ or $\log k$ and the Gibbs free energy of partition or retention to be calculated.

The total Gibbs free energy of partition (retention) is calculated as the difference between the interaction (solvation) Gibbs free energies in 1-octanol and in water (in the stationary and mobile phases):

$$\Delta G^{o/w} = \Delta G^o - \Delta G^w \quad (5a)$$

$$\Delta G^{s/m} = \Delta G^s - \Delta G^m. \quad (5b)$$

In the present work, the modelling of the phases is based on a model of polarized continuum; the Gibbs free energies in the individual phases must be therefore expressed. The total Gibbs free energy of solvation, with the various contributions specified, is expressed as

$$\Delta G^{o/w} = (\Delta G_{\text{elst}}^o - \Delta G_{\text{elst}}^w) + (\Delta G_{\text{dr}}^o - \Delta G_{\text{dr}}^w) + (\Delta G_{\text{cav}}^o - \Delta G_{\text{cav}}^w) \quad (6a)$$

$$\Delta G^{s/m} = (\Delta G_{\text{elst}}^s - \Delta G_{\text{elst}}^m) + (\Delta G_{\text{dr}}^s - \Delta G_{\text{dr}}^m) + (\Delta G_{\text{cav}}^s - \Delta G_{\text{cav}}^m), \quad (6b)$$

where ΔG_{elst} is the electrostatic contribution, ΔG_{dr} is the dispersion-repulsion contribution, and ΔG_{cav} is the cavitation contribution.

CONTRIBUTIONS TO THE GIBBS FREE ENERGY OF SOLVATION

Electrostatic Contribution

The Coulomb part of the electrostatic contribution to the Gibbs energy of solvation can be approximated by the extended Born equation according to Jano³³:

$$\Delta G_{\text{coul}} = -(1/2)(1 - 1/\varepsilon) \sum_{\mu\nu} Q_{\mu} Q_{\nu} / (4\pi\varepsilon_0 r_{\mu\nu}), \quad (7)$$

where ε is the relative permittivity of solvent, Q_{μ} and Q_{ν} are charges at the atoms of the molecule obtained by quantum chemical calculation, and $r_{\mu\nu}$ is approximated as³⁴

$$r_{\mu\nu} = r_{\text{AB}} + r_{\text{A}}^{\text{vdW}} \quad \mu \in \text{A} \quad (8a)$$

$$r_{\mu\mu} = r_{\text{A}}^{\text{vdW}} \quad \nu \in \text{B}, \quad (8b)$$

where $r_{\text{A}}^{\text{vdW}}$ is the van der Waals radius of atom A and r_{AB} is the interatomic distance.

The inclusion of the Coulomb energy only is often insufficient. The electrostatic contribution can be obtained more accurately by using the model by Miertuš and coworkers³⁵⁻³⁷, where the interaction of a molecule of the substance with the solvent is approximated by infinite polarizable continuum with a relative permittivity ε . The solvated molecule is accommodated in a cavity formed in the dielectric from overlapping spheres with centres in the nuclei of the atoms constituting the molecule and with radii identical with their van der Waals radii. The point charges induced on the cavity surface by the charge distribution of the solvated molecule are calculated. Their magnitude is determined by numerical solving of the Laplace equation by an iterative procedure, taking into account the solute-solvent polarization as well as the solvent self-polarization.

The final expression, which has been derived³⁵⁻³⁷ for charges $q_{\text{K}_i}^m$ on the individual

surface elements of the cavity ΔS_{K_i} , is

$$q_{K_i}^m = q_{K_i}^o - [(\varepsilon - 1)/(4\pi\varepsilon)] \{(\Delta S_{K_i}/|\delta_{K_i}|) \sum_{L_j \neq K_i} q_{L_j}^{m-1} [(|\mathbf{r}_{K_i} + \delta_{K_i}) - \mathbf{r}_{L_j}|^{-1} - |\mathbf{r}_{K_i} - \mathbf{r}_{L_j}|^{-1}] - 2\pi q_{K_i}^{m-1} \cdot \{1 - [\Delta S_{K_i}(4\pi R_K^2)^{-1}]^{1/2}\} \}, \quad (9)$$

where K and L denote atoms, i and j surface elements on the spheres, m is the number of self-polarization cycles, ε is the relative permittivity of solvent, \mathbf{r} is the positional vector of the element, δ is the vector of numerical differentiation of the potential, and R_K is the radius of the K -th sphere. The second right-hand term in this equation has the meaning of the mutual polarization of elements $L_j \neq K_i$, whereas the third term is the contribution from the self-polarization of element K_i .

The induced charges on the individual surface elements of the cavity are calculated; their sum, forming the potential V_σ , is included in the Hamiltonian of the solute molecule. The quantum chemical solution of the problem rests in expressing the electrostatic energy of solvation ΔE_{elst} as the SCF difference for solute with and without the V_σ potential included:

$$\Delta E_{\text{elst}} = \langle \Psi | \mathbf{H}_0 + V_\sigma | \Psi \rangle - \langle \Psi | \mathbf{H}_0 | \Psi \rangle. \quad (10)$$

According to this theory, the electrostatic contribution to the Gibbs energy of solvation can be written as

$$\Delta G_{\text{elst}} = -(1/2) \int_S \sigma V_\sigma dS \approx -(1/2) \sum_i V_i q_i, \quad (11)$$

where σ is the surface charge density of the solute molecule, V_σ is the potential arising from the solute charge distribution, q_i is the i -th charge component calculated on the cavity surface, and V_i is the potential in the centre of the i -th element of the cavity wall. A detailed description of this model can be found in refs^{31,35-37}.

Dispersion and Repulsion Contribution

The dispersion and repulsion contribution to the interaction energy can be expressed by means of the London relation for the dispersion term³⁸ and the Born relation for the repulsion term³⁹. Modification for the model treated gives³⁷

$$\Delta G_{\text{dr}} = B \sum_{i=1}^n \alpha_{i,\text{so}} [(r_{i,\text{so}}/r_{\text{sv}}) + 1]^{-3.91} \cdot (S_i/S), \quad (12)$$

where

$$B = -(3/4) \alpha_{\text{sv}} [\bar{\varepsilon}_{\text{so}} \bar{\varepsilon}_{\text{sv}} / (\bar{\varepsilon}_{\text{so}} + \bar{\varepsilon}_{\text{sv}})] (1.01\pi/r_{\text{sv}}^6), \quad (13)$$

n is the number of atoms in the solute molecule, $r_{i,so}$ is the van der Waals radius of the i -th atom of solute, r_{sv} is the radius of solvent, α_i is atomic polarizability (which can be found in ref.⁴⁰), $\bar{\epsilon}$ is the mean excitation energy, S_i is the area of the corresponding atomic element of the cavity, and S is the total cavity surface area. The subscripts so and sv refer to the solute and solvent, respectively.

Cavitation Contribution

Cavitation energy is the energy required for the formation in the solvent of a cavity (with a defined volume V), in which a molecule of the substance is subsequently placed. This is a destabilization of the system, which in the model corresponds to a redistribution of the solvent molecules. The cavitation energy is largely expressed in one of two ways, either according to Sinanoglu and Halicioglu⁴¹ or according to Pierotti⁴².

Sinanoglu and Halicioglu expressed the cavitation energy $\Delta G_{cav,SH}$ (the subscript SH refers to the Sinanoglu–Halicioglu approach) based on the microscopic surface tension theory as

$$\Delta G_{cav,SH} = \gamma_{sv} k_{sv}(sv/so) \cdot S, \quad (14)$$

where γ_{sv} is the macroscopic surface tension of solvent and $k_{sv}(sv/so)$ is a function of the radii of the solvent and solute molecules transforming the macroscopic surface tension to microscopic dimensions. The dependence

$$k_{sv}(sv/so) = 1 + (r_{sv}/r_{so})^2 [k_{sv}(1) - 1], \quad (15)$$

where $k_{sv}(1)$ is the microscopic cavity factor³¹, is used. S is the surface area of the spheric cavity ($S = 4\pi r_{so}^2$).

Pierotti derived a relation for the Gibbs energy of cavitation $\Delta G_{cav,P}$ (the subscript P refers to Pierotti's approach) by means of the hard sphere approximation. The approximation of the molecular shape by a sphere, employed in that approach, is actually too crude, and the calculation has been therefore modified³⁷ so that the individual atomic spheres are accounted for in the calculation and the total Gibbs energy of cavitation is calculated as the sum of the atomic contributions,

$$\Delta G_{cav} = \sum_{i=1}^n [A(r_{so-sv}^i)^2 - Br_{so-sv}^i + C] (S_i/S), \quad (17)$$

where S_i is the protruding part of the surface of the i -th atom, $r_{so-sv}^i = r_{i,so} + r_{sv}$ is the sum of radii of the i -th atom of solute and of solvent, and A , B and C are constants characteristic of the solvent^{31,36}.

The contributions to the Gibbs energy of solvation thus obtained are inserted in Eqs (6a, b), the total Gibbs energy of solvation is calculated, and correlation equations

between the experimental values of $\log K_D$ or $\log k$ and the calculated values of the Gibbs free energy of partition or retention (or the individual contributions), of the types

$$\log K_D = a \Delta G^{o/w} + b \quad (18)$$

$$\log k = c \Delta G^{s/m} + d, \quad (19)$$

are set up. These correlations are then evaluated statistically with respect to the agreement between the theoretical and experimental values and their statistical significance. We used the correlation coefficient r and tested the linearity or the correlation function by means of the F -criterion⁴³, viz. by comparison with the critical F -distribution values $F_{\alpha(v_1, v_2)}$ for the degrees of freedom $v_1 = k$ and $v_2 = n - k - 1$, where k is the number of independent variables in the correlation function and n is the number of substances in the series studied; α is the significance level.

Details with respect to the calculation of the solvation energies can be found in refs^{36,37}. The CNDO/2 semiempirical quantum chemical method⁴⁴ was applied to the calculation of the charge distribution at the atoms and the structure optimization. The all-trans conformation with the standard bond lengths r , bond angles α and dihedral angles θ (ref.⁴⁵) was used as the basic structure of the carbon chains in the alcohols.

The experimental $\log K_D$ and $\log k$ values were taken from ref.³². The distribution constants refer to the 1-octanol–water system at 25°C, the $\log k$ values to RP-HPLC experiments on a commercial column with Zorbax ODS packing using the methanol–water 1 : 1 mobile phase at 45°C. The values were determined by methods whose error generally does not exceed $\pm 5\%$. We found by testing that such an error in the experimental values does not affect the statistical parameters (r , F) to an extent such as to bring about a change in the qualitative conclusions of this work.

RESULTS AND DISCUSSION

The calculated contributions for the substances studied (Table I) are summarized in Table II.

The factors treated contribute to the Gibbs free energy of solvation to a different extent. The absolute values of the ΔG_{elst} contributions are considerably higher than those of the G_{coul} contributions, which is not surprising in view of the fact that the former include not only the Coulomb contribution but also the polarization contribution. On the other hand, the fact that these values grow more negative with increasing length of the nonpolar alkyl chain is astonishing; this is probably due to the increasing polarization of the molecular alkyl chain. The cavitation energies obtained depend considerably on the calculation method used, those calculated according to Pierotti being approximately three times as high as those calculated according to

Sinanoglu and Halicioglu. It is difficult to decide which of the two methods is more appropriate, both of them mirroring the molecular size in the cavitation contribution basically correctly. Thus, it is more suitable, when evaluating the relationship between molecular structure and partition (retention) properties, to investigate the total Gibbs free energies of solvation (or their differences for different two-phase systems), or the differences between the various contributions to them. Of importance are also their trends in series of substances, i.e. their relative changes in relation to the experimental characteristics. The differences in the contributions are given in Table III. Table IV gives the differences in the total Gibbs free energies of solvation for the 1-octanol–water system. Four variants are treated: the inclusion of the Coulomb contribution (Eq. (7)) or the electrostatic contribution (Eq. (11)), and for each of them, the application of the Pierotti approach or the Sinanoglu–Halicioglu approach to the calculation of the cavitation contribution.

Partition Between Two Phases

The correlation dependences and their statistical characteristics were established for single-parameter equations of the type $\log K_D = f(\Delta G_i)$ where ΔG_i is the difference in the pertinent contribution to the Gibbs free energy of partition. The best correlation was obtained with the $\Delta G_{\text{cav,SH}}$ value ($r = 0.994$, $F = 869.3$; $\alpha < 0.005$), the poorest, with the ΔG_{coul} value ($r = 0.336$, $F = 1.108$; $\alpha > 0.01$); the correlation with ΔG_{elst} was better than with ΔG_{coul} ($r = 0.936$, $F = 77.3$; $\alpha < 0.005$), hence the polarized continuum model suits considerably better to the description of the electrostatic interaction. Single-parameter correlation equations were also set up for the differences in the total Gibbs free energies of solvation in the four variants as mentioned above (Table IV). The four linear dependences obtained exhibited a high degree of statistical significance. With regard to the fact that the electrostatic contribution is

TABLE I
Substances studied

Labelling	Compound	Labelling	Compound
<i>I</i>	ethanol	<i>VIII</i>	benzyl alcohol
<i>II</i>	1-propanol	<i>IX</i>	tetrahydrofuran
<i>III</i>	1-butanol	<i>X</i>	<i>cis</i> -2,5-dimethyl- tetrahydrofuran
<i>IV</i>	1-pentanol	<i>XI</i>	diethyl ether
<i>V</i>	1-hexanol	<i>XII</i>	dipropyl ether
<i>VI</i>	1-heptanol	<i>XIII</i>	dibutyl ether
<i>VII</i>	1-octanol		

TABLE II
Contributions to the Gibbs free energy of solvation (kJ mol^{-1}) in 1-octanol and in water

Com- pound	ΔG_{coul}^a		ΔG_{elst}^b		ΔG_{dr}^c		$\Delta G_{\text{cav,p}}^d$		$\Delta G_{\text{cav,SH}}^e$	
	f	g	f	g	f	g	f	g	f	g
I	-21.69	-23.72	-42.58	-47.31	-36.04	-41.27	45.98	81.32	18.95	41.90
II	-19.89	-21.75	-51.62	-57.36	-46.96	-52.68	58.98	104.35	22.00	51.90
III	-20.14	-22.02	-57.23	-63.59	-56.06	-64.08	71.93	127.28	25.04	61.87
IV	-20.03	-21.90	-63.41	-70.46	-66.05	-74.44	84.64	149.80	28.03	71.67
V	-20.54	-22.47	-72.43	-80.50	-76.15	-86.91	97.74	173.01	31.11	81.79
VI	-19.38	-21.20	-78.46	-87.17	-85.29	-97.27	110.24	195.15	34.04	91.42
VII	-20.10	-21.99	-81.70	-90.78	-93.59	-106.66	121.68	215.42	36.73	100.23
VIII	-19.78	-21.63	-57.74	-64.16	-66.89	-71.17	72.28	126.58	26.30	66.02
IX	-21.17	-23.16	-40.55	-45.06	-44.69	-49.60	59.69	106.37	22.38	53.15
X	-25.87	-28.29	-74.61	-82.90	-69.73	-78.54	87.15	153.92	28.92	74.61
XI	-18.70	-20.45	-51.06	-56.74	-57.44	-65.17	71.39	126.22	25.02	61.82
XII	-18.44	-20.16	-71.87	-79.86	-77.66	-88.14	97.22	171.96	31.11	81.78
XIII	-18.55	-20.29	-82.31	-91.66	-96.66	-109.55	123.06	217.70	37.19	101.75

^a Eq. (7); ^b Eq. (12); ^c Eq. (17); ^d Eq. (14); ^e Eq. (14); ^f in 1-octanol; ^g in water.

better expressed in terms of ΔG_{elst} , the following equations are given for comparing the applicability of the various approaches to the calculation of the cavitation contribution:

$$\log K_D = -2.275 - 0.076\Delta G_{\text{E,P}} \quad (20)$$

($r = 0.994$, $F = 863.4$, $n = 13$, $\alpha < 0.005$), and

$$\log K_D = -2.032 - 0.123\Delta G_{\text{E,SH}} \quad (21)$$

($r = 0.983$, $F = 323.2$, $n = 13$, $\alpha < 0.005$).

In both equations, the negative sign in front of the linear term is consistent with the physical concept. The higher values of the r and F parameters for Eq. (20) suggest that Pierotti's approach is better suited to expressing the cavitation contribution to the Gibbs free energy of partition for the group of substances studied.

The problem of the absolute term arises when comparing Eqs (20) and (21) with the corresponding Eq. (2). This term probably expresses the absolute error of the approximations used in modelling the partition with respect to the process actually taking place.

TABLE III

Differences between the contributions to the Gibbs free energy of solvation (kJ mol^{-1}) in 1-octanol and in water

Compound	ΔG_{coul}^a	ΔG_{elst}	ΔG_{dr}	$\Delta G_{\text{cav,P}}$	$\Delta G_{\text{cav,SH}}$
<i>I</i>	2.03	4.73	5.23	-35.34	-22.95
<i>II</i>	1.86	5.74	6.63	-45.37	-29.90
<i>III</i>	1.89	6.36	8.02	-55.35	-36.83
<i>IV</i>	1.88	7.05	9.39	-65.16	-43.66
<i>V</i>	1.92	8.05	10.76	-75.26	-50.68
<i>VI</i>	1.82	8.72	11.98	-84.91	-57.37
<i>VII</i>	1.88	9.08	13.07	-93.74	-63.50
<i>VIII</i>	1.85	6.42	4.25	-54.30	-39.72
<i>IX</i>	1.98	4.51	4.91	-45.68	-30.77
<i>X</i>	2.42	8.29	8.60	-66.77	-45.69
<i>XI</i>	1.75	5.67	7.73	-54.83	-36.80
<i>XII</i>	1.73	7.99	10.48	-74.73	-50.67
<i>XIII</i>	1.74	9.15	12.90	-94.64	-64.56

^a Symbols as in Table II.

In addition to the correlation equation interrelating the distribution constant and the Gibbs free energy of partition, the statistical significance was also assessed for

TABLE IV

Differences between the total Gibbs free energies of solvation (kJ mol^{-1}) in 1-octanol and in water, for the different approaches to the calculation of the energy contributions

Compound	$G_{C,P}^a$	$G_{C,SH}$	$G_{E,P}$	$G_{E,SH}$
<i>I</i>	-28.08	-15.61	-25.38	-12.99
<i>II</i>	-36.88	-21.41	-33.00	-17.18
<i>III</i>	-45.45	-26.92	-40.97	-22.45
<i>IV</i>	-53.89	-32.39	-48.72	-27.48
<i>V</i>	-62.58	-37.83	-56.45	-31.87
<i>VI</i>	-72.11	-43.58	-64.21	-36.68
<i>VII</i>	-78.78	-48.54	-71.59	-41.31
<i>VIII</i>	-48.20	-33.61	-43.63	-29.06
<i>IX</i>	-38.79	-23.88	-36.27	-21.36
<i>X</i>	-55.74	-34.67	-49.87	-28.80
<i>XI</i>	-45.35	-27.31	-41.42	-23.39
<i>XII</i>	-62.53	-38.46	-56.27	-32.21
<i>XIII</i>	-80.01	-49.92	-72.60	-42.52

^a Indices C and E indicate that the Coulomb contribution (Eq. (7)) or the electrostatic contribution (Eq. (11)) were inserted in Eq. (6). Indices P and SH refer to the cavitation contribution calculated according to Pierotti or Sinanoglu and Halicioglu, respectively.

TABLE V

Comparison of experimental and theoretical values of the distribution constant

Compound	$\log K_D$			Compound	$\log K_D$		
	exp	calc ^a	calc ^b		exp	calc ^a	calc ^b
<i>I</i>	-0.32	-0.36	-0.36	<i>VIII</i>	1.23	1.02	1.04
<i>II</i>	0.34	0.22	0.22	<i>IX</i>	0.22	0.47	0.45
<i>III</i>	0.88	0.82	0.82	<i>X</i>	1.22	1.49	1.52
<i>IV</i>	1.40	1.41	1.40	<i>XI</i>	0.83	0.86	0.84
<i>V</i>	2.03	1.99	1.99	<i>XII</i>	2.03	1.98	1.98
<i>VI</i>	2.60	2.58	2.58	<i>XIII</i>	3.21	3.21	3.21
<i>VII</i>	3.15	3.14	3.13				

^a From Eq. (20); ^b from Eq. (22).

three-parameter equations of the dependence of the distribution constant and differences between the contributions to the Gibbs free energy of partition. The following equations were obtained:

$$\log K_D = -2.314 - 0.056\Delta G_{\text{elst}} - 0.080\Delta G_{\text{dr}} - 0.075\Delta G_{\text{cav,P}} \quad (22)$$

($r = 0.993$, $F = 214.0$, $n = 13$, $\alpha < 0.005$)

$$\log K_D = -2.109 - 0.100\Delta G_{\text{elst}} + 0.004\Delta G_{\text{dr}} - 0.096\Delta G_{\text{cav,SH}} \quad (23)$$

($r = 0.995$, $F = 277.7$, $n = 13$, $\alpha < 0.005$).

Correlations of this kind are warranted with regard to the non-unique theoretical background of the calculation of the contributions. Still, the sign in front of the ΔG_{dr} term in Eq. (23) definitely disagrees with the physical concept of the model.

The correlation equations obtained by regression analysis can be conversely employed for calculating the "theoretical" $\log K_D$ values of the substances concerned; a comparison of these values with the experimental data is given in Table V. The agreement is fairly good, particularly in the homologous alcohol series (compounds I–VII), benzyl alcohols and cyclic ethers showing deviations. However, because of lack of data from different laboratories, it is not impossible that the differences are partly due to errors of measurement. In spite of these differences, the equations can be employed for calculating the $\log K_D$ values of related substances such as higher alcohols or ethers.

Chromatographic Retention

With regard to the nature of the model of the stationary and mobile RPLC phases used, the calculated contributions to the Gibbs free energy of solvation in 1-octanol and in water can be also employed when modelling the chromatographic process. Although this process is more complex than the partition in the 1-octanol–water system, the correlation $\log k = f(\log K_D)$ was linear with statistical parameters $r = 0.972$, $F = 184.6$ ($n = 13$, $\alpha < 0.005$), giving evidence that the lipophilic properties play a major role in the RPLC separation. As in the case of partition modelling, correlation equations of the type of $\log k = f(\Delta G_i)$ were set up, ΔG_i being the difference in the corresponding contribution to the Gibbs free energy of retention. The poorest correlation was again obtained for ΔG_{coul} ($r = 0.304$, $F = 1.122$; $n = 13$, $\alpha > 0.01$), indicating that this is a very crude approximation to the electrostatic contribution. The correlation with ΔG_{elst} was considerably better ($r = 0.901$, $F = 47.43$ for $\alpha < 0.005$), although the statistical characteristics were poorer than for the $\log K_D$ correlation. The interactions in the chromatographic system are more complex in general, and so the correlations are poorer for all the contributions to the

Gibbs free energy of retention. Nevertheless, the correlation equations of the type of $\log k = f(\Delta G_{i,j})$ (i.e. with the Gibbs energies of retention calculated in the different ways) still possess high statistical parameters:

$$\log k = -1.720 - 0.045\Delta G_{E,P} \quad (24)$$

($r = 0.981$, $F = 288.9$; $n = 13$, $\alpha < 0.005$)

$$\log k = -1.559 - 0.073\Delta G_{E,SH} \quad (25)$$

($r = 0.965$, $F = 147.7$; $n = 13$, $\alpha < 0.005$).

The higher statistical characteristics in Eq. (24) again indicate that Pierotti's approach is well suited to the calculation of the cavitation contribution; the significance level, however, is the same for the two equations. The three-parameter statistical dependences were obtained as

$$\log k = -1.529 - 0.142\Delta G_{elst} - 0.023\Delta G_{dr} - 0.050\Delta G_{cav,P} \quad (26)$$

($r = 0.985$, $F = 94.7$; $n = 13$, $\alpha < 0.005$)

$$\log k = -1.339 - 0.165\Delta G_{elst} + 0.034\Delta G_{dr} - 0.063\Delta G_{cav,SH} \quad (27)$$

($r = 0.984$, $F = 94.4$; $n = 13$, $\alpha < 0.005$).

The statistical characteristics of the two equations are virtually identical; Eq. (26), however, can be regarded as more appropriate from the physical point of view because the signs of the terms agree with their physical meaning.

TABLE VI

Comparison of experimental and theoretical values of the capacity factor

Compound	log <i>k</i>			Compound	log <i>k</i>		
	exp	calc ^a	calc ^b		exp	calc ^a	calc ^b
<i>I</i>	-0.548	-0.570	-0.560	<i>VIII</i>	0.093	0.256	0.117
<i>II</i>	-0.240	-0.225	-0.235	<i>IX</i>	0.033	0.077	-0.004
<i>III</i>	0.077	0.136	0.142	<i>X</i>	0.521	0.539	0.424
<i>IV</i>	0.391	0.487	0.502	<i>XI</i>	0.295	0.156	0.220
<i>V</i>	0.740	0.837	0.832	<i>XII</i>	1.024	0.829	0.821
<i>VI</i>	1.070	1.189	1.190	<i>XIII</i>	1.791	1.569	1.593
<i>VII</i>	1.401	1.523	1.554				

^a From Eq. (24); ^b from Eq. (26).

A comparison of the capacity factors calculated from Eq. (26) with those obtained experimentally is given in Table VI. The differences between them are probably due to additional effects occurring in the chromatographic column during the separation, such as adsorption, steric effects, etc., which are not included in the model.

Theoretically, it is feasible to set up six-parameter correlation equations involving the Gibbs free energies of solvation in the two phases as the independent variables. Such equations might enable us to assess the effect of the individual contributions and provide physical substantiation of the trends. Given the series of 13 substances studied, however, such equations would be of dubious statistical value.

In conclusion, based on the obtained correlation equations between the experimental $\log K_D$ or $\log k$ values and the calculated values of the Gibbs free energy of partition or retention, the model used can be considered satisfactory to account for the physical nature of the phenomena involved. The correlations with $\log K_D$ possess higher statistical parameters (r , F) than those with $\log k$, due to the complexity of the process associated with chromatographic separation. A more extensive collection of structurally unrelated substances or other series or compounds should be included for testing the general validity of the model used.

It is an asset of this model that it is exactly based on the calculation of the Gibbs free energy of partition (retention) and its relation to the distribution constant (capacity factor). Its physically warranted background should make it possible to apply this approach to structurally unlimited types of substances. However, this study indicates that a high variability in the structure results in a decrease in the statistical significance of the correlations, and so the method is rather suitable for the treatment of structurally related substances. In that case, the correlation equations enable the $\log K_D$ or $\log k$ values to be predicted for other compounds structurally similar to the group examined. This approach may find use particularly for predicting the chromatographic retention of substances whose standards are unavailable.

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