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The development of a hydration factor ω and its relation to correction terms in current hydrophobic fragmental systems *

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Summary

From a number of experimental log P data, it is suggested that deviations from additivity can be expressed as multiples of a ω-factor which is 1/4 of Rekker's C_M factor. This ω-factor appears to relate to the hydrophobic fragmental system of Rekker and that of Leo and Hansch, since the correction terms in the latter system can also be expressed as multiples of ω. Theoretical considerations suggest the ω-factor to be related to the molar volume of water and to the way in which water molecules are packed around a solute. A Collander-type equation can also be formulated which includes the ω-factor. It is thus concluded that the ω-factor may be an expression of hydration/dehydration phenomena in partitioning processes.

Introduction

The partition coefficient (log P values) is of current interest in chemistry, biochemistry and medicinal chemistry due to its relationship with biological activities. In the last two decades values of over 10,000 compounds have been determined, and large collections of data are available (Hansch and Leo, 1979). The observation that log P values have in a first approximation an additive-constitutive character has led to the development of several substituent constant or fragmental constant

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systems (Hansch and Leo, 1979; Leo et al., 1971, 1975; Rekker, 1977; Rekker and de Kort, 1979).

In a previous paper (Mayer et al., 1982a), we have discussed and compared the possibilities and limits of the fragmental systems of Leo and Hansch (Leo et al., 1975; Hansch and Leo, 1979), and of Rekker (1977; Rekker and de Kort, 1979). Both systems display a set of correction factors. Although rules are presented to apply these correction factors, the proposed procedures not infrequently lead to unsatisfactory or poor predictions. The authors of both systems admit that a better knowledge of hydration and solvation of partitioning solutes would greatly improve the fundamental understanding of any fragmental system. In the present paper we develop a hypothesis based on experimental and theoretical considerations which may be a first step towards an improved understanding of hydration and solvation in partitioning processes.

The partition coefficient of functionalized alkylpyridines

Introduction of the ω-factor

We have recently published the log $P_{octanol}$ values, measured with the greatest possible accuracy, of pyridylalkanols, pyridylalkanamides and pyridylalkylamines where the side-chain is either at position 2-, 3- or 4- of the pyridyl ring (3 regioisomeric series), and where the side-chain has a length of 1, 2, 3, 4 or 5 carbon atoms, with the substituent in the terminal position. This study also includes the corresponding pyridylalkylammonium monocations, and the analogs phenylalkanols, phenylalkylamines and phenylalkylammonium cations (Mayer et al., 1982b, c). When in each homologous series the log P values are plotted as a function of the number of C atoms in the side-chain, a good linearity ($r^2 = 0.99$–0.999) exists for usually 4 points out of 5, a consistent exception being the arylmethyl derivatives due

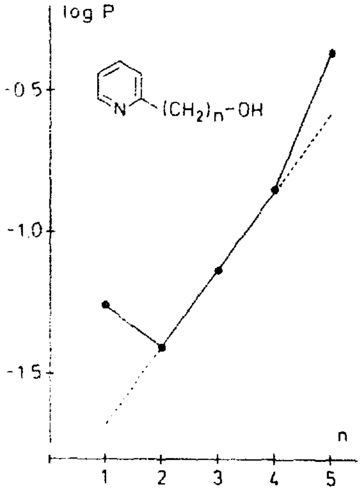

Fig. 1. The partition coefficient of (2-pyridyl)alkanols in the system dibutyl ether-water (Mayer and Testa, unpublished observations).

to inductive effects. Other exceptions exist with the protonated amines (Mayer et al., 1982c). Initial studies in the system dibutyl ether–water (Mayer and Testa, unpublished observation) show a similar behaviour (e.g., Fig. 1). The outlying points deviate from the calculated straight line by values in the range 0.131–0.586. Attempts to express these deviations as a multiple of n (n = 1, 2, 3, 4,...) of Rekker's 'magic' constant $C_M = 0.289$ (Rekker and de Kort, 1979) are not satisfactory. This constant term C_M was obtained by Rekker from the statistical analysis of over 1000 compounds; although its physical significance is not clear, it is believed that this factor is related to hydration (Rekker, 1977; Rekker and de Kort, 1979).

We have postulated that the systematic deviations from linearity found in our results might be related to Rekker's C_M term, more specifically that they might be expressed as fractions of C_M (C_M/m; m = 2, 3, 4, 5,...). Following this approach, we find that the best approximation is obtained for $n \cdot C_M/4$, i.e. $n \cdot 0.072$. As an illustration, the 3 regioisomeric pyridylalkylamines yield log P vs $(CH_2)_n$ plots which are linear ($r^2 = 0.998$) for n = 2, 3, 4 and 5. The 3 isomeric pyridylmethylamines, however, have log P values which are 0.143 ± 0.020 units higher than extrapolated, in other terms $2 \cdot 0.072$ (residual 0.001). In Fig. 1, it is seen that the deviations can be expressed as $6 \cdot 0.072$ (residual 0.009) and $3 \cdot 0.072$ (residual 0.000), respectively. That the same treatment is applicable to the octanol–water and dibutyl ether–water systems suggests the predominance of hydration contributions (see section on Collander-type equations).

At this stage of the presentation, the factor 0.072 may well be artefactual or even illusory. The value 0.072 is indeed a very small one, and it can correctly be argued that the smaller the denominator, the smaller the residuals. Furthermore, this factor originates from a limited number of experimental observations. In the remainder of this paper, we want to show: (a) that the factor 0.072 fits other data, in particular the correction factors of Leo and Hansch (1979); and (b) that a physicochemical rationale can be postulated. For simplicity, we designate the factor 0.072 as the ω-factor.

The case of the morpholino and amino-acetamido fragments

In order to examine the influence of electronic intramolecular interactions on hydrophobicity, Le Thérizien et al. (1980) have determined the hydrophobic fragmental constants, f_i, of the morpholino, $O(CH_2CH_2)_2N—$, and amino-acetamido, $—NHCOCH_2N\langle$, fragments. The values (Table 1) were obtained from 8 morpholino derivatives and from 8 N′,N′-dialkylamino-acetamides. Following Rekker's approach, the difference between these experimental f_i values and the values calculated as Σf_{Rekker} represent the hydrophobic increment due to intramolecular interactions. In neither case is this increment a multiple of C_M, since it represents $2.5 \cdot C_M$ and $4.5 \cdot C_M$ for the morpholino and amino-acetamido fragment, respectively (Table 1). In contrast, the two hydrophobic increments are multiples of ω, since they represent $10 \cdot \omega$ and $18 \cdot \omega$, respectively, with small residuals.

This example points to a shortcoming of C_M, and brings a second indication of the utility of the ω-factor.

TABLE 1

HYDROPHOBIC FRAGMENTAL VALUES OF THE MORPHOLINO AND AMINO-ACETAMIDO FRAGMENTS

	$O(CH_2CH_2)_2N—$	$—NHCOCH_2N\langle$
fragmental value f_i [a]	−0.880	−2.720
Σf_{Rekker} [b]	−1.604	−4.012
$f_i - \Sigma f_{Rekker}$	0.724	1.292
$(f_i - \Sigma f_{Rekker})/C_M$	2.5	4.5
$m \cdot 0.072$	10	18
(residual)	(0.004)	(−0.004)

[a] Le Thérizien et al., 1980.

[b] Rekker and de Kort, 1979.

The hydrophobic fragmental system of Leo and Hansch

Rekker (Rekker, 1977; Rekker and de Kort, 1979) has developed a fragmental system starting from over 1000 log P values and using statistical methods. Fragmental constants are thus mean values, and correction factors were forced as multiples of C_M. In contrast, Leo (Leo et al., 1975; Hansch and Leo, 1979) started with a limited set of small molecules (e.g. H_2, alkanes) and introduced a considerable variety of correction factors which become especially necessary when the calculated structures are relatively complex. Indeed, Leo's system is very well adapted for small molecules, since his fragmental constants (f′) derive from such compounds.

We have already (Mayer et al., 1982a) pointed to a fundamental connection between Rekker's and Leo's fragmental systems. Indeed, the values for the H fragment (f_H and f'_H, respectively) are related to its exposed volume in alkyl groups and in H_2, respectively:

$$\frac{f'_H}{f_H} = \frac{0.23}{0.182} \simeq \frac{5.81\ \text{cm}^3/\text{mol}}{4.62\ \text{cm}^3/\text{mol}} \qquad (1)$$

Hansch and Leo (1979) have also mentioned the importance of exposed volume when discussing the effect of multiple halogenation.

Here, we suggest a second fundamental connection between the two fragmental systems, namely that their sets of correction factors are related and display a common denominator which is the ω-factor. Inspection of Leo's correction factors (Table 2) shows values ranging from −1.42 to 1.0; particularly interesting in the present perspective are the very small factors −0.08 and −0.09. The expression of these correction factors in terms of multiples of ω is shown in Table 2. Some residuals are minute, while others are relatively large, an inevitable result when one remembers that these correction factors are approximations or means. Thus, Table 2 cannot and does not bring any sort of proof that Leo's factors are multiples of ω. Table 2 merely shows the good compatibility between these factors and the ω-factor. It must nevertheless be noted that when Leo's factors are expressed as multiples of $C_M/3$, $C_M/5$, $C_M/6, \ldots$, the mean residual values are proportionately less favourable then when using ω.

Table 2 thus indicates that the correction factors in the two fragmental systems may be related through the ω-factor, as they are related through some exposed volumes. This relationship can only be accepted if it is the expression of a physicochemical phenomenon, in which case our understanding of partitioning processes would be significantly improved. The remainder of this paper explores the possible physicochemical meaning of the ω-factor.

TABLE 2

LEO'S CORRECTION FACTORS AS MULTIPLES OF ω

Factors [a]	As m·ω	m	residual
$F_{=}$: −0.55	−0.576	−8	0.026
$F^{\varphi}_{=}$: −0.42	−0.432	−6	0.012
$F^{\varphi\varphi}_{=}$: −0.00	0	0	–
$F_{\equiv}$: −1.42	−1.44	−20	0.020
$F^{\varphi\varphi}_{\equiv}$: 0.00	0	0	–
F_b^{chain}: −0.12(n − 1)	−0.144	−2	0.024
F_b^{ring}: −0.09(n − 1)	−0.072	−1	−0.018
F_{bYN}: 0.20	−0.216	−3	0.016
F_{bYP}: −0.31	−0.288	−4	−0.022
F_{cBr}: −0.13	−0.144	−2	0.014
F_{gBr}: −0.22	−0.216	−3	−0.004
F_{rCl}: −0.45	−0.432	−6	−0.018
F_{mhGn}: 0.30(n = 2)	0.288	4	0.012
0.53(n = 3)	0.504	7	0.026
0.72(n = 4)	0.720	10	0.000
F_{mhVn}: 0.28(n − 1)	0.288	4	−0.008
F_{P1}: $-0.42\Sigma(f_1 + f_2)$	−0.432	−6	0.012
F_{P2}: $-0.26\Sigma(f_1 + f_2)$	−0.288	−4	0.028
F_{P3}: $-0.10\Sigma(f_1 + f_2)$	−0.072	−1	−0.028
$F_{\underline{P1}}$: $-0.32\Sigma(f_1 + f_2)$	−0.288	−4	−0.032
$F_{\underline{P2}}$: $-0.20\Sigma(f_1 + f_2)$	−0.216	−3	0.016
$F^{\varphi}_{\underline{P1}}$: $-0.16\Sigma(f_1 + f_2)$	−0.144	−2	−0.016
$F^{\varphi}_{\underline{P2}}$: $-0.08\Sigma(f_1 + f_2)$	−0.072	−1	−0.008
F_{HBN}: 0.60	0.576	8	0.024
F_{HBO}: 1.0	1.008	14	−0.008
			$\bar{x} = 0.003 \pm 0.019$

[a] From Hansch and Leo, 1979.

The relationship between log P and molar volume. A physical interpretation of the ω-factor

In a recent publication, Testa and Seiler (1981) have derived an equation (Eqn. 2) describing the relationship between Rekker's f_i values and van der Waals volume V_i:

$$f_i = 0.0534\ V_i + \Lambda_i \tag{2}$$

The parameter Λ was called a lipophobicity term, and is believed to be related to hydration effects. Its values are negative ones. If one now assumes that the factor $\omega(=0.072)$ accounts for solvation/hydration effects, one can write:

$$\Lambda_i = m_i \cdot \omega \tag{3}$$

where m is a multiplicity factor. When the original 83 Λ values of Testa and Seiler (1981) are divided by 0.072 the results are mostly close to an integer, bearing in mind that f and V are not known with full accuracy. Combination of equations 2 and 3 gives:

$$f_i = 0.0534\ V_i - 0.072\ m_i \tag{4}$$

or

$$f_i = 0.072\ (0.74\ V_i - m_i) \tag{5}$$

Surprisingly 0.74 is not just a random number but is the factor denoting the closest packing of spheres. In Eqn. 5, the dimensions of this factor 0.74 are those of a reciprocal volume.

In a paper on molar volumes, King (1969) states that above a certain minimum size all molecules of a given type have the same packing density with a limiting value close to the packing density of spheres (i.e. 0.74). It follows that Eqn. 5 must be valid not only for fragments, but can be rewritten for entire molecules:

$$\log P = \Sigma f_i = \omega \cdot (0.74\ \Sigma V_i - \Sigma m_i) \tag{6}$$

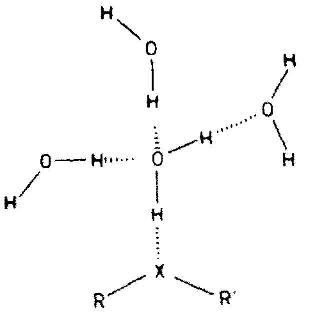

Fig. 2. A model of hydration by a cluster of 4 water molecules.

The equations of King (1969) and Edward et al. (1977) indicate that closest packing is obtained for molecules with molar volume above approximately 300 cm^3/mol. However, smaller molecules seem to display the same behaviour. This can be understood by assuming that solute molecules act sphere-like in an ice-like hydration sphere. Frank and Wen (1957) have developed a model of water based on the concept that hydrogen bonds are not formed or broken one by one, but several together. In this way nearly spherical clusters of water molecules are formed. The term ice-like structures was introduced by Frank and Evans (1945); the water molecules in the hydration sphere are, like in ice, tetracoordinated. Many theoretical studies (Geiger et al., 1979; Rossky and Karplus, 1979; Scheraga, 1979; Hallenga et al., 1980; Franks, 1979) confirm the structuring of water around a solute. When all kinds of different solutes are surrounded by ice-like structures it can be understood that they are packed in a comparable manner, and this fact may be related to the factor 0.74. A recent Monte-Carlo study (Okazaki et al., 1981) has shown that stabilization and structuration of water do not change monotonically with the size of the solute. This is in agreement with the view that hydration takes place by addition of clusters of water molecules, in particular clusters of four (Fig. 2).

The molar volume of water as determined from molecular weight–density measurements is 18.05 cm^3/mol at 20°C and 19.64 cm^3/mol for ice (Weast, 1972). A water molecule in an ice-like hydration sphere can be expected to have a molar volume intermediate between these two values. This is of interest in Eqn. 6. Indeed, rewriting this equation yields:

$$\frac{1}{0.74} \cdot \frac{1}{\omega} \cdot \log P = V - \frac{m}{0.74} \tag{7}$$

or

$$18.77 \log P = V - \frac{m}{0.74} \tag{8}$$

where $V = \Sigma V_i$ and $m = \Sigma m_i$. The dimensions of the factor 18.77 are those of a volume (see above), and indeed this factor can be postulated to represent the volume of a water molecule in an ice-like cluster. Based on this hypothesis, Eqn. 9 is obtained:

$$\log P = \frac{V_{solute}}{V_{H_2O}} - \frac{m}{0.74\, V_{H_2O}} \tag{9}$$

or

$$\log P = \frac{V_{solute}}{V_{H_2O}} - m \cdot \omega \tag{10}$$

since (compare Eqns. 7 and 8):

$$\omega = \frac{1}{0.74\ V_{H_2O}} \qquad (11)$$

Eqn. 11 suggests that the ω-factor is related to the volume of a water molecule and to the way these molecules are packed around a solute. One way to interpret Eqn. 11 would be to postulate that the ω-factor reflects the participation (binding or release) of one molecule of water, and that the term $m \cdot \omega$ expresses a correction factor in terms of the number of water molecules involved. In this hypothesis, Rekker's C_M reflects the participation of a cluster of 4 water molecules (Fig. 2). Apparently a hydration sphere is built up by clusters packed in an ideal way (explaining the factor 0.74). The abundance of $4\omega = C_M$ must be due to the fact that water molecules in the hydration shell tend to be tetracoordinated. However, it might be expected that in a number of cases involvement of a cluster of 4 water molecules is not favoured for steric or other reasons, and multiples of C_M do not fit experimental log P values, as shown in foregoing Sections.

Collander-type equations

The intercorrelation between two sets of partition coefficient values measured in two different solvent systems was recognized by Collander (1951) and can be expressed as:

$$\log P_{(\text{solvent } x)} = a \log P_{(\text{solvent } y)} + b \qquad (12)$$

Leo et al. (1971) have compiled a large number of these equations and distinguished 3 classes of compounds: H-donors, H-acceptors and neutral. Empirical equations like Eqn. 12 are not fully understood, and several attempts have been made to derive more meaningful equations of this type.

Seiler (1974) has introduced increments for hydrogen bonding (I_H) for 17 different molecular fragments and has proposed Eqn. 13:

$$\log P_{\text{solvent}} = \log P_{\text{octanol}} + b - \Sigma I_H \qquad (13)$$

Rekker (1977) has tried to incorporate his 'magic' constant C_M. Based on the assumption that:

$$f_{\text{solvent}} = \rho f_{\text{octanol}} + kn \cdot C_M \qquad (14)$$

Eqn. 15 is obtained:

$$\log P_{\text{solvent}} = \rho' \log P_{\text{octanol}} \pm 0.268\rho' \Sigma kn \qquad (15)$$

where 0.268 is the mean magic constant defined as

$$\sum_{i=1}^{n} C_{M(solvent\,i)}/n$$

and where $\rho' = C_{M(solvent)}/C_{M(octanol)}$. It must be noted that only $C_{M(octanol)}$ is well developed on a statistical basis.

The ω-factor as formulated in Eqn. 6 can be used to derive a new simple equation of the Collander-type. When Eqn. 6 is written for octanol and for any other solvent, and if one assumes:

$$(\Sigma V_i)_{solvent} \simeq (\Sigma V_i)_{octanol} \qquad (16)$$

then Eqn. 17 is obtained.

$$\log P_{solvent} = \log P_{octanol} + \omega[(\Sigma m_i)_{octanol} - (\Sigma m_i)_{solvent}] \qquad (17)$$

or in a simplified form:

$$\log P_{solvent} = \log P_{octanol} \pm m \cdot \omega \qquad (18)$$

The similarity of Eqns. 13 and 18 is apparent. An illustration of Eqn. 18 is given by the log P values of *n*-alcohols in the *n*-octanol–water and chloroform–water systems (see Table 3) (Hansch and Leo, 1979). The correspondence with multiples of ω is apparent only when calculated log P values are used, i.e. when experimental errors are distributed and eliminated as far as possible. It is certainly not easy to detect the small ω-factor from heterogenous experimental data. However, the above example suggests that ω indeed can play a role in solvent system conversions.

In the case of Eqn. 18, the $m \cdot \omega$ term can be postulated to represent, for a given solute (and not for a series of compounds, see below), a difference in hydration/dehydration in two solvent systems. In this hypothesis, the higher affinity of alcohols for *n*-octanol than for $CHCl_3$ (Table 3) could mean that alcohols must strip off more water molecules when entering the chloroform than the octanol phase. The difference in the number of water molecules involved would then be given by $m \cdot \omega$ (Table 3). Interesting is also the observation that the log P difference between the two systems decreases with increasing lipophilicity of the solute. Perhaps the higher alcohols enter chloroform with more hydration molecules, or enter octanol with less hydration molecules, than the lower alcohols.

It must be emphasized that Eqn. 18 is valid for a given compound, not for a series. When the entire series of alcohols in Table 3 is considered, Eqn. 12 applies and takes the following values:

$$\log P^{calc}_{CHCl_3} = 1.132 \log P^{calc}_{oct} - 0.551 \qquad (19)$$

$(n = 7;\ r = 1.000)$

TABLE 3

PARTITION COEFFICIENTS FOR *n*-ALCOHOLS (HANSCH AND LEO, 1979)

	C_n	log P_{oct}^{exp}	log P_{oct}^{calc} [a]	log $P_{CHCl_3}^{exp}$	log $P_{CHCl_3}^{calc}$ [b]	[log P_{oct}^{calc} − log $P_{CHCl_3}^{calc}$]	m	residual
methanol	C_1	−0.79	−0.811	−1.36	−1.469	0.658	9	0.010
ethanol	C_2	−0.32	−0.251	−0.85	−0.835	0.584	8	0.008
n-propanol	C_3	0.28	0.309	−0.31	−0.201	0.510	7	0.006
n-butanol	C_4	0.89	0.869	0.40	0.433	0.436	6	0.004
n-pentanol	C_5	1.40	1.429	1.05	1.067	0.362	5	0.002
n-hexanol	C_6	2.03	1.989	1.69	1.701	0.288	4	0.000
n-heptanol	C_7	–	2.549	2.41	2.335	0.214	3	−0.002

[a] log $P_{oct}^{calc} = 0.560\ C_n - 1.371$.

[b] log $P_{CHCl_3}^{calc} = 0.634\ C_n - 2.103$.

Discussion and conclusion

Starting from experimental log P values, a correction factor ω has been postulated. In a subsequent step, this ω-factor was suggested to be a common denominator relating correction factors in the hydrophobic fragmental systems of Rekker and of Hansch and Leo. Introducing the ω-factor into equations relating log P values and molar volumes, and in Collander-type equations, has also lead to interesting conclusions, in particular the potentially meaningful Eqns. 10, 11 and 18.

Based on molar volume considerations, our interpretation is that the ω-factor represents one molecule of water, and that the term $m \cdot \omega$ thus expresses a correction in terms of a number of water molecules.

The partitioning process is certainly a complex one. Four factors can be expected to be operative, namely hydration and solvation in the solvent-saturated aqueous phase, and solvation and hydration in the water-saturated organic phase. But as stressed by Kühne et al. (1981), the partition coefficient is a global quantity which does not explain single events in a given phase. The decomposition of the partition coefficient into a volume-dependent hydrophobic contribution and a polarity-related lipophobic contribution as shown by Testa and Seiler (1981) and as apparent in Eqn. 10 is a first step towards discriminating the solvation and hydration processes. Indeed, the volume term in Eqns. 2 and 10 can be postulated to account for solvation and for hydrophobic water-structuring effects around the solute, while the Λ_i (Eqn. 2) or $m \cdot \omega$ term (Eqn. 10), as indicated earlier, would represent genuine hydration.

This paper shows that an improved understanding of partitioning processes calls for a good knowledge of molar volumes and volume-related effects. Calculated molar volumes as reported in the literature exhibit considerable differences, e.g. values of the CH_2 fragmental volume range from 6.74 cm^3/mol (Bultsma, 1980) to 16.58 cm^3/mol (Moriguchi et al., 1976). The best way to obtain molar volume is certainly by very accurate density measurements (e.g. Perron and Desnoyers 1979; Shahidi, 1981), but much remains to be done in this field. The solvent dependency of molar volumes is also being investigated, and obviously Eqn. 16 is an approximation. Generally, a partial molar volume can be written as:

$$\bar{V}^0 = V_w + V_v \pm \Delta V_{ss} \qquad (20)$$

where V_w is the intrinsic volume of a molecule, sometimes called the Van der Waals volume; V_v is the dead (empty, or void) volume arising from the geometrical orientation of the solute molecule in the solvent, and is thus associated with the packing of the solute in the solvent—this term, like the conformation, is solvent-dependent, and is also smaller when a group is more hydrophilic; and ΔV_{ss} reflects effects due to mutual interactions of solute and solvent (Edward et al., 1977; Shahidi et al., 1977). The exact meaning of 'molar volume' is thus far from clear at present, and further investigations, both experimental and theoretical, are warranted.

In conclusion, the interpretation presented in this paper is hypothetical yet intriguing because it has been reached through a number of independent approaches. Volume and hydration effects have been confirmed as major contributions to partitioning processes. The ω-factor at this stage has a double interest, namely to offer a fresh investigational approach to assessing these contributions, and also to unify and simplify correction terms used in hydrophobic fragmental systems. But whether the physicochemical reality of the ω-factor will ultimately be confirmed or disproved, our understanding of partition processes, and QSAR-oriented parametrization of molecular properties, can only benefit from a prejudice-free approach.

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