Lipophilicity Measurement of Drugs by Reversed Phase HPLC over Wide pH Range Using an Alkaline-Resistant Silica-Based Stationary Phase, XBridge™ Shield RP_{18}

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We propose a reversed phase HPLC (RP-HPLC) with an alkaline-resistant silica-based stationary phase, XBridge™ Shield RP_{18}, for the determination of the lipophilicity of drugs with diverse chemical nature ranging from acidic to basic. A set of 40 model compounds with well-defined solvatochromic parameters was selected to allow a broad distribution of structural properties. The chromatographic results showed that the lipophilicity index $\log k_w$ obtained with XBridge™ Shield RP_{18} was well correlated with experimental $\log P_{oct}$ values ($r^2=0.96$). Linear solvation free-energy relationship (LSER) analyses revealed that the retention mechanism of the stationary phase and 1-octanol/water partitioning were controlled by almost the same balance of intermolecular forces (hydrophobicity as expressed by the van der Waals volume V_w, H-bond acceptor basicity β, and dipolarity/polarizability π^*). The results showed that XBridge™ Shield RP_{18} phase overcomes the shortcomings of the silica-based stationary phases, the application of which to lipophilicity measurements had been limited to neutral and acidic compounds.

Key words lipophilicity; partition coefficient; linear solvation free-energy relationship; reversed phase-HPLC

The lipophilicity of solutes, conventionally expressed by their partition coefficient in the 1-octanol/water system ($\log P_{oct}$), is of high significance from both physicochemical and pharmacological viewpoints.[1,2] A number of intermolecular forces between a solute and its environment (*i.e.*, solvents) determine the partitioning process and its equilibration. In pharmacology, the forces are particularly important because they control the migration of solutes (drugs) to biomembranes. Not a few studies have been reported on the relationship between $\log P_{oct}$ and adsorption/permeation of drugs in cell cultures and/or tissue preparations.[3—7]

The reference procedure to measure $\log P_{oct}$ is shake-flask method. The method is, however, time-consuming and narrow in applicable range (*ca.* $-3<\log P<4$). The reversed-phase HPLC (RP-HPLC) came to be a promising alternative to the shake-flask method, because it has advantages such as high throughput rate (which is of key importance to pharmaceutical industry with a vast number of potential drug candidates), insensitivity to impurities and/or degradation products, broad applicable range, low sample consumption, good accuracy and automation possibilities. In RP-HPLC, lipophilicity indices are derived from the capacity factor $\log k$, which is calculated from Eq. 1,

$$k=(t_r-t_0)/t_0 \quad (1)$$

where t_r and t_0 are the retention times of the solute and of an unretained compound, respectively. Some workers have used isocratic $\log k$ values, measured in an appropriate mobile phase, as a lipophilicity parameter.[8—10] However, the majority of investigators use the capacity factors extrapolated to the 100% water ($\log k_w$) condition in order to eliminate the effects of organic solvent.[11—15] Indeed, the $\log k_W$ has been proved to be useful for the investigation of a series of solutes covering broad lipophilicity range. Generally, the extrapolation is based on a quadratic relationship between the isocratic capacity factor $\log k$ and the volume fraction of organic solvent in the mobile phase, φ.[16] When methanol is used as an organic modifier, a linear relationship (Eq. 2) is often obtained for neutral solutes,[17,18]

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

where S and $\log k_w$ are the slope and the intercept of the regression curve, respectively.

Until recently, most lipophilicity studies based on RP-HPLC had employed octadecyl silica (ODS) stationary phases[19,20] and silanol deactivated stationary phases.[15,21,22] As for ODS stationary phases, the correlations between $\log P_{oct}$ and $\log k_w$ (or $\log k$) are generally good for structurally related solutes.[19,20] The decrease in correlation between them with increasing structural diversity of solutes is attributed to the specific interactions between the compounds and the residual silanol groups in such stationary phases.[23] Some studies have been done on silanol deactivated stationary phases, Supelcosil LC-ABZ and Discovery RP Amide C18, where their alkyl chains contain amide groups that electrostatically shield silanols from highly polar analytes. High correlations were found between $\log P_{oct}$ and $\log k_w$ values for a wide range of structurally diverse neutral and acidic compounds.[15,21,22] However, in spite of such improvement in silanol deactivation, the application of this type of stationary phases is still limited to the pH below 8 because of their instability in alkaline media. As a result, lipophilicity cannot be determined directly for neutral form of basic amines.

Recently, a novel RP-HPLC column (XBridge™ Shield RP_{18}) produced by organic/inorganic Hybrid Particle Technology[24] has become available; it affords wide pH resistance

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Table 1. Investigated Compounds and Their Physicochemical Parameters

Number	Solutes[a)]	V_w [b),c)]	π^* [b),d)]	β [b),e)]	α [b),f)]	log P_{oct} [b)]	pK_a [g)]	log k_w [h)] on XBridge™ Shield RP_{18}
	Model solutes							
	Bases							
1	Acridine	174.9	1.57	0.52	0.00	3.40	5.58	2.42
2	$C_6H_5NH_2$	98.0	0.94	0.41	0.06	0.90	4.60	0.70
3	$C_6H_5NHC_2H_5$	133.0	0.78	0.45	0.03	2.16	5.12	1.48
4	2-Cl–$C_6H_4NH_2$	111.8	1.06	0.41	0.06	1.91	2.64	1.30
5	2-NH_2–C_6H_4–C_6H_5	173.9	1.55	0.41	0.18	2.84	3.82	2.26
6	4-$CH_3C_6H_4CH_2NHCH_3$	149.5	0.80	0.70	0.08	1.96	9.93	1.10
7	4-$CH_3C_6H_4CH_2NHCH_2CH_3$	166.1	0.80	0.70	0.08	2.38	10.04	1.35
8	4-$CH_3C_6H_4CH_2NH(CH_2)_2CH_3$	183.4	0.80	0.70	0.08	2.96	9.98	1.75
9	4-$CH_3C_6H_4CH_2NH(CH_2)_3CH_3$	199.4	0.80	0.70	0.08	3.49	9.98	3.15
10	4-$CH_3C_6H_4CH_2NH(CH_2)_4CH_3$	217.7	0.80	0.70	0.08	4.26	10.08	3.75
11	4-$CH_3C_6H_4CH_2NH(CH_2)_5CH_3$	234.2	0.80	0.70	0.08	4.96	10.17	4.36
12	4-$CH_3C_6H_4CH_2NH(CH_2)_6CH_3$	251.8	0.80	0.70	0.08	5.12	10.02	4.96
	Neutrals							
13	$C_6H_5CH_2CN$	121.5	1.22	0.45	0.00	1.56	—	1.24
14	C_6H_5–CO–CH_3	122.3	1.12	0.51	0.00	1.58	—	1.08
15	$C_6H_5NO_2$	107.6	1.01	0.28	0.00	1.85	—	1.36
16	2-$ClC_6H_4NO_2$	122.0	1.13	0.28	0.00	2.24	—	1.93
17	$C_6H_5(CH_2)_2C_6H_5$	196.9	0.99	0.20	0.00	4.80	—	4.00
18	$C_6H_5CH_2OH$	111.6	0.84	0.58	0.33	1.08	—	0.65
19	4-Cl–$C_6H_4CH_2OH$	126.3	0.96	0.58	0.33	1.96	—	1.39
	Acids							
20	3-Cl–C_6H_4OH	107.8	0.84	0.16	0.69	2.49	9.11	2.08
21	3-NO_2–C_6H_4–OH	112.9	1.54	0.23	0.79	2.00	8.40	1.53
22	$C_6H_5(CH_2)_2COOH$	146.0	1.12	0.45	0.60	1.89	4.52	1.27
23	$C_6H_5(CH_2)_3COOH$	162.4	1.12	0.45	0.60	2.42	4.72	1.75
24	$C_6H_5(CH_2)_4COOH$	179.8	1.12	0.45	0.60	2.85	4.59	2.20
25	C_6H_5COOH	111.8	0.74	0.40	0.59	1.96	4.20	1.31
26	4-BrC_6H_4COOH	133.8	0.94	0.40	0.59	2.86	3.97	2.31
27	3-ClC_6H_4COOH	126.2	0.86	0.30	0.59	2.71	3.83	2.17
28	4-IC_6H_4COOH	141.6	0.96	0.42	0.59	3.13	3.96	2.53
29	1-Naphthoic acid	158.5	1.05	0.40	0.59	3.10	3.69	2.52
	Drugs							
30	Flurbiprofen	223.1	1.78	0.49	0.60	3.81	3.91	3.62
31	Indomethacin	283.5	1.86	1.29	0.60	4.27	4.50	3.76
32	Ketoprofen	239.1	2.12	0.99	0.60	2.77	4.29	2.18
33	Naproxen	216.5	1.64	0.79	0.60	3.06	4.15	2.24
34	Phenytoin	228.3	1.45	1.02	0.60	2.68	8.33	1.57
35	Sulfabenzamide	233.6	2.48	1.25	0.33	1.46	1.70/4.57	1.09
36	Sulfacetamide	174.8	2.58	1.25	0.33	−0.16	1.78/5.28	−0.51
37	Sulfamethazine	237.5	2.72	1.90	0.33	0.25	2.73/7.52	0.01
38	Sulfamethoxazole	207.5	2.59	1.64	0.36	0.72	2.28/5.68	0.60
39	Sulfamethoxypyridazine	229.6	2.93	2.38	0.33	0.35	2.09/7.02	0.17
40	Sulfanilamide	139.1	1.89	1.26	0.60	−0.69	2.15/10.42	−0.87

a) The structures of the drugs are shown in Fig. 1. *b*) Taken from ref. 34. *c*) Van der Waals volume. *d*) Dipolarity/polarizability. *e*) H-bond acceptor basicity. *f*) H-bond donor acidity. *g*) Taken from refs. 35, 37 and Bioloom software.[38] *h*) $0.01 \leq$S.D.≤ 0.15.

(1—12) to silica-based materials that has the same alkyl chains as those in the LC-ABZ and Discovery RP Amide C18. The column is expected to make it possible to measure lipophilicity not only for neutral and acidic compounds, but also for basic ones. The objective of the present study is, therefore, to assess lipophilicity of diverse compounds including basic drugs using XBridge™ Shield RP_{18} stationary phase. For this purpose, a set of 40 compounds having well-defined structural parameters and covering broad range of the parameters and log P_{oct} values were selected. Good relationship between log k_w and log P_{oct} was established for the compounds examined. Linear solvation free-energy relationships (LSERs) based on the solvatochromic parameters[25—29] was used to unravel the retention mechanism of the solutes on this novel stationary phase and to compare the mechanism with the partitioning mechanism in 1-octanol/water. In addition, the log k_w/log P_{oct} relationship was validated using a test set of 13 neutral, acidic and basic drugs.

Experimental

Materials The 40 compounds examined to study the relationship between log k_w and log P_{oct} were listed in Table 1. In addition, a test set of 13 structurally diverse neutral, acidic and basic drugs as shown in Table 2 were used to validate the log k_w/log P_{oct} relation. The chemical structures of complex drugs were shown in Fig. 1. The (4-methylbenzyl)alkylamines (**6**—**12** in Table 1) were synthesized according to the literature.[30] All other compounds were obtained from Sigma-Aldrich, Steinheim, Germany; Carl Roth, Karlsruhe, Germany; and VWR, Leuven, Belgium in the highest available purity. Distilled water, HPLC grade methanol (Alfa Aesar, Karlsruhe, Germany) and 1-octanol (Sigma-Aldrich) were used throughout.

Methods Capacity factors were measured with a liquid chromatograph equipped with a HPLC pump SYSTEM GOLD 125 solvent module, a SYSTEM GOLD 507e autosampler and a SYSTEM GOLD UV/Vis 168 detector

Table 2. Compounds in the Test Set

Number	Solutes[a)]	$\log P_{oct}$ [b)]	pK_a [c)]	$\log k_w$ [d)] on XBridge™ Shield RP_{18}	$\log P$ [e)]
41	Antipyrine	0.17	1.44	−0.04	0.44
42	Aspirin	1.19	3.48	0.40	0.89
43	Estradiol	4.01	—	3.36	3.94
44	Hydrocortisone	1.55	—	0.81	1.31
45	Mefenamic acid	5.12	4.33	4.34	4.95
46	Metoprolol	1.95	9.56	1.00	1.51
47	Penbutolol	4.62	9.40	4.06	4.66
48	Phenylbutazone	3.16	4.70	2.35	2.90
49	Pindolol	1.75	9.54	0.71	1.21
50	Progestrone	3.57	—	3.37	3.95
51	Promethazine	4.81	9.11	4.08	4.68
52	Propranolol	3.48	9.47	2.78	3.34
53	Testosterone	3.32	—	2.68	3.24

a) The structures of the drugs are shown in Fig. 1. *b*) Taken from refs. 22, 35. *c*) Taken from Bioloom Software.[38] *d*) $0.01 \leq S.D. \leq 0.15$. *e*) Partition coefficient predicted by Eq. 4.

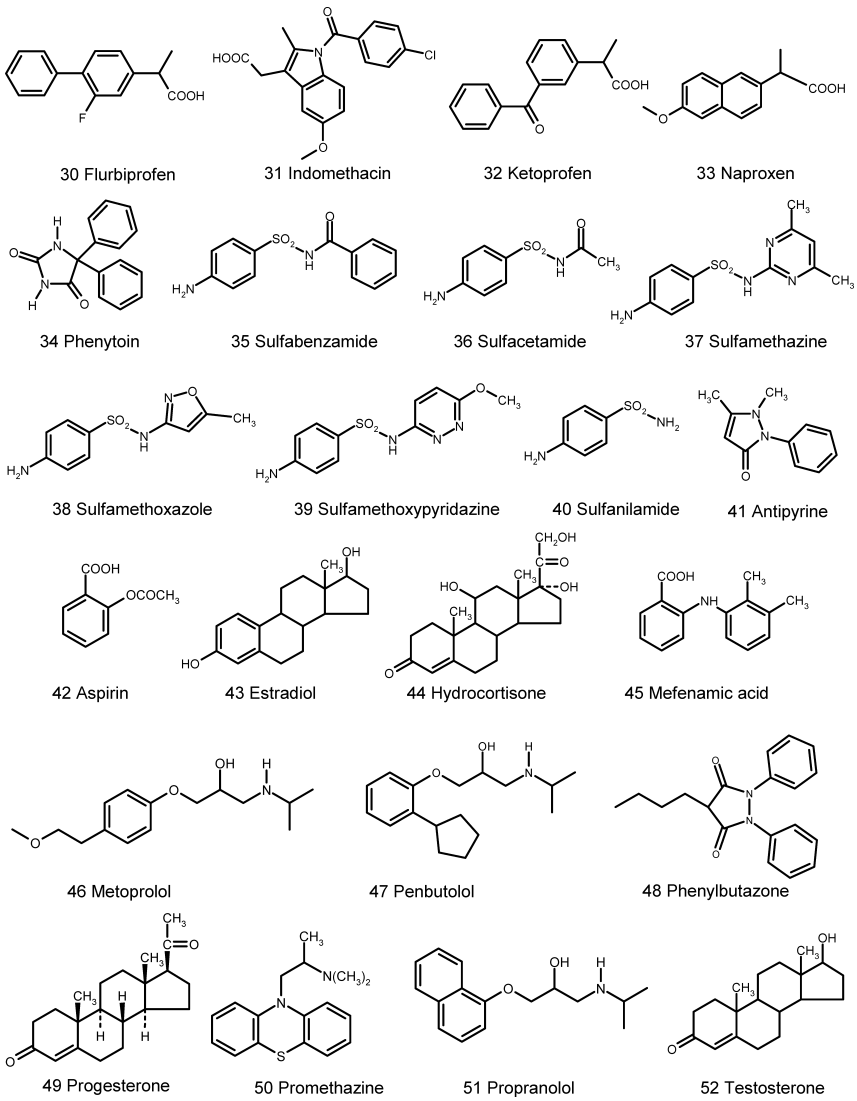

Fig. 1. Structure of the Drugs under Study

(all from Beckmann Coulter, INC. Fuerton, CA, U.S.A.).

The column used was a XBridge™ Shield RP_{18} (5 cm×4.6 mm ID, 5 μm) from Waters (Milford, MA, U.S.A.). The mobile phase consisted of 0.02 M phosphate buffer and methanol in varying proportions from 70 to 10% (v/v). The phosphate buffer was adjusted to pH 7.0 for all nonionizable compounds, and to a pH value where the neutral form was in large excess for the acidic, ampholytic and basic compounds (pH 2.5 for solutes **20**—**34**, **42** and **45**; pH 4.0 for solutes **35**—**40**; pH 11.5 for solutes **6**—**12**, **46**, **47**, **49**, **51** and **52** in Table 1) according to their pK_a values. To increase the similarity with 1-octanol/buffer partitioning,[15,21,22] a 0.25% (v/v) amount of 1-octanol was

added to methanol, and 1-octanol saturated water was used to prepare the buffer. The phosphate buffer was filtered under vacuum through a 0.45 μm HA Millipore filter (Millipore, Milford, MA, U.S.A.) before being mixed with methanol. The retention times were measured at ambient temperature by the UV/Vis detector under the maximum absorption wavelength λ_{max} of the analytes.

The solutions to be injected (10^{-4} to 10^{-3} M) were each prepared by dissolving a solute in an appropriate mobile phase; the injection volume was 10 μl. Uracil was used as an unretained compound. The measurements were carried out at a flow rate 1.0 or 0.5 ml/min for the compounds with $\log P_{oct}$ values higher or lower than 1, respectively. In all cases, three different methanol concentrations were used for the extrapolation to $\log k_w$. Methanol concentrations were adapted to the $\log P_{oct}$ values of the solutes, as described in Table 3.

The capacity factor $\log k$ was calculated by Eq. 1. The $\log k$ values were obtained from the average of k for the measurements in triplicate. The $\log k$ values were then extrapolated to the 100% water condition using Eq. 2. All regression analyses were performed *via* the Microcal Origin statistical software package version 6.0 (Microcal Origin Software Inc., Northapton, MA, U.S.A.).

Results and Discussion

Selection of the Compounds to be Examined Linear solvation free-energy relationships (LSERs) have been known to give highly informative interpretation on the retention of solutes on RP-HPLC stationary phases. The relationships have also been used to evaluate partitioning mechanisms of solutes in various organic/aqueous biphasic systems.[31—33] The LSERs can be expressed by Eq. 3:

$$S_p = v \cdot V_w + p \cdot \pi^* + a \cdot \alpha + b \cdot \beta + c \quad (3)$$

Table 3. Concentrations of Organic Modifier (Methanol) Used with XBridge™ Shield RP C_{18} Stationary Phase

$\log P_{oct}$ of the solutes	MeOH
>3	60, 65, 70
1—3	30, 35, 40
<1	10, 15, 20

where S_p is a given molecular property of a neutral organic solute (*i.e.*, $\log k_w$ or $\log P_{oct}$ in the present study). The four structural parameters are the van der Waals volume V_w that accounts for hydrophobic and dispersive forces, and polar terms known as solvatochromic parameters (dipolarity/polarizability π^*, H-bond donor acidity α, and H-bond acceptor basicity β) that account for polar interactions between solute and solvents. The regression coefficients v, p, a and b reflect the relative contribution of each solute parameter to S_p.

In the present study, therefore, we carefully selected the compounds having relatively rigid structures and well-defined structural parameters (V_w, π^*, β and α), and covering broad range of structural parameters and $\log P_{oct}$ values (−0.69—5.12) as far as possible so as to establish $\log k_w/\log P_{oct}$ relation and LSERs equations. The parameters were listed in Table 1. It is clear that the values of parameters for the selected compounds were distributed in broad range, as shown in Fig. 2.

Relationship between $\log k$ and φ A linear relationship between $\log k$ and φ was found for all compounds retained on the XBridge™ Shield RP_{18} stationary phase. The squared correlation coefficient (r^2) was higher than 0.99 for all compounds except nitrobenzene and ketoprofen (**15** and **32** in Table 1) (r^2=0.96), as well as (4-methylbenzyl)ethylamine and 5-phenylvaleric acid (**7** and **24** in Table 1) (r^2=0.97). The $\log k_w$ values of the compounds for this stationary phase, calculated using Eq. 2, are listed in the rightmost column in Table 1.

Correlation between $\log P_{oct}$ and $\log k_w$ Equation 4 and Fig. 3 show the correlation between $\log P_{oct}$ and $\log k_w$ values on the XBridge™ Shield RP_{18} stationary phase for the 40 compounds:

$$\log P_{oct} = 1.03(\pm 0.07) \log k_w + 0.48(\pm 0.15) \quad (4)$$
$$n=40;\quad q^2=0.96;\quad r^2=0.96;\quad s=0.26;\quad F=968$$

where the values in the parentheses are the 95% confidence

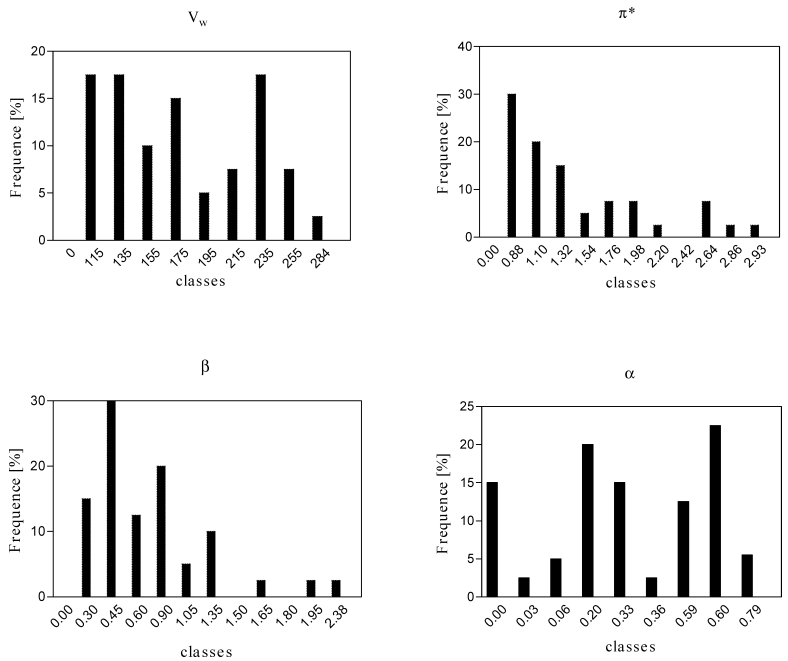

Fig. 2. Distribution of the 40 Investigated Compounds (Table 1) in the Parameter Spaces of van der Waals Volume V_w, Dipolarity/Polariability π^*, H-Bond Acceptor Basicity β and H-Bond Donor Acidity α

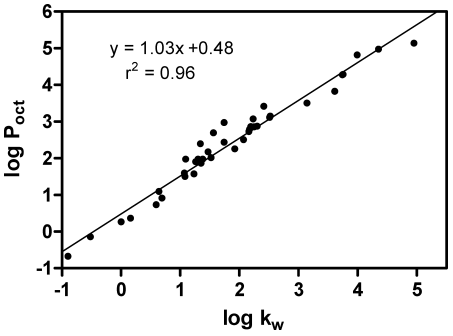

Fig. 3. Relationship between $\log P_{oct}$ and $\log k_w$ Obtained with the XBridge™ Shield RP C_{18} Stationary Phase

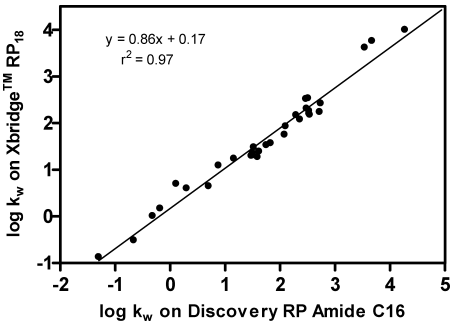

Fig. 4. Relationship between $\log k_w$ Values Obtained with the XBridge™ Shield RP C_{18} and Discovery RP Amide 16 Stationary Phases

The data for discovery RP Amide 16 were cited from our previous paper.[21]

limits; n, q^2, r^2, s and F are the number of compounds, the cross-validated correlation coefficient, the squared correlation coefficient, and the standard deviation and Fisher's test, respectively.

The results show that $\log k_w$ values obtained with the XBridge™ Shield RP_{18} phase are significantly correlated with the $\log P_{oct}$ values for the whole set of neutral, acidic, ampholytic and basic compounds, although the $\log k_w$ values are not the same as the $\log P_{oct}$ values as indicated by the intercept (+0.48) of Eq. 4. This indicates that the rapid and reliable determination of $\log P_{oct}$ values not only for neutral and acidic compounds, but also for basic analytes with high pK_a values (compounds **6**—**12**, **46**, **47**, **49**, **51**, **52**) is possible by RP-HPLC with XBridge™ Shield RP_{18} column, which is highly stable over a wide pH range (1—12). Until recently, reliable determination of $\log P_{oct}$ by RP-HPLC was achieved only for neutral and acidic drugs on silica-based stationary phases with silanol deactivation, such as LC-ABZ[15] and Discovery RP Amide C16 phases (our previous studies).[21,22] Although lipophilicity measurement of basic compounds was carried out by the first author (X.L.) and her coworkers using Zorbax Extend C18 phase (with hydrophobic C18 alkyl chains and stable in pH 2.0—11.5) at pH 10.5 by isocratic mobile phase conditions,[36] the correlation between $\log P_{oct}$ and isocratic $\log k$ was found to be less significant. The results of this study are of interest for high-throughput lipophilicity screening in drug discovery phase.

Both of the significant correlation between $\log P_{oct}$ and $\log k_w$ on the XBridge™ Shield RP_{18} phase and the nearly unity slope of Eq. 4 mean that there is a great similarity between the partitioning process in 1-octanol/water and the chromatographic retention process on this stationary phase.[22] One possible explanation for the similarity lies in the amido groups embedded in this stationary phase. As shown in previous studies,[21,22] the silica-based Discovery-RP-Amide-C16 phase (which has the same amido groups as the XBridge™ Shield RP_{18} phase) yielded a significant correlation between $\log P_{oct}$ and $\log k_w$ for neutral and acidic drugs. Equation 5 and Fig. 4 show the correlation between the $\log k_w$ values obtained with two stationary phases for the 32 common compounds. This correlation is indeed a highly significant one, despite the different characteristics of the materials to which the alkyl chains are bound. This finding verifies that the polar amido groups embedded in the alkyl chains of the two stationary phases are very important for yielding $\log k_w$ values highly correlated with $\log P_{oct}$ values.

$$\log k_w(\text{XBridge}^{TM}\ \text{Shield RP}_{18}) = 1.03(\pm 0.06)\log k_w(\text{Discovery RP Amide C16}) + 0.17(\pm 0.12) \quad (5)$$
$$n=32;\quad q^2=0.97;\quad r^2=0.97;\quad s=0.20;\quad F=926$$

In order to verify the ability of $\log k_w$ from the XBridge™ Shield RP_{18} to be used as a predictor of $\log P_{oct}$, the predictive power of Eq. 4 was established on a test set of 13 drugs with a wide structural diversity and known $\log P_{oct}$ values (Table 2). The $\log k_w$ values from the XBridge™ Shield RP_{18} phase and the $\log P$ values predicted by Eq. 4 are also listed in the rightmost and the second rightmost columns in Table 2.

For these 13 structurally diverse neutral, acidic and basic drugs with a $\log P_{oct}$ range from 0.17 to 5.12, the lipophilicity index $\log k_w$ gives a satisfactory estimation of $\log P_{oct}$ as shown in Eq. 6, further confirming the successful application of the XBridge™ Shield RP_{18} stationary phase in $\log P_{oct}$ prediction under the present experimental conditions.

$$\log P_{oct} = 0.94(\pm 0.09)\log P(\text{est. from } \log k_w) + 0.27(\pm 0.30) \quad (6)$$
$$n=13;\quad q^2=0.98;\quad r^2=0.98;\quad s=0.25;\quad F=429$$

It can be concluded that XBridge™ Shield RP_{18} phase can yield $\log k_w$ values highly correlated with $\log P_{oct}$ values for all types of compounds. This phase overcomes the shortcomings of the silica-based stationary phases that can only be used for neutral and acidic compounds.

Comparison by LSERs Analysis between the Retention Mechanism on the XBridge™ Shield RP_{18} Phase and the Partitioning Mechanism in 1-Octanol/Water The $\log k_w$ values obtained with the XBridge™ Shield RP_{18} stationary phase were analyzed by linear solvation free-energy relationships (LSERs) for the 40 compounds with known solvatochromic parameters (see Table 1), statistically significant equation (Eqs. 7, 7a) that described the structural properties governing retention mechanism were obtained,

$$\log k_w = 2.61\cdot 10^{-2}(\pm 0.41\cdot 10^{-2})\cdot V_w - 0.64(\pm 0.48)\cdot \pi^* - 2.00(\pm 0.66)\cdot \beta - 0.09(\pm 0.65)\cdot \alpha - 0.32(\pm 0.65) \quad (7)$$
$$n=40;\quad q^2=0.84;\quad r^2=0.85;\quad s=0.51;\quad F=52$$

After the removal of the non-significant variable α,

$$\log k_w = 2.61\cdot 10^{-2}(\pm 0.41\cdot 10^{-2})\cdot V_w - 0.66(\pm 0.45)\cdot \pi^* - 1.98(\pm 0.64)\cdot \beta - 0.33(\pm 0.64) \quad (7a)$$
$$n=40;\quad q^2=0.84;\quad r^2=0.85;\quad s=0.50;\quad F=69$$

Equation 7a shows that the main factors governing the retention are the solute's molecular volume (V_w, an expression of its hydrophobicity) and H-bond acceptor basicity (β), while the importance of dipolarity/polarizability (π^*) is smaller and H-bond donor acidity (α) is not significant.

To allow a comparison, the $\log P_{oct}$ values of the same set of compounds were also analyzed by LSERs, yielding Eq. 8,

$$\log P_{oct} = 2.76 \cdot 10^{-2}(\pm 0.35 \cdot 10^{-2}) \cdot V_w - 0.83(\pm 0.40) \cdot \pi^* - 2.06(\pm 0.55) \cdot \beta - 0.05(\pm 0.55) \cdot \alpha + 0.26(\pm 0.55) \quad (8)$$
$$n=40;\quad q^2=0.90;\quad r^2=0.91;\quad s=0.43;\quad F=86$$

After removal of the non-significant variable α:

$$\log P_{oct} = 2.76 \cdot 10^{-2}(\pm 0.34 \cdot 10^{-2}) \cdot V_w - 0.84(\pm 0.37) \cdot \pi^* - 2.05(\pm 0.53) \cdot \beta + 0.25(\pm 0.54) \quad (8a)$$
$$n=40;\quad q^2=0.90;\quad r^2=0.91;\quad s=0.42;\quad F=118$$

One can see from Eq. 8a that V_w and β are the two main structural properties that govern the partitioning mechanism in 1-octanol/water, whereas π^* is of lesser significance and α is devoid of any significance. The ratios of the normalized regression coefficients in Eqs. 7a and 8a are nearly identical (details not shown), meaning that the same balance of intermolecular forces is encoded by $\log P_{oct}$ and $\log k_w$ measured on the XBridge™ Shield RP_{18} phase. This finding confirms the highly significant correlation between these two parameters as shown in Eq. 4.

Conclusion

Using a wide range of structurally diversed neutral, acidic, ampholytic and basic solutes (including drugs) and eluents enriched in 1-octanol, the Xbridge™ shield RP_{18} phase yielded a lipophilicity index $\log k_w$ highly correlated with $\log P_{oct}$ values. An LSERs analysis showed that retention on the Xbridge™ shield RP_{18} phase and partitioning in 1-octanol/water are controlled by the same balance of structural properties, namely Van der Waals volume (V_w), H-bond acceptor basicity (β) and dipolarity/polarizability (π^*). The study showed that this novel stationary phase overcomes the shortcomings of the silica-based stationary phases, whose application in lipophilicity measurements is limited to neutral and acidic compounds. The results of this study are of potential interest for the high-throughput screening of lipophilicity in drug discovery, where basic compounds predominate.

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