European Journal of Pharmaceutical Sciences 168 (2022) 106066

Contents lists available at ScienceDirect

European Journal of Pharmaceutical Sciences

journal homepage: www.elsevier.com/locate/ejps

Molecular characteristics of several drugs evaluated from solvent/water partition measurements: Solvation parameters and intramolecular hydrogen bond indicator

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ARTICLE INFO

Keywords:
Solvent partition of drugs
Abraham descriptors of drugs
Intramolecular hydrogen bond indicator
Implicit solvation models
SMD

ABSTRACT

A wide set of well-known drugs, most of them included in the Abraham's reference database, covering a wide variety of chemical structures and therapeutical functionalities were chosen in order to determine some molecular properties from solvent/water partition measurements. Partition data from aqueous solutions and four different solvents (n-dodecane, toluene, chloroform and n-octanol) were measured and reported. From them, Abraham's molecular descriptors of selected compounds (A, B and S, accounting for hydrogen bond donor, hydrogen bond acceptor and dipolarity/polaritzability, respectively) were estimated. A and B values derived from the experimental measurements strongly agree with the tabulated ones showing the suitability of the used procedure to achieve reliable values for new molecules. However, obtained S values differ from those previously reported for several compounds. Moreover, values for a new indicator of the propensity to form intramolecular hydrogen bonds ($\Delta\log P_{oct\text{-}tol}$) were estimated from the experimental data and also calculated according to both, the Abraham's model and the molecular structures (SMD). The quality of both series of calculated descriptors was evaluated by contrast with the experimental values and satisfactory results were obtained in both instances. Thus, the Abraham's way is useful when molecular descriptors are available but very good estimations can be achieved by SMD, which only requires the drug's molecular structure.

1. Introduction

Lipophilicity is a key property in the physicochemical characterization of bioactive substances since it is strongly related to the ability of compounds to cross cell membranes. In fact, partition of non-charged drugs between wet n-octanol and buffered water, log $P_{oct/w}$, has been taken for years as a powerful indicator of the potential efficiency of drugs to reach the target (Leo et al., 1971; Hansch and Leo, 1979; Sangster, 1997; Seydel and Schaper 1981). According to its high physiological significance, different lipophilicity calculation software, from just the drug chemical structure, have been developed. For example, amongst many others, log $P_{oct/w}$ values can be successfully estimated by means of clogP through ChemDraw11, which uses the algorithm developed by the Medicinal Chemistry Project and BioByte12 on the basis of fragment-based methods Chem Draw Ultra 1986−2007; Biobyte; Pallicer et al. (2014). Despite log $P_{oct/w}$ is still a widely used lipophilicity descriptor, several more specific parameters have gained relevance to explain the physiological behaviour of chemical compounds. Thus, the Abraham's molecular descriptors related to the drug solvation abilities allow valuable interpretations of solute behaviours both in simple solutions and in biological partition processes. These parameters are *E, V, A, B* and *S* which account for excess molar refraction, molecular volume, hydrogen bond acidity, hydrogen bond basicity and dipolarity/polarizability, respectively (M.H. Abraham, 1993a, Pure Appl. Chem; M.H. Abraham, 1993b, Chem.Soc.Rev.; Abraham et al., 2001; Du et al., 2001). Therefore, attempts to calculate the mentioned solvation parameters just from the molecular structures, for instance QSPR models derived from multilinear regression analysis (MLRA) and computational Neural Networks (CNN) (Jover et al., 2004), were proposed or, more recently, a useful calculation software such as ABSOLV

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https://doi.org/10.1016/j.ejps.2021.106066
Received 29 June 2021; Received in revised form 3 November 2021; Accepted 5 November 2021
Available online 9 November 2021

Table 1
Molecular parameters of extracting solvents.

Solvent	E_T^N [a]	ε	α	β	π*
cyclohexane	0.006	2.02[a]	0.00[c]	0.00[c]	0.00[c]
n-dodecane	0.012	2.014[b]	0.0[f]	0.0[f]	0.03[f]
Toluene	0.099	2.38[b]	0.00[a]	0.11[a]	0.49[a]
			0.00[d,e]	0.11[d,e]	0.54 [d,e]
chloroform	0.259	4.89[a]	0.20[a]	0.10[a]	0.69[a]
			0.20[e]	0.10[e]	0.53[e]
			0.44[d]	0.10[d]	0.58[d]
n-octanol	0.537	10.3[b]	0.82	0.80	0.57
			0.77[d]	0.8[d]	0.40[d]
Water	1.000	78.36[a]	1.17[a]	0.47[a]	1.09[a]

[a] Reichardt, 2003;.
[b] CRC Handbook (at 20 °C);.
[c] By definition;.
[d] Leggett, 1993;.
[e] Hofmann et al., 2008;.
[f] because of the lack of the n-dodecane values, those referred to n-decane have been included here, Leggett, 1993.

was developed (ACD/ABSOLV, 2015). From this last approach the two first mentioned parameters (*E* and *V*) are estimated with high accuracy, but the results achieved for the remaining ones (*A, B* and *S*), based on molecular fragments conducted by the own software, show very acceptable evaluations of properties for many drugs but they are not as satisfactory as the former molecular descriptors. Thus, it is commonly admitted that, sometimes, calculated values should be tested experimentally, in particular when new kinds of molecular structures need to be investigated. Then, an independent and reliable way to contrast the calculated *A, B* and *S* values should be very useful in pharmaceutical laboratories, particularly to judge new molecules often involved in drug discovery steps. Since the above mentioned properties are closely related with solvation and, therefore, with their distribution between immiscible solvents, an attempt to establish robust methodology to determine *A, B* and *S* values from partition measurements between water and several selected organic solvents was proposed. The method was successfully validated by means of a set of 13 drugs, which show a variety of molecular structures (Zissimos et al., 2002). Therefore, the suggested methodology is used in this work in order to experimentally characterize a widespread set of well-known drugs with a wide variety of molecular properties and pharmaceutical functionalities. Obtained values have been compared with those included in the most significant database devoted to drug description parameters (Ulrich et al., 2017). This database was built from a huge number of experimental and calculated data obtained in different laboratories, through various measurement techniques and tailed by means of a critical selection of reported final values.

At the present time, partition values derived from a variety of extracting solvents with well-known specific characteristics, log $P_{solv/w}$, allow fruitful experimental approximations to drug affinities and, actually, the relationship between partition parameters obtained with properly selected solvents has become a useful tool in drug discovery laboratories. For instance, distribution parameters of several drugs in n-octanol/water and in toluene/water systems have been used to evaluate the tendency of several molecules to build intramolecular hydrogen bonds (IMHB) and, consequently, to estimate their potential biological activity (Shalaeva et al., 2013; Ermondi et al., 2014). In this work, a comparison between calculated and experimental values of the mentioned parameter, Δlog $P_{oct-tol}$, has been performed in order to confirm the used calculation approaches as common and suitable tools in drug discovery field.

In short, the purpose of this work is to emphasize the agreement between experimental lipophilicity and solvation parameters and those calculated by means of the above mentioned ways. Thus, the validation of the calculation approaches to quickly estimate the polarity and hydrogen bond capabilities of the drugs as well as their ability to generate intramolecular hydrogen bonding has been performed. This has been done in order to facilitate the everyday work in pharmaceutical laboratories devoted to drug discovery.

2. Experimental

2.1. Drugs and solvents

Forty compounds with acid-base properties, most of them drugs showing a variety of therapeutical capabilities, commonly from Sigma-Aldrich ≥ 98% (www.sigmaaldrich.com) and a few from Fisher (www.fishersci.com), were chosen. Partition solvents were from Sigma-Aldrich: Methanol (HPLC grade, ≥ 99.9%, 34860), n-octanol (HPLC grade, ≥ 99.9%, 293245), chloroform (anhydrous ≥ 99%, 288306), toluene (ACS reagent, ≥ 99.5%, 179418) and n-dodecane (anhydrous, ≥ 99%, 297879). Table 1 shows the solvatochromic parameters referred to the pure extracting solvents, but it should be noticed that water-saturated n-octanol and water-saturated chloroform involve significant amounts of water (x_{H2O} is about 0.28 and 0.02 for wet n-octanol and wet chloroform, respectively) (Sangster, 1997; (Garzón and Martínez, 2004)). In the same way, parameters assigned to pure water can slightly change because of the saturation of the aqueous phase by the organic solvent. Selected compounds are listed in Table 2.

2.2. Methods

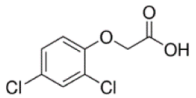
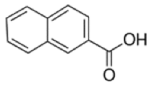
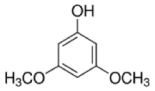
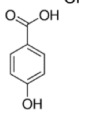
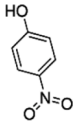
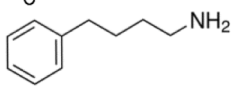
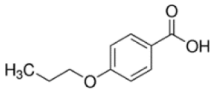
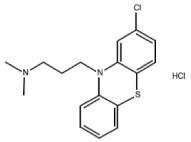
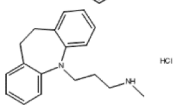
pK_a and log $P_{solv/w}$ measurements were performed on the Pion SiriusT3 (Pion Inc.) and Sirius D-PAS & GLpKa (Sirius Analytical Instruments Ltd.) using the potentiometric procedure and, for some pK_a measurements, the spectrometric technique (Avdeef, 1983; Tam and Takacs-Novak, 2001; Avdeef and Comer, 1993). All the obtained data were processed using the Pion software SiriusT3 v.2.0.0.

Acidity constants, pK_a values, were determined by titration of the fully dissolved drug using the spectroscopic (UV-metric) and the potentiometric (pH-metric) techniques. UV-metric titrations were performed for UV-active ionisable groups between pH 1.5 and 12.5 at concentrations of 150 – 20 μM. pH-metric technique was carried out when ionisable groups were remote from chromophores and titrations were performed between pH 2.0 and 12.0 at concentrations of 2.0 – 0.5 mM weighing sample powder into a glass vial. For basic compounds, the solution was pre-acidified to pH 1.5 or 2.0 with 0.5 M HCl and titrated with 0.5 M KOH solution. In case of acids, the titration was performed in the opposite direction. Spectrometric pK_a values were obtained from UV/pH applying the Target Factor Analysis methodology (Tam et al., 2001). Potentiometric pK_a values were derived from titration curves by applying charge and mass balance equations and the pK_a value that provides the best fit of calculated titration data to the measured ones is taken as the final pK_a value. The pK_as value correspond to the average pK_a from a minimum of three individual results. For poorly soluble drugs, pK_a values were measured at several methanol/water compositions and aqueous pK_a was obtained by extrapolation from the Yasuda-Shedlovsky model (Avdeef et al., 1993). Supplementary Material (Figure 1S) shows the Yasuda-Shedlovsky plot and the parameters of the model obtained for the poorly soluble compounds.

Partition values, log $P_{solv/w}$, were obtained by potentiometric titrations as described for aqueous pK_a determination but in presence of a partition~~ing~~ solvent (octanol, toluene, chloroform and dodecane) at concentrations of 2.0 – 0.5 mM. The log $P_{solv/w}$ was calculated by the difference between the aqueous pK_a and the apparent p_oK_a (pK_a measured in presence of a partition solvent) at several phase ratios (partition solvent:water) between 0.01:1 and 2.60:1 depending on the expected partition value.

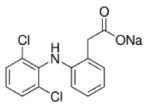
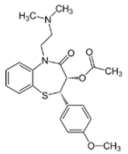
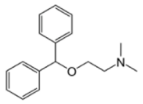
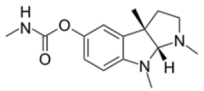
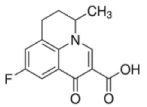
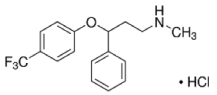
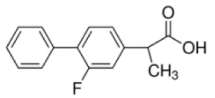
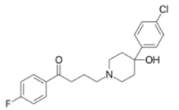
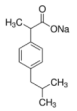
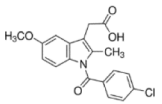
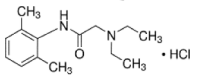
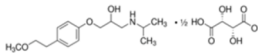
All measurements were taken at 25 °C, under an inert gas atmosphere, and at least three titrations were made for each compound (Avdeef et al., 1993; Avdeef et al., 1993). Several titrations were carried out at the measurement limit conditions of the potentiometric

Table 2
Experimental and calculated partition values and differences between log $P_{octanol/water}$ and log$P_{toluene/water}$ at 25 °C and 0.15 M ionic strength.

Compound	Type	Molecular structure	pK_a	Experimental log $P_{solvent/water}$				Calculated log $P_{solvent/water}$			Δlog $P_{octanol/toluene}$		
				Octanol	Chloroform	Toluene	Dodecane	Octanol Consensus[a]	Toluene SMD	Toluene Eq. (2)	Exp.	Toluene SMD	Toluene Eq. (2)
2,4-dichlorophenoxyacetic acid	HA		2.64 (0.01)	2.81[d]	1.35 (0.01)	1.11 (0.04)	−0.77 (0.03)	2.84	1.09	0.70	1.70	1.75	0.56
2-Iodophenol	HA		8.44[b]	2.47 (0.01)	1.97 (0.06)	1.64 (0.01)	0.81 (0.01)	2.5	NA	1.94	0.83	NA	2.14
2-naphthoic acid	HA		3.88 (0.02)	3.33 (0.01)	2.18 (0.01)	1.87 (0.02)	0.72 (0.01)	3.18	1.69	1.99	1.46	1.49	1.19
3,5-dimethoxyphenol	HA		9.09 (0.01)	1.79 (0.01)	1.16 (0.02)	0.73 (0.01)	−0.97 (0.06)	1.66	0.55	0.69	1.06	1.11	0.97
3-chlorophenol	HA		8.85 (0.01)	2.55 (0.01)	0.74 (0.01)	0.98 (0.01)	−0.34 (0.01)	2.49	0.50	1.14	1.57	1.99	1.35
4-hydroxybenzoic acid	HA		4.34/8.98 (0.01/0.01)	1.51 (0.01)	−0.36 (0.05)	−0.75 (0.05)	−0.99 (0.08)	1.6	−2.40	−0.65	2.26	4.00	2.25
4-nitrophenol	HA		6.90 (0.01)	2.03 (0.01)	0.20 (0.02)	−0.09 (0.01)	−1.69 (0.07)	1.71	−0.31	0.21	2.12	2.02	1.50
4-phenylbutylamine	BH^+		10.51 (0.01)	2.47 (0.01)	2.89 (0.01)	1.69 (0.01)	0.99 (0.07)	2.23	2.32	2.09	0.78	−0.09	0.14
4-propoxybenzoic acid	HA		4.54[c]	3.09[e]	2.16 (0.02)	1.52 (0.02)	0.44 (0.05)	2.73	1.23	2.08	1.57	1.50	0.65
Aniline	BH^+		4.59 (0.01)	0.90[d]	1.32 (0.01)	0.84 (0.01)	−0.19 (0.01)	1.17	0.65	0.90	0.06	0.52	0.27
Chlorpromazine HCl	BH^+		9.24 (0.02)	5.09 (0.02)	6.74 (0.03)	6.60 (0.02)	4.77 (0.01)	5.36	6.19	6.21	−1.51	−0.83	−0.85
Desipramine HCl	BH^+		10.32 (0.01)	4.17 (0.01)	5.48 (0.03)	4.16 (0.01)	3.04 (0.01)	4.28	4.82	5.37	0.01	−0.54	−1.09

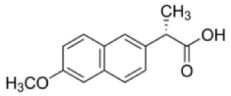
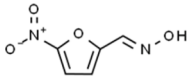
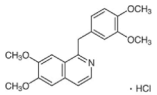
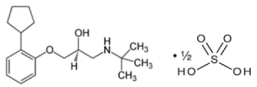
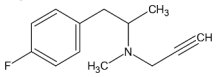
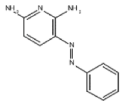
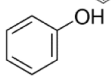
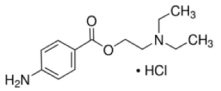
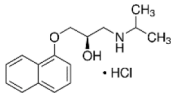
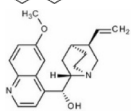
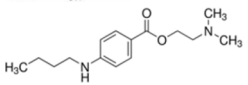
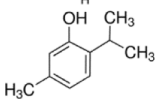
(*continued on next page*)

Table 2 (*continued*)

Compound	Type	Molecular structure	pK_a	Experimental log $P_{solvent/water}$ Octanol	Chloroform	Toluene	Dodecane	Calculated log $P_{solvent/water}$ Octanol Consensus[a]	Toluene SMD	Toluene Eq. (2)	Δlog $P_{octanol/toluene}$ Exp.	Toluene SMD	Toluene Eq. (2)
Diclofenac Na	HA		4.04 (0.01)	4.32 (0.01)	3.73 (0.01)	3.11 (0.01)	1.79 (0.02)	4.48	2.75	3.60	1.21	1.73	0.88
Diltiazem	BH^+		8.00 (0.01)	3.02 (0.01)	5.44 (0.02)	3.44 (0.02)	1.10 (0.02)	3.43	3.01	3.55	−0.42	0.42	−0.12
Diphenhydramine	BH^+		9.07 (0.01)	3.40 (0.01)	5.04 (0.02)	3.80 (0.02)	2.68 (0.02)	3.71	4.58	4.09	−0.40	−0.87	−0.38
Eserine	BH^+		8.12 (0.01)	1.68 (0.01)	2.90 (0.02)	0.98 (0.01)	−0.87 (0.07)	1.54	0.92	1.12	0.70	0.62	0.42
Flumequine	HA		6.23 (0.01)	1.98 (0.03)	2.85 (0.02)	1.50 (0.06)	−0.72 (0.04)	1.61	−0.4	1.62	0.48	2.01	−0.01
Fluoxetine HCl	BH^+		10.09 (0.01)	4.77 (0.01)	5.59 (0.01)	4.93 (0.01)	3.57 (0.01)	4.27	4.13	4.71	−0.16	0.14	−0.44
Flurbiprofen	HA		4.17 (0.02)	3.93 (0.01)	3.45 (0.01)	3.07 (0.01)	1.97 (0.02)	3.82	3.07	2.68	0.86	0.75	1.14
Haloperidol	BH^+		8.61 (0.05)	4.30[f]	4.65 (0.02)	3.20 (0.01)	1.57 (0.03)	3.48	4.17	2.89	1.10	−0.69	0.59
Ibuprofen Na	HA		4.32 (0.01)	4.28 (0.02)	3.43 (0.01)	2.89 (0.01)	2.26 (0.03)	3.37	3.17	2.57	1.39	0.20	0.80
Indomethacin	HA		4.01 (0.02)	4.30 (0.02)	4.11 (0.03)	3.47 (0.01)	0.97 (0.02)	4.02	2.95	3.12	0.83	1.07	0.90
Lidocaine HCl	BH^+		7.95 (0.02)	2.35 (0.01)	4.13 (0.01)	2.29 (0.01)	0.91 (0.02)	1.33	1.33	2.81	0.06	0.00	−1.48
Metoprolol tartrate	BH^+		9.54 (0.02)	1.88 (0.01)	2.70 (0.01)	1.05 (0.01)	−0.68 (0.03)	1.85	0.55	1.07	0.83	1.30	0.78

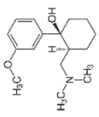
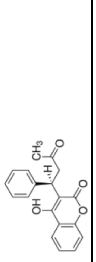
(*continued on next page*)

Table 2 (*continued*)

Compound	Type	Molecular structure	pK_a	Experimental log $P_{solvent/water}$				Calculated log $P_{solvent/water}$			Δlog $P_{octanol/toluene}$		
				Octanol	Chloroform	Toluene	Dodecane	Octanol Consensus[a]	Toluene SMD	Toluene Eq. (2)	Exp.	Toluene SMD	Toluene Eq. (2)
Naproxen	HA		4.18 (0.01)	3.31 (0.01)	2.93 (0.01)	2.32 (0.01)	0.50 (0.01)	2.98	2.19	2.55	0.99	0.79	0.43
Nifuroxime	HA		9.57 (0.01)	1.61 (0.02)	0.78 (0.04)	0.02 (0.10)	−0.94 (0.06)	0.74	−0.91	0.14	1.59	1.65	0.60
Papaverine HCl	BH^+		6.39 (0.01)	3.03 (0.01)	5.28 (0.05)	3.24 (0.03)	0.72 (0.01)	3.2	1.88	3.13	−0.21	1.32	0.07
Penbutolol sulfate	BH^+		9.92 (0.06)	4.28 (0.10)	5.56 (0.03)	4.08 (0.01)	3.15 (0.02)	3.97	4.73	4.39	0.20	−0.76	−0.42
p-Fluorodeprenyl	BH^+		7.42 (0.01)	3.14 (0.01)	4.26 (0.01)	3.59 (0.02)	2.63 (0.01)	2.85	3.05	3.50	−0.45	−0.20	−0.65
Phenazopyridine HCl	BH^+		5.07 (0.01)	2.98 (0.01)	2.59 (0.04)	1.90 (0.02)	0.01 (0.03)	2.77	0.16	0.98	1.08	2.61	1.79
Phenol	HA		9.78 (0.01)	1.31 (0.02)	0.05 (0.01)	0.11 (0.09)	−1.05 (0.04)	1.63	0.45	0.20	1.20	1.18	1.43
Phenylacetic acid	HA		4.10 (0.02)	1.41[d]	0.08 (0.02)	−0.25 (0.01)	−1.57 (0.05)	1.53	−0.07	−0.11	1.66	1.60	1.64
Procaine HCl	BH^+		2.29/9.04 (0.01/0.01)	2.15 (0.02)	2.38 (0.01)	1.26 (0.01)	−0.24 (0.01)	2.13	1.03	1.04	0.89	1.10	1.09
Propranolol HCl	BH^+		9.53 (0.01)	3.33 (0.01)	3.50 (0.01)	2.59 (0.01)	1.34 (0.01)	3.26	3.06	2.20	0.74	0.20	1.06
Quinine	BH^+		4.24/8.55 (0.09/0.04)	3.33 (0.01)	2.80 (0.01)	1.33 (0.01)	−0.22 (0.01)	3.02	1.81	1.54	2.00	1.21	1.48
Tetracaine	BH^+		2.29/8.50 (0.01/0.01)	3.37 (0.01)	4.69 (0.01)	3.29 (0.01)	1.67 (0.01)	3.3	2.82	3.56	0.08	0.48	−0.26
Thymol	HA		10.35 (0.01)	3.42 (0.06)	2.82 (0.06)	2.17 (0.02)	1.67 (0.02)	3.08	2.33	2.67	1.25	0.75	0.41

(*continued on next page*)

Table 2 (*continued*)

Compound	Type	Molecular structure	pK_a	Experimental log $P_{solvent/water}$				Calculated log $P_{solvent/water}$			Δlog $P_{octanol/toluene}$		
				Octanol	Chloroform	Toluene	Dodecane	Octanol Consensus[a]	Toluene SMD	Toluene Eq. (2)	Exp.	Toluene SMD	Toluene Eq. (2)
Tramadol	BH^+		9.49 (0.01)	2.65 (0.01)	4.33 (0.02)	2.72 (0.01)	1.82 (0.04)	2.54	2.46	3.09	−0.07	0.08	−0.55
Verapamil	BH^+		8.72 (0.07)	3.95 (0.01)	7.04 (0.09)	4.95 (0.01)	1.52 (0.07)	3.95	3.98	4.59	−1.00	−0.03	−0.64
Warfarin	HA		4.94 (0.01)	3.31 (0.01)	3.75 (0.01)	2.50 (0.01)	−0.1 (0.02)	3.11	2.33	1.87	0.81	0.78	1.24

[a] log $P_{oct/w}$ Consensus values have been used to derive Δlog $P_{octanol/toluene}$ quantities for which log $P_{tol/w}$ is estimated by SMD or Eq. (2).
[b] van Hooidonk and Ginjaar, 1967.
[c] Jones and Speakman, 1944.
[d] Leo et al. 1971.
[e] Howard and Meylan, 1997.
[f] Laduron, 1976.

technique. In these instances, the cautions for log $P_{oct/w}$ determination previously described were considered (Ràfols et al., 2012).

2.3. Calculations

a) log $P_{solv/w}$. Partition values were estimated and refined by a weighted non-linear least-squares procedure, where the aqueous pK_a values were used as unrefined contribution. log $P_{solv/w}$ values determined from different phase volume ratios were averaged and the ion-pair partitioning of charged species was also characterized.
b) Abraham's molecular descriptors. Values of E and V were readily estimated by means of the well-known ABSOLV program (ACD/ABSOLV, 2015), whereas *A, B* ad *S* descriptors were obtained from the experimental log $P_{solv/w}$ values by means of the described procedure and the selected set of extracting solvents (Abraham and Acree Jr., 2004; Zissimos et al., 2002). Solver (MS Excel) approach was used for calculations.
c) log $P_{tol/w}$. It has been calculated by means of two different estimation ways: 1) From the Abraham's partition equation ($\log P_{tol/w} = eE + aA + bB + sS + vV + c$), where *e, a, b, s* and *v* are the coefficients associated to the partition system and *c* is an offset correction, and the appropriate solute solvation parameters. These last ones were calculated by means of the ABSOLV software (ACD/ABSOLV, 2015); 2) From the molecular structures and conformational analysis generated from the SMILES codes using the structure generator of the open-source chemistry toolbox OpenBabel (OBoyle et al., 2011). The molecular geometries of the conformations for each compound were fully optimized at the B3LYP/6–31G(d) level of theory to 0 K, thermal correction were considered to determine the gas phase energy to 293 K. The time required at this step depends on the number of atoms of the molecule, thus, for the molecules of this study the time range was between 1 and 6 h. The solvation contribution of water and toluene on the geometrical parameters of solutes was considered in geometry optimizations, which were performed using the Minnesota's solvation models SMD. For the purpose of this study, we have used the B3LYP/6–31G(d) version of the quantum-mechanical SMD continuum solvation method, which relies on the quantum mechanical charge density of a solute molecule interacting with a continuum description of the solvent. It is considered a universal method regarding its applicability for any neutral or charged solute where the only requirement is to give a valid chemical structure, and in any liquid medium where the key descriptors are the dielectric constant, refractive index, bulk surface tension, and acidity and basicity parameters (Marenich et al., 2009). Single-point calculations in the gas phase and in solution were performed for the optimized geometries of the compounds to estimate the free energy of solvation (ΔGsol) in the two solvents, this is a relatively quick step that can take from 30 min to 1 h. All calculations were performed using Gaussian 09 (Frisch et al., 2009). The water/toluene partition coefficient was determined using a Boltzmann's weighting scheme to the relative stabilities of the conformational species determined for all compounds in the two solvents. In the particular case of warfarin, tautomeric forms were taking into account.

3. Results and discussion

According to Zissimos et al. proposal (Zissimos et al., 2002) four extracting solvents with different solvation properties were chosen in order to determine the partition coefficients of a representative set of basic or acidic compounds, most of them pharmaceutical drugs. From obtained results, the Abraham's *A, B* and *S* values for each compound as well as the Δlog $P_{oct\text{-}tol}$ (log $P_{oct/w}$ - log $P_{tol/w}$) quantity, related to the propensity of drugs to form intramolecular hydrogen bonds, were calculated. The proficiency of used methodology to evaluate the mentioned descriptors is properly tested. All these items are grouped and discussed as follows:

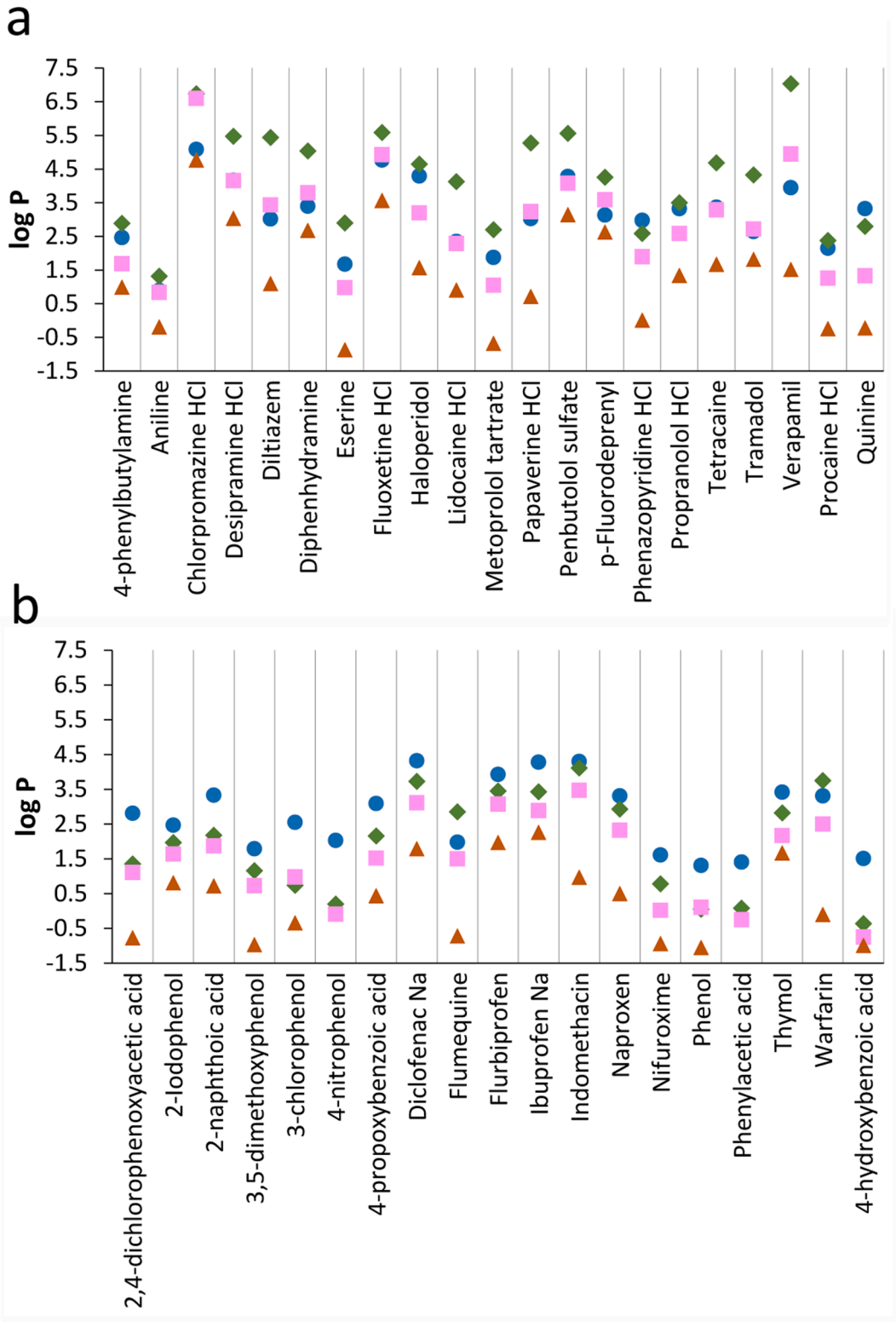


Fig. 1. log $P_{solvent/water}$ for the studied compounds. Octanol (●), chloroform (◆), toluene (■), dodecane (▲). a) basic compounds, b) acidic compounds.

3.1. Drug partitions in four different solvent/water systems

The originally proposed partition solvent set involves cyclohexane, toluene, chloroform and n-octanol, being cyclohexane the extracting agent with minimum ability to interact with solutes (Zissimos et al., 2002). In this work, cyclohexane has been substituted by n-dodecane, a non-cyclic solvent which shows similar solvation abilities than cyclohexane (see Table 1), but it is less volatile and avoids evaporation problems in titration processes. Moreover, n-dodecane mixes well with water on stirring and prevents the formation of micro-emulsions, so it is

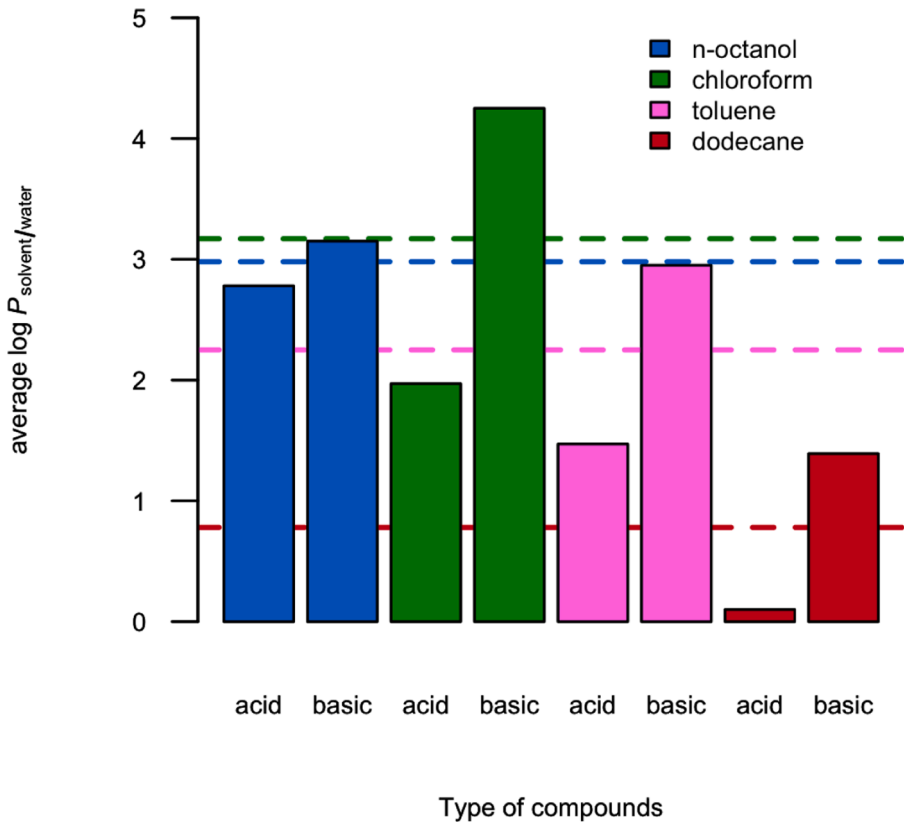


Fig. 2. Average log $P_{solv/w}$ values of acidic and basic drugs in the selected partition systems. Horizontal lines show the mean values of all compounds.

extremely useful to reach high quality results (Box et al., 2006). Measured partition values for each drug and solvent system are given in Table 2 and Fig. 1. Some regular trends in the obtained results should be noticed.

Thus, as shown in Fig. 1a, for basic drugs log $P_{dod/w}$ display the lowest values whereas log $P_{chlor/w}$ are the highest ones. Since n-octanol shows much stronger hydrogen bond abilities but lower polarity/polarizability than chloroform, the affinity of the extracting solvent with basic compounds seems to be more conditioned by this last characteristic than by hydrogen bond capability. However, two exceptions can be observed since log $P_{oct/w}$ values are higher than log $P_{chlor/w}$ for phenazopyridine and quinine. This is because these drugs are the only ones involving a pyridine ring (pyridinium $pK_a < 5.5$) and, therefore, in neutral solutions they show a lone electron pair able to accept a hydrogen bond. Therefore, the higher the α value of the extracting solvent the higher the extraction efficiency (see α values of n-octanol and chloroform, Table 1). In addition, log $P_{oct/w}$ and log $P_{tol/w}$ values for most analysed basic drugs are rather close because π* values of both extracting solvents are similar.

By contrast, acidic substances also show the lowest log $P_{dod/w}$ but log $P_{oct/w}$ values are the highest ones for the most examined compounds. Here, the exceptions are flumequine and warfarin for which log $P_{chlor/w}$ show the largest values (see Fig. 1b). The anomalous behaviour of these molecules can be explained because of the most stable forms in solution, which were derived from the SMD solvation model (see Fig. 2S). Thus, flumequine, in its most stable conformation, presents an intramolecular hydrogen bond, which decreases the interaction of the hydroxyl belonging to the carboxylic group with the *n*-octanol. In case of warfarin, and agreeing with previous studies (Guasch et al., 2015), the most stable form in aqueous solution seems to be a 4-hydroxycoumarin cyclic hemiketal tautomer, and brings as consequence a structural change of an enolic and ketonic group by a hemiketal group. In both cases, flumequine and warfarin, the hydrogen bond acidity is significantly reduced and this fact is translated into a lesser capacity of *n*-octanol to extract these compounds. Moreover, drugs which show a heterocyclic O or N atom belonging to a condensed structure, as the mentioned flumequine and warfarin, also show some hydrogen bond acceptor character that brings its behaviour nearer than the one exhibited by basic compounds. In fact, the stated effect is also noticed for indomethacin and nifuroxime, which show a heterocyclic N or O too, but it is not so large as for flumequine and warfarin, and these compounds display the described regular partition behaviour. In all instances log $P_{chlor/w}$ is higher than log $P_{tol/w}$, and both values are quite similar for many compounds. This is because chloroform and toluene show close solvation parameters with the exception of α, which is higher for chloroform (Table 1). Then, it seems that the extracting solvent hydrogen bond donor ability is not relevant in the solvation of most acidic compounds. Fig. 2 summarizes the distribution mean values of basic and acidic compounds for each partition system.

The present results agree with those previously published for a series of 47 compounds, most of them with basic or acidic character, and four organic extracting solvents (cyclohexane, toluene, chloroform and n-octanol). Thus, for the mentioned series, log $P_{cyclohex/w}$ show the lowest values for both kind of compounds, whereas for bases log $P_{chlor/w}$ is the highest one and for acids it is log $P_{oct/w.}$ The only exceptions are o-nitroaniline and o-nitrophenol, due to the well-known *orto* effect, and propylamine. According to our own results already explained, quinine shows a log $P_{oct/w}$ value higher than log $P_{chlor/w}$. (Zissimos et al., 2002).

Thus, n-dodecane is the solvent with weaker ability to interact with studied drugs, both bases and acids, and, the one that mostly differs from the other selected extracting agents. It seems, therefore, the best reference solvent. Nevertheless, Ermondi et al. prefer to use toluene as the reference solvent in their studies about the hydrogen bond donor ability of solutes through Block Relevance (BR) analysis (Ermondi et al., 2014). They argue that most compounds with pharmaceutical interest are insoluble in any alkane, such as n-dodecane or cyclohexane, but show

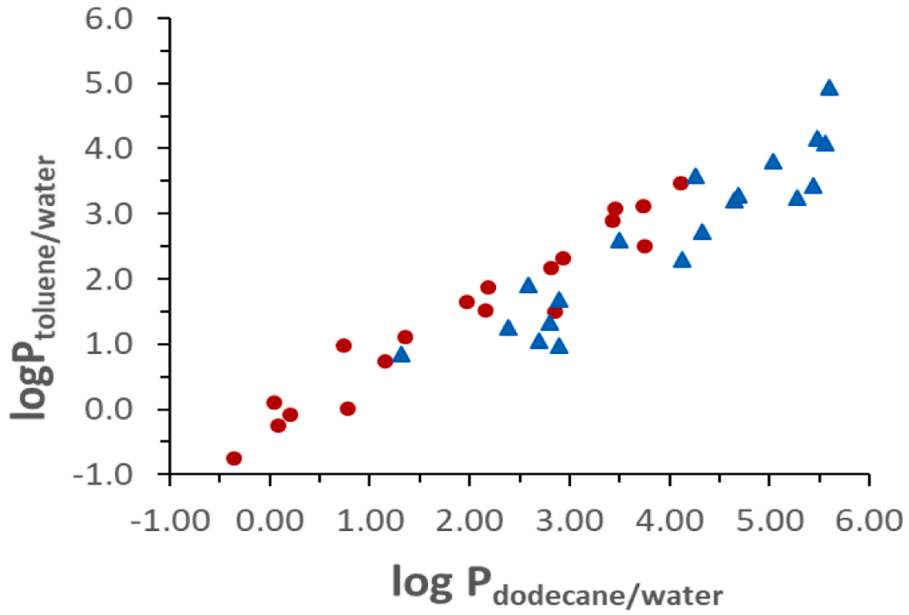


Fig. 3. log $P_{toluene/water}$ vs log $P_{dodecane/water}$. Basic compounds (●), acidic compounds (▲).

Table 3
Calculated descriptors (E and V)[a] and experimental descriptors (A, B and S).

Compound	*E*	*V*	*A*	*B*	*S*	SUM Sq Error
2,4-dichlorophenoxyacetic acid	1.04	1.376	0.862	0.480	1.376	0.011
2-Iodophenol	1.33	1.033	0.361	0.448	0.769	0.023
2-naphthoic acid	1.47	1.301	0.639	0.463	0.961	0.029
3,5-dimethoxyphenol	0.83	1.174	0.578	0.532	1.319	0.012
3-chlorophenol	0.91	0.898	0.804	0.155	0.879	0.016
4-hydroxybenzoic acid	0.98	0.990	0.612	0.835	0.000	0.062
4-nitrophenol	1.05	0.949	0.906	0.291	1.255	0.002
4-phenylbutylamine	0.77	1.380	0.209	0.789	0.652	0.120
4-propoxybenzoic acid	0.81	1.413	0.631	0.605	0.757	0.009
Aniline	0.86	0.816	0.109	0.512	0.954	0.001
Chlorpromazine	2.26	2.406	0.000	0.947	1.805	0.169
Desipramine	1.80	2.261	0.019	1.279	1.136	0.062
Diclofenac	1.81	2.025	0.528	1.005	1.007	0.002
Diltiazem	2.42	3.137	0.000	2.222	2.241	0.169
Diphenhydramine	1.36	2.187	0.000	1.284	1.091	0.059
Eserine	1.68	2.141	0.140	1.666	1.706	0.020
Flumequine	1.70	1.791	0.300	1.053	2.194	0.033
Fluoxetine	1.01	2.240	0.208	0.969	0.989	0.019
Flurbiprofen	1.50	1.839	0.421	0.938	0.711	0.016
Haloperidol	2.00	2.798	0.316	1.882	1.011	0.004
Ibuprofen	0.78	1.777	0.531	0.839	0.132	0.000
Indomethacin	2.24	2.530	0.592	1.306	2.012	0.075
Lidocaine	1.10	2.059	0.000	1.381	1.356	0.054
Metoprolol	1.10	2.260	0.219	1.773	1.197	0.041
Naproxen	1.54	1.782	0.555	0.827	1.511	0.000
Nifuroxime	1.03	0.967	0.519	0.570	0.817	0.063
Papaverine	2.19	2.591	0.037	1.583	2.638	0.087
Penbutolol	1.25	2.516	0.022	1.574	0.643	0.003
p-fluorodeprenyl	0.92	1.734	0.000	0.926	0.749	0.025
Phenazopyridine	2.03	1.639	0.546	0.770	1.803	0.026
Phenol	0.78	0.775	0.526	0.360	0.895	0.002
Phenylacetic acid	0.75	1.073	0.624	0.647	0.923	0.005
Procaine	1.11	1.977	0.303	1.453	0.961	0.063
Propranolol	1.76	2.148	0.252	1.443	0.863	0.025
Quinine	2.40	2.551	0.515	1.937	1.089	0.000
Tetracaine	1.02	2.259	0.137	1.302	1.335	0.000
Thymol	0.84	1.339	0.436	0.582	0.303	0.065
Tramadol	1.23	2.234	0.000	1.573	0.850	0.139
Verapamil	1.76	3.786	0.000	2.408	2.851	0.000
Warfarin	1.98	2.308	0.510	1.222	2.372	0.004

[a] Calculated by means of ABSOLV software.

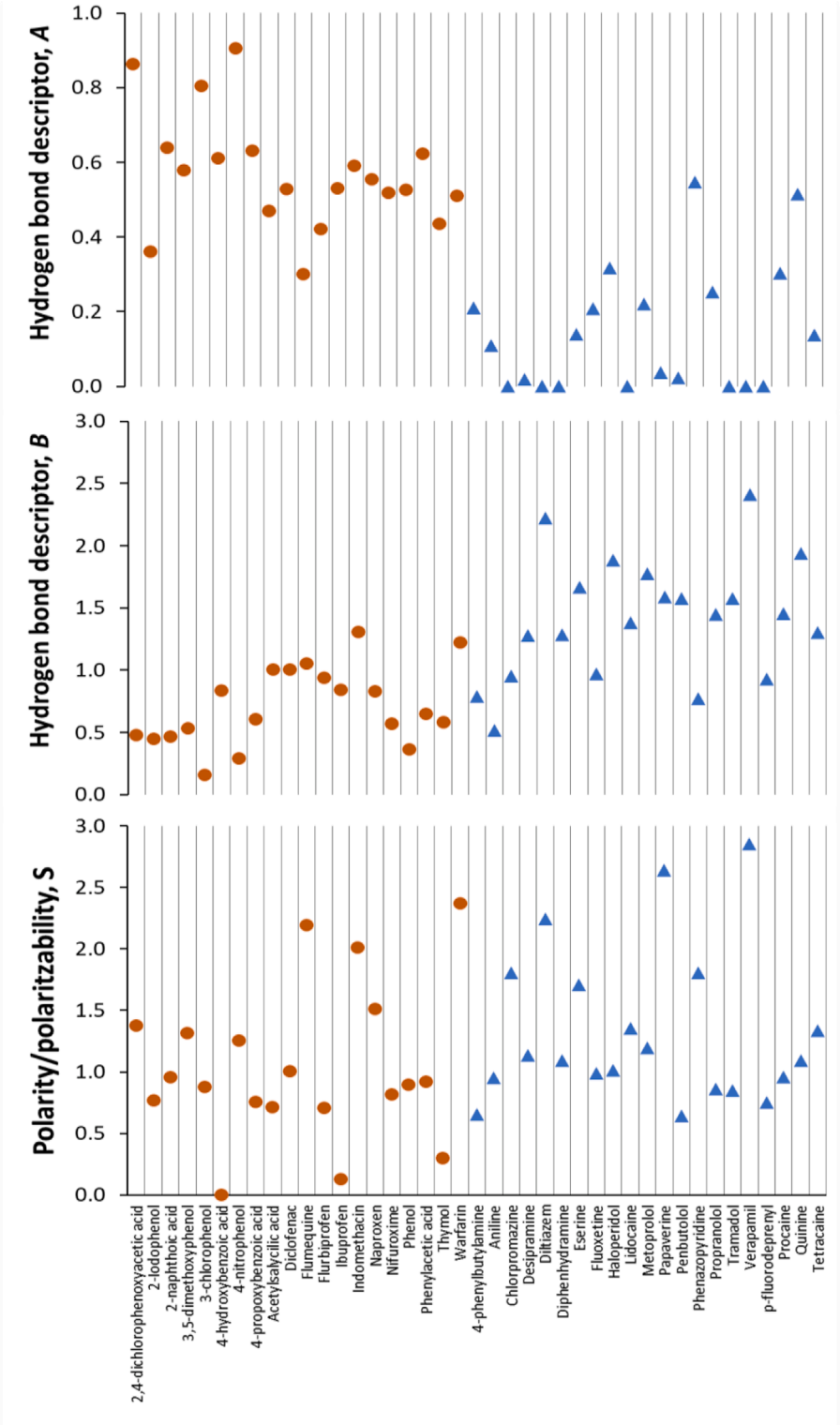


Fig. 4. A, B and S descriptors for the studied compounds. Basic compounds (●), acidic compounds (▲).

measurable solubility in toluene. In fact, all these alkanes lack heteroatoms or functional groups and only the aromatic character of toluene points out the difference (see π^* values in Table 1). Since right log $P_{dod/w}$ measurements has been properly obtained for the drugs selected in this work, the correlation between the two series of log $P_{solv/w}$ values is given in Fig. 3, which shows a roughly linear trend with positive slope but poor correlation. This fact confirms that toluene and n-dodecane are different enough to be included in this partition study to estimate drug solvation parameters.

3.2. Estimation of drug solvation parameters

Each solvent/water system can be described using the well-known Abraham's model shown in the experimental part. Thus, the following equations for the chosen extracting systems Eqs. (1)–(4), have been used in further calculations. However, whereas Eq. (4) was derived using data

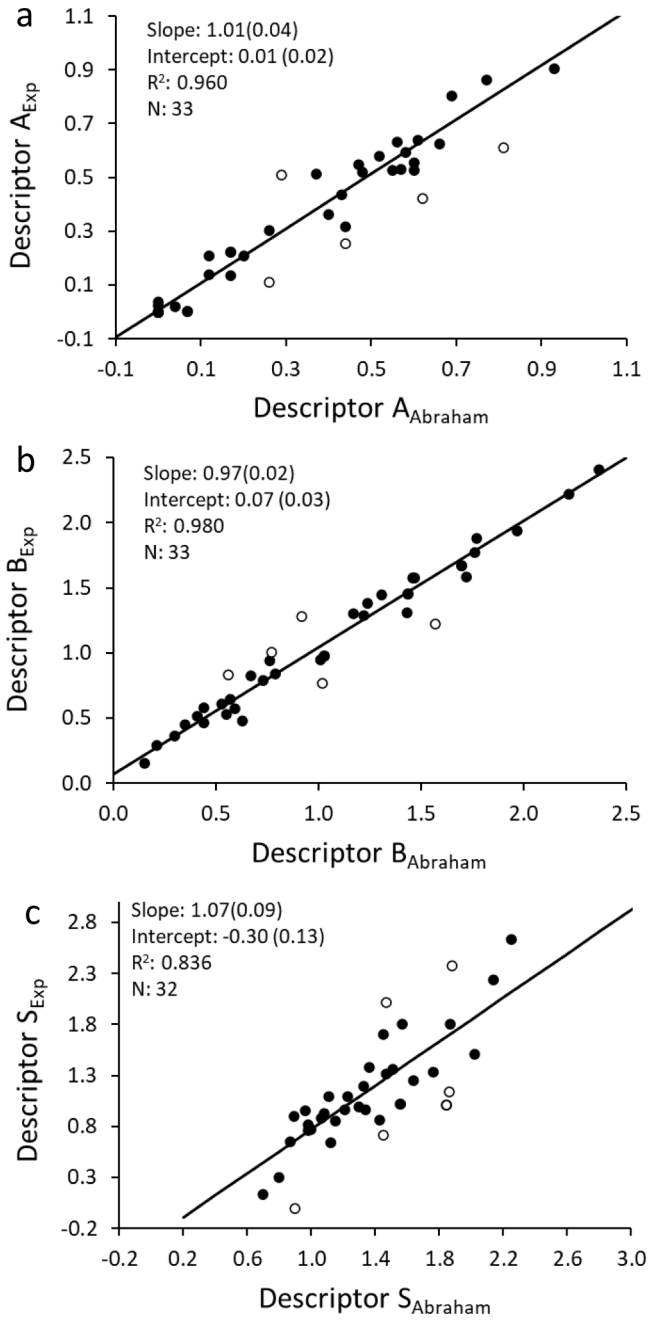


Fig. 5. Experimental descriptors versus database values. Points with residual standard higher than 2 (○) have been excluded in final correlations.

obtained from wet-octanol, that is water-saturated n-octanol, Eqs. (1)–3 were established from data of both, wet and dry extracting solvents (Abraham et al., 2010)

$$\log P_{dod/w} = 0.668E - 3.545A - 5.006B - 1.644S + 4.459V + 0.114 \quad (1)$$

$$\log P_{tol/w} = 0.527E - 3.010A - 4.824B - 0.720S + 4.545V + 0.143 \quad (2)$$

$$\log P_{chlor/w} = 0.105E - 3.112A - 3.514B - 0.403S + 4.395V + 0.191 \quad (3)$$

$$\log P_{oct/w} = 0.562E + 0.034A - 3.460B - 1.054S + 3.814V + 0.088 \quad (4)$$

It should be noted that wet-octanol is as strong hydrogen-bond base as the water is (*a*-coefficient almost zero in Eq. (4)), but it shows a weaker hydrogen-bond acidic ability (negative *b*-coefficient). By contrast, n-dodecane shows the weaker hydrogen bond acidic and basic character of the selected partition solvents (most negative *a* and *b* coefficients). As already mentioned, the most significant difference between n-dodecane and toluene is due to the aromatic character of the last one (see *s* coefficient values). Finally, the partition system involving chloroform shows the lowest sensitivity with respect to excess molar refraction and polarizability of the solute to be extracted (the values of *e* and *s* coefficients are the closest to zero of the whole set of solvent systems). Thus, the extracting ability of each solvent is mainly due to its specific characteristics, which significantly differ for each one of them Table 1) and, therefore, the selected solvent-set is able to estimate properly the molecular properties of any tested drug. Consequently, from Eqs. (1–(4) and the experimental log $P_{solv/w}$ values (Table 2), A, B and S parameters for each drug have been calculated. Results, as well as the minimum square error values, are given in Table 3 and Fig. 4.

A descriptor is shown in Fig. 4 for all the studied compounds. Most acids show *A* values higher than 0.4 whereas most of those calculated for basic drugs are below this threshold. As expected, acidic compounds can easily donate hydrogen bonds and, therefore, they show high *A* values. Nevertheless, it should be noticed that some basic groups may also be able to donate weak hydrogen bonds, e.g., -NH_2, whereas others cannot, *e.g.*, -$N(CH_3)_2$. Thus, *A* values for basic compounds are more varied but, usually, lower than those for the acidic ones. Regarding to *B* descriptor, it is above 0.8 for most bases, a higher value than those attributed to almost all acidic drugs, as shown in Fig. 4. The higher the value of *B* the stronger is the hydrogen bond basicity of the compound. It should be taken into account, however, that acidic functional groups can also have a lone pair of electrons able to accept weak hydrogen bonds, e.g., ibuprofen, which show a carboxylic group, -COOH. Hence, the examined acidic compounds still have positive *B* values indicating some hydrogen bond basicity. Fig. 4 shows that *S* descriptor is independent of the acidic or basic character of the drug and show a wide range of values (from 0 to 2.8) despite most of them being located in the 0.8–1.8 range.

As already mentioned, most of the analysed compounds are included in the reference database (Ulrich et al., 2017). Fig. 5(a-c) allows the comparison of solute descriptors determined in this work with those previously published. As expected, both A and B experimental values nicely agree with those from the reference database showing the ability of the proposed methodology to achieve accurate measurements for a large variety of chemical structures. It should also be noticed that a slightly poorer regression analysis are obtained when A and B values calculated by means of ABSOLV software are used, showing that, for many purposes, this last one is an appropriate estimation way too. Nevertheless, the contrast of experimental S values, as well as those obtained by ABSOLV calculator, with the ones included in Abraham's database is not as satisfactory. Thus, relevant drugs out of linearity shown in Fig. 5c are acidic (indomethacin and warfarin) or basic (chlorpromazine, papaverine, procaine, fluoxetine and desipramine) compounds but, even excluding these outliers, the final correlation is disappointing. Then, it seems that the present experimental approximation is useful for the determination of hydrogen bonding descriptors of new compounds but it is not able to evaluate properly their dipolarity/polarisability. Therefore, a deeper exam about the origin of S values included in the reference database has been carried out. It shows that some literature references proceed from different non-experimental approaches and final S values are not directly available. Some other references (Barra et al., al.,2000; Perlovich et al., 2003; Zissimos et al., 2002) refer to thermodynamic studies mainly associated to the solubility or lipophilicity of several drugs in various solvents, but final S values are not explicitly given. Therefore, results shown in this paper seem to be the only ones directly derived from partition measurements and calculated from the well-recognized Abraham's equation, which has allowed the good estimation of A and B molecular descriptors. Then, the S values achieved in this work for the selected drugs seem to be, at least, as reliable as those included in the reference database. Flumequine and p-fluorodeprenyl were not previously characterized and, as far as we know, data derived in the present study are the only ones published until

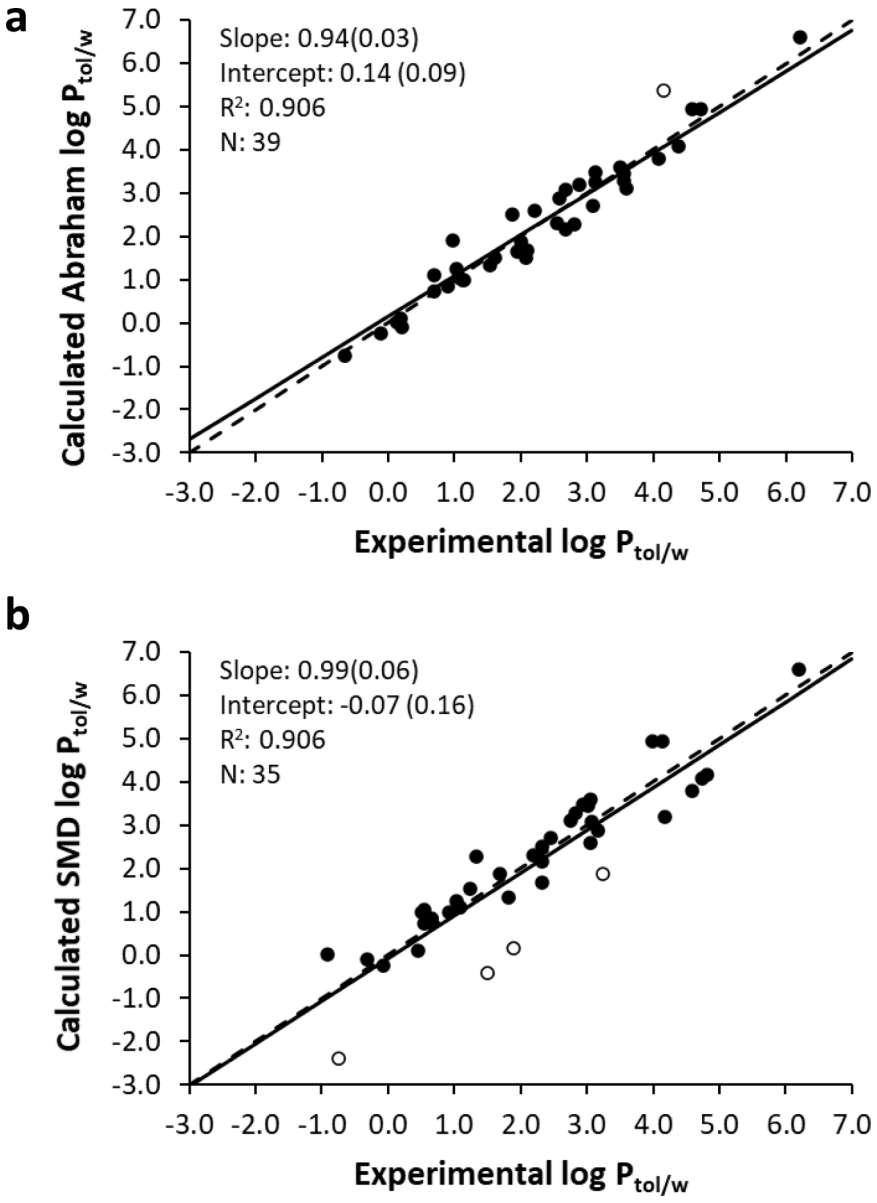


Fig. 6. Comparison between experimental and Abraham's model (a) and SMD model (b) toluene/water log P. Empty points stand for the compounds with the largest errors (> 1.2 log units).

now.

It should also be noticed that profiles logD/pH of selected drugs could be of interest, but the used methodology allows only the determination of the lipophilicity of pure species (neutral and ionized), mainly the neutral. From these values, a good estimation of the lipophilicity/pH profile can be easily derived. Nevertheless, to get the true experimental profile, accurate measurements by means of the shake-flask method in several intermediate pH buffered solutions, where both neutral and ionic species are present, are required. According to former research, both approaches lead to consistent results at least for a set of amphoteric and zwitterionic drugs shown in (Ràfols et al. (2017).

3.3. Drug intramolecular hydrogen bonding indicator

Drug distribution in different partitioning systems reveals the relative strength of intra-/intermolecular interactions involving the solute, including hydrogen bonding. Thus, the difference in partitioning between water and a strong hydrogen-bonding solvent like wet n-octanol (log $P_{oct/w}$) and the distribution between water and a non-hydrogen-bonding solvent such as toluene (log $P_{tol/w}$), can provide a useful measurement of desolvation potential, Δlog $P_{oct\text{-}tol}$, of the analysed drug. This approach assumes that the hydrophobic effect will be similar for both extracting solvents and, therefore, the difference in partitioning reflects the ability of n-octanol to accommodate the hydrogen-bonding requirement of the solute. The new Δlog $P_{oct\text{-}tol}$ parameter has gained relevance in drug discovery field because it accounts for the hydrogen bond donor ability of solutes and, in addition, it describes the propensity of compounds to form intramolecular hydrogen bonds (IMHB) (Shalaeva et al., 2013). However, whereas experimental and/or calculated log $P_{oct/w}$ values are critically tabulated for many drugs, or can be estimated with very acceptable accuracy for new compounds, only a few reliable partition values between water and toluene are given in literature. Thus, the experimental results presented in this work should allow the evaluation of calculated log $P_{tol/w}$ values, which can be achieved by means of two different ways.

The first one involves the log $P_{tol/w}$ calculation by means of Eq. (2) and the appropriate solvation parameters of the drug under study, which can be easily calculated by means of ABSOLV software. Results are

presented in Fig. 6a, which allows the comparison between calculated and experimental values showing a good correlation with only one outlier, desipramine. When solvation parameters from reference database (Ulrich et al., 2017) are used the correlation is also fine, confirming the robustness of both approximation modes.

The second way is based on the chemical structure of the drug and involves the calculation procedure described in the experimental part. Thus, Fig. 6b shows the performance of Minnesota's solvation model, SMD, for predicting the experimental log $P_{tol/w}$ of the chosen set of molecules, which involves a wide chemical variability. The DFT functional selected was B3LYP, which has proven to work successfully in the prediction of partition coefficients (Michalík and Lukeš, 2016). The root-mean square deviation (rmsd) between computed results and experimental data is 0.72 log units, which is in line with the reported accuracy of quantum mechanical (QM) based continuum solvation methods, on average, 0.60 log P units (Işık et al., 2020; Zamora et al., 2020; Patel et al., 2020; (Klamt et al., 2016)). The largest discrepancies, considering an error in the predicted log $P_{tol/w}$ that deviates about three times the QM-based continuum solvation model uncertainty, are represented by 4-hydroxybenzoic acid, flumequine, papaverine, and phenazopyridine (Fig. 6b). These molecules were predicted with an underestimated log $P_{tol/w}$ value and can be classified as two aromatic carboxylic acids (4-hydroxybenzoic acid and flumequine) and two heterocyclic amines with extended aromatic systems (papaverine and phenazopyridine). The divergence between predicted and experimental values may contemplate, at least in part, the impact of aggregation on solubility and log $P_{tol/w}$ (Reker et al., 2019) as noted for substituted benzoic acids especially in non-polar solvents (di Tomaso, 2013) but also in papaverine even in hydrochloride solutions (Güntzel et al., 2020). Thus, it is proved that implicit solvation models the SMD calculation approach furnishes a very acceptable estimation of log $P_{tol/w}$ values.

In summary, both estimation approaches are satisfactory despite the linear parameters, slope and intercept of the calculated/experimental regression, seem to be slightly better for SMD model. These conclusions stand for an interesting issue because of the growing interest of $\Delta\log P_{oct\text{-}tol}$ parameter in drug discovery field and the lack of experimental log $P_{tol/w}$ values in literature.

4. Conclusions

The experimental way to determine solvation parameters of chemical compounds based in partition measurements between an aqueous phase and four different solvents (n-dodecane, toluene, chloroform and n-octanol) is a reliable and successful approach for characterization of drugs. Obtained solvation values for a wide set of well-known drugs with different structures and physiological functionalities are reliable and consistent with the ones included in the reference database (Ulrich et al., 2017). The mentioned solvation parameters, which account for polarity/polarizability and hydrogen bond capabilities of solutes, allow the interpretation of drug affinities of interest in the pharmaceutical field. In addition, intramolecular hydrogen bonding data can be derived from water/n-octanol and water/toluene partition values and this information useful in the explanation of the drug biological behaviour. To facilitate the prevision of new drugs behaviour, two different estimation approaches for water/toluene partition have been successfully tested. The practical interest of this last contribution is related to the lack of experimental values associated to water/toluene partition.

CRediT authorship contribution statement

Rebeca Ruiz: Data curation, Methodology, Writing – review & editing. **William J. Zamora:** Software, Writing – review & editing. **Clara Ràfols:** Conceptualization, Methodology, Validation, Writing – review & editing. **Elisabeth Bosch:** Conceptualization, Validation, Writing – original draft, Writing – review & editing.

Acknowledgements

The authors from the University of Barcelona are grateful for the financial support of the Spanish government (Project PID2020–115374GB-100). We acknowledge the computational facilities provided by the Consorci de Serveis Universitaris de Catalunya (CSUC). We also thanks J. Comer and K. Box Sirius Analytical Instruments Ltd for helpful discussions.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ejps.2021.106066.

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