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A new method to define the hydrophilic-lipophilic balance

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Experimental values of the molecular hydrophobicity (R_{M0}) determined by reverse-phase thin-layer chromatography (RP-TLC) for four isomeric pairs of *bis*-dinitrophenyl-Kryptofix-22 derivatives (**1a, 1b**; **1c, 1d**; **1e, 1f**; and **1g, 1h**) were correlated ($R^2 > 0.970$) by means of values of the hydrophilic-lipophilic balance (HLB) calculated by a new method involving several physico-chemical characteristics: the Ghose-Crippen octanol-water partition coefficient (*AlogP*), Molecular Surface Area (*MSA*), energy of dispersion forces between molecules (*D*), energy of dipolar intermolecular forces between molecules (*P*), hydrophobic surface area (*HySA*), surface area (*SA*) and a statistical factor ($SF_{f(ST)}$) which depends on the surface tension. The same strategy involving HLB values was applied for 50 alcohols, 37 amines and 15 ethers, this time involving comparisons with experimental *logP* values; good correlations were obtained for alcohols ($R^2 = 0.855$), amines ($R^2 = 0.922$) and ethers ($R^2 = 0.901$).

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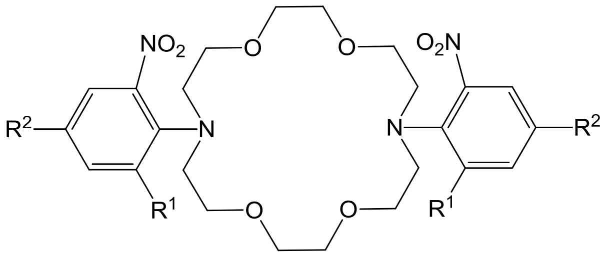
Keywords: Molecular hidrophobicity R_{M0}, Hydrophilic-lipophilic balance, *logP*, QSPR, Alcohols, Amines, Ethers

1. Introduction

The macrocyclic compound Kryptofix K22 (1,7,10,16-tetraoxa-4,13-diazacyclooctadecane), like other crown ether compounds, is used for separations, recovery or removal of specific species, ion selective electrodes, biological mimics and reaction catalysts [1,2], due to its ionophoric properties [3,4]. On the other hand, the K22 macrocycle is an important starting material for the synthesis of *azacoronands* with different properties depending on the substituents at the nitrogen atoms [5-7]. Some of these *azacoronands* have a antifungal [8], anticoccidial activity [9] or antitumoral activities [10].

In the present paper we report quantitative structure–property relationships (QSPR) for R_{M0} hydrophobic parameters of four isomeric pairs of *bis*-dinitrophenyl-kriptofix-22 derivatives (**1a–1h**) [5,7] and a new method for calculating the hydrophilic-lipophilic balance (HLB) of these compounds. To validate the model, we correlated calculated HLB values according to the new method with experimental values of the molecular hydrophobicity (R_{M0}) determined for these compounds [5,7]. This strategy was successfully applied for 50 alcohols, 37 amines and 15 ethers, checking the correlation between their calculated HLB values with their available experimental *logP* data.



Pairs of isomers:
a,b; **c,d**; **e,f** and **g,h**

a $R^1=NO_2$; $R^2=H$ and **b** $R^1=H$; $R^2=NO_2$;
c $R^1=NO_2$; $R^2=CF_3$ and **d** $R^1=CF_3$; $R^2=NO_2$;
e $R^1=NO_2$; $R^2=CN$ and **f** $R^1=CN$; $R^2=NO_2$;
g $R^1=NO_2$; $R^2=COOH$ and **h** $R^1=COOH$; $R^2=NO_2$.

Fig. 1. The four isomeric pairs of bis-dinitrophenyl-Kryptofix-22 derivatives (1a–1h)

2. Experimental

The hydrophobic-hydrophilic balance (HLB), widely used by chemists for surfactants, was originally defined by Griffin [11,12], but it cannot be applied for compounds **1a–h.** Interaction of the molecules with water is an essential factor in most chemical and biological processes. Many existing methods for calculating interactions of molecules with water and other solvents exist and are used [13-18], one of the most important being the hydrophilic-lipophilic balance, because this parameter may indicate the contribution of each part of the molecule to the hydrophilic-lipophilic property. In the literature other methods were also suggested for calculating HLB [19-22].

The molecular hydrophobicity R_{M0} for isomeric pairs of compounds **1a–1h** has been calculated from experimentally measured RP-TLC data [5,7] according to Eqs. (1) and (2) [23,24].

$$R_M = \log (1/R_f - 1) \quad (1)$$

$$R_M = R_{M0} + bK \quad (2)$$

where: R_{M0} is the extrapolated R_M for zero concentration in the water–organic solvent mixture, and b is the change in the R_M value caused by increasing the concentration (K) of the organic component in the mobile phase.

3. Results and Discussion

3.1. Pairs of bis-dinitrophenyl-Kryptofix-22 derivatives

In this paper we present a new relationship to calculate HLB as shown in Eq. (3), which can give indications on structural contributions due to interactions at the interface between water and an organic solvent.

$$HLB = A\log P + MSA^{\frac{1}{D+P}} \cdot \frac{HySA}{SA} + SF_{f(ST)} \quad (3)$$

where: *AlogP* is the Ghose-Crippen octanol-water partition coefficient, calculated using Dragon program [18,25]; *MSA* is the Molecular Surface Area, calculated using the ArgusLab program [26]; *D* is the energy of dispersion forces between molecules; *P* is the energy of dipolar intermolecular forces between molecules; *HySA* represents the hydrophobic surface area; *SA* is the surface area; $SF_{f(ST)}$ is a statistical factor which depends on the surface tension *ST* according to equation (4).

$$SF = INT\left[\left(\frac{ST}{23}\right) - 1\right] \quad (4)$$

where INT denotes the nearest integer; *D*, *P* parameters are part of the 3-D Hansen solubility parameter [27] are calculated using Molecular Modeling Pro program (trial version) [28], *HySA* or *SA* parameters are calculated using the same program and *ST* is surface tension, calculated using ACD/ChemSketch Freeware program [29]. Table 1 shows the structural parameters that enter into the relationship for HLB calculation (Eq. 3).

Table 1. Values of parameters involved in Equation (3) for compounds 1a–1h

Comp	*A*logP	*MSA*	*D*	*P*	*HySA*	*SA*	*ST*	*SF*	HLB
1a	2.676	538.4	21.72	6.029	10.40	39.01	53	1	4.010
1b	2.676	574.5	20.45	4.482	11.25	38.52	53	1	4.053
1c	4.560	586.4	20.60	5.227	15.47	44.08	44.7	0	5.009
1d	4.560	629.9	19.49	3.882	16.33	43.98	44.7	0	5.049
1e	2.433	536.9	21.12	6.342	8.391	41.92	83.4	2	4.685
1f	2.433	588.9	19.92	5.093	9.229	40.87	83.4	2	4.724
1g	1.884	590.8	21.02	6.263	8.387	43.12	62.6	1	3.130
1h	1.884	598.1	19.83	5.021	9.226	43.15	62.6	1	3.161

The HLB values obtained using Eq. (3) were used for calculating the molecular hydrophobicity (R_{M0}) of isomeric pairs for *bis*-dinitrophenyl-Kryptofix-22 derivatives (**1a–1h**), obtaining a correlation coefficient $R^2 = 0.977$ (Eq. 5).

$$R_{M0} = 1.379(\pm 0.085)\text{HLB} - 3.615 \quad (5)$$

$$N = 8, \quad R^2 = 0.977, \quad SD = 0.173, \quad F = 263.1, \quad R^2(CV) = 0.922$$

The experimental and calculated values R_{M0} for isomeric compounds **1a–1h**, are presented in Table 2.

Table 2. Experimental and calculated R_{M0} (Equation 5) and calculated HLB (Equation 3) values for isomeric pairs of compounds 1a–1h

Comp.	HLB Eq. 3	R_{M0} (exp.)[5,7]	R_{M0} (calcd.) Eq. 5	Residual
1a	3.997	1.819	1.915	–0.096
1b	4.039	1.987	1.974	0.013
1c	4.998	3.134	3.292	–0.158
1d	5.030	3.246	3.348	–0.102
1e	4.674	2.897	2.846	0.051
1f	4.707	3.201	2.899	0.302
1g	3.123	0.551	0.701	–0.150
1h	3.148	0.884	0.744	0.140

Fig. 2 shows a good correlation between R_{M0} (exp.) [5,7] and R_{M0} values calculated by Eq. (5), validating the possibility of direct assessment this parameters using the HLB parameters calculated by Eq. (3).

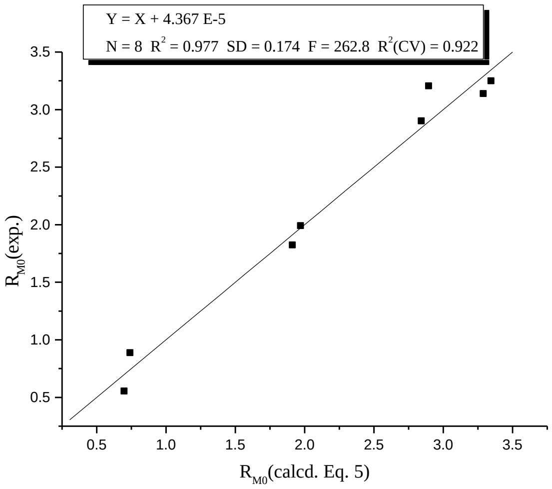


Fig. 2. Experimental (R_{M0}) vs. estimated R_{M0}, Equation 5, values for isomeric compounds 1a–1h.

The results presented in Table 2 show that the *ortho,ortho'*-dinitrophenyl isomers are more hydrophobic than the *ortho,para*-dinitrophenyl isomers; the reason can be found in structural parameters (Eq. 3).

3.2. Alcohols, amines and ethers

It is known that the hydrophobic/hydrophilic property of alcohols, amines and ethers has a significant theoretical and practical importance. In these compounds the experimental or calculated *logP* parameter is normally used for evaluating hydrophobic / hydrophilic properties.

Based on these considerations we have tried to prove the validity of Eq. (3) for three classes of compounds: alcohols, amines and ethers. The results of calculations were checked by using experimental *logP* parameters for which literature data were found [30-34].

3.2.1. Alcohols

In Table 3 are presented the results of calculations involving Eq. (3) for 50 alcohols; in the same table the experimental *logP* values [30-34] found in literature are mentioned.

$$\mathrm{logP} = 0.704(\pm 0.042)\mathrm{HLB} - 0.358 \qquad (6)$$

$N = 50$, $R^2 = 0.855$, $SD = 0.279$, $F = 282.6$, $R^2(CV) = 0.811$

Table 3. Parameters involved in Eq. (3) for alcohols and experimental logP values

Compound	*A*logP	*MSA*	*D*	*P*	*HySA*	*SA*	*ST*	*SF*	HLB	*logP* (exp.)
methanol	–0.358	50.61	15.11	12.28	2.228	3.615	18.8	–1	–0.647	–0.66
ethanol	–0.009	67.72	15.76	8.803	3.573	4.961	22.3	–1	–0.154	–0.32
2,2,2-trifluoroethanol	0.649	83.68	14.76	6.959	3.265	6.074	16.5	–1	0.308	0.37
n-propanol	0.515	86.76	15.87	6.871	3.482	6.314	24.5	0	1.186	0.34
2-propanol	0.368	85.64	15.76	6.120	4.919	6.308	22.6	–1	0.324	0.14
n-butanol	0.971	106.8	16.14	5.653	4.835	7.667	26	0	1.752	0.88
2-butanol	0.892	102.7	15.78	5.706	6.273	7.663	24.3	0	1.908	0.61
2-methyl–1-propanol	0.834	102.4	15.68	5.741	5.338	7.671	24.3	0	1.698	0.61
2-methyl-2-propanol	0.573	102.6	15.35	5.597	6.394	7.784	23.6	0	1.598	0.37
n-pentanol	1.427	125.6	16.03	4.495	6.188	9.021	27.1	0	2.295	1.40
2-pentanol	1.348	122.1	16.22	4.911	7.627	9.016	25.6	0	2.410	1.14
3-pentanol	1.416	122.7	15.88	4.807	7.155	9.017	25.6	0	2.417	1.14
2-methyl–1-butanol	1.223	123.8	15.65	4.554	6.193	9.024	25.6	0	2.094	1.14
3-methyl–1-butanol	1.290	120.8	15.51	4.512	6.192	9.026	25.6	0	2.162	1.14
2-methyl-2-butanol	1.097	118.1	15.51	4.729	7.747	9.138	25	0	2.170	0.89
3-methyl-2-butanol	1.211	121.9	15.64	4.916	7.633	9.022	24.2	0	2.280	0.91
2,2-dimethyl–1-propanol	1.108	118.1	15.15	4.438	6.910	9.242	25	0	2.062	1.36
1-penten-3-ol	1.160	118.9	16.24	5.344	6.475	8.517	27.3	0	2.109	0.81
3-penten-2-ol	1.039	118.2	15.42	5.276	7.109	8.498	26.3	0	2.093	0.81
4-penten–1-ol	1.036	121.8	16.52	5.279	5.684	8.516	27.2	0	1.868	1.04

Compound	*A*logP	*MSA*	*D*	*P*	*HySA*	*SA*	*ST*	*SF*	HLB	*logP* (exp.)
n-hexanol	1.883	146.9	16.21	3.914	7.542	10.37	27.9	0	2.815	1.84
2-hexanol	1.804	140.1	15.83	6.156	8.980	10.36	26.6	0	2.888	1.61
3-hexanol	1.872	141.3	15.55	6.047	8.509	10.37	26.6	0	2.904	1.61
cyclohexanol	1.500	108.3	17.50	4.042	6.755	8.804	32.4	0	2.454	2.37
2-methyl-2-pentanol	1.553	136.5	15.24	5.963	9.101	10.49	26	0	2.647	1.39
3-methyl-2-pentanol	1.668	134.5	15.07	6.051	8.989	10.38	25.3	0	2.760	1.41
4-methyl-2-pentanol	1.600	136.6	15.34	6.161	8.986	10.38	25.3	0	2.689	1.41
2-methyl-3-pentanol	1.735	138.8	15.07	6.051	8.516	10.38	25.3	0	2.772	1.41
3-methyl-3-pentanol	1.621	136.8	14.98	5.861	9.103	10.50	26	0	2.719	1.39
3,3-dimethyl–1-butanol	1.429	139.8	15.43	3.871	7.761	10.59	26	0	2.375	1.86
2,3-dimethyl-2-butanol	1.416	135.4	14.77	5.968	9.110	10.49	24.7	0	2.515	1,17
1-hexene-3-ol	1.616	137.8	16.59	4.654	7.829	9.871	26.6	0	2.616	1.31
2-hexene-4-ol	1.562	138.1	15.56	4.513	7.812	9.854	27.3	0	2.575	1.31
2-methyl-4-penten-3-ol	1.479	134.4	16.05	4.658	8.013	9.874	25.3	0	2.507	1.11
n-heptanol	2.339	161.9	17.68	3.596	8.896	11.73	28.5	0	3.302	2.34
2-methyl-2-hexanol	2.009	156.7	15.62	5.353	10.46	11.85	26.8	0	3.132	1.87
3-methyl-3-hexanol	2.077	154.1	15.38	5.271	10.46	11.85	26.8	0	3.204	1.87
2,3-dimethyl-2-pentanol	1.873	155.1	14.96	5.274	10.47	11.86	25.7	0	3.006	1.67
2,4-dimethyl-2-pentanol	1.805	149.4	15.19	5.357	10.46	11.85	25.7	0	2.931	1.67
2,2-dimethyl-3-pentanol	2.009	153.1	14.96	5.274	10.08	11.95	25.7	0	3.092	1.69
2,3-dimethyl-3-pentanol	1.940	150.8	14.96	5.274	10.46	11.85	25.7	0	3.071	1.67
2,4-dimethyl-3-pentanol	2.054	152.1	15.03	5.428	9.881	11.74	25.1	0	3.130	1.71
3-ethyl-3-pentanol	2.144	148.6	15.14	5.189	10.46	11.85	26.8	0	3.273	1.87
benzyl alcohol	1.226	135.9	18.40	6.293	5.053	8.142	40.7	0	1.983	1.10
n-octanol	2.796	185.8	17.65	3.231	10.25	13.08	29	0	3.802	2.84
2-phenylethanol	1.547	155.2	19.42	4.254	6.659	9.491	39.6	0	2.415	1.36
2,2,3-trimethyl-3-pentanol	2.214	168.9	14.87	4.673	12.03	13.42	26	0	3.379	1.99
n-nonanol	3.503	204.9	17.63	2.933	11.61	14.43	29.5	0	4.544	3.15
2-phenyl–1-propanol	1.866	175.2	18.94	3.784	8.018	10.85	37.4	0	2.794	1.88
diphenylcarbinol	2.838	209.5	20.87	4.948	10.11	12.68	45.3	0	3.818	2.67

The satisfactory correlation of HLB calculated values using Eq. (3) allows the estimation of *logP* values (Eq. 6) for the 50 alcohols involved in this study (Table 4). Figure 3 shows the correlation between *logP* (exp.) [30-34] and *logP* values calculated by Eq. (6), validating the possibility of direct assessment this parameters using the HLB parameters calculated by Eq. (3).

Table 4. Experimental and calculated logP (Equation 6) and calculated HLB (Equation 3) values for 50 alcohols

Compound	*HLB*	*logP* (exp.)	*logP* (calcd.)	Resid.
methanol	–0.647	–0.66	–0.813	0.153
ethanol	–0.154	–0.32	–0.466	0.146
2,2,2-trifluoroethanol	0.308	0.37	–0.141	0.511
n-propanol	1.186	0.34	0.477	–0.137
2-propanol	0.324	0.14	–0.13	0.270
n-butanol	1.752	0.88	0.875	0.005
2-butanol	1.908	0.61	0.985	–0.375

Compound	*HLB*	*logP* (exp.)	*logP* (calcd.)	Resid.
2-methyl–1-propanol	1.698	0.61	0.837	–0.227
2-methyl-2-propanol	1.598	0.37	0.767	–0.397
n-pentanol	2.295	1.40	1.258	0.142
2-pentanol	2.410	1.14	1.339	–0.199
3-pentanol	2.417	1.14	1.344	–0.204
2-methyl–1-butanol	2.094	1.14	1.116	0.024
3-methyl–1-butanol	2.162	1.14	1.164	–0.024
2-methyl-2-butanol	2.170	0.89	1.170	–0.280
3-methyl-2-butanol	2.280	0.91	1.247	–0.337
2,2-dimethyl–1-propanol	2.062	1.36	1.094	0.266
1-penten-3-ol	2.109	0.81	1.127	–0.317
3-penten-2-ol	2.093	0.81	1.115	–0.305
4-penten–1-ol	1.868	1.04	0.957	0.083
n-hexanol	2.815	1.84	1.624	0.216
2-hexanol	2.888	1.61	1.675	–0.065
3-hexanol	2.904	1.61	1.686	–0.076
cyclohexanol	2.454	2.37	1.370	1.000
2-methyl-2-pentanol	2.647	1.39	1.505	–0.115
3-methyl-2-pentanol	2.760	1.41	1.585	–0.175
4-methyl-2-pentanol	2.689	1.41	1.535	–0.125
2-methyl-3-pentanol	2.772	1.41	1.593	–0.183
3-methyl-3-pentanol	2.719	1.39	1.556	–0.166
3,3-dimethyl–1-butanol	2.375	1.86	1.314	0.546
2,3-dimethyl-2-butanol	2.515	1.17	1.413	–0.243
1-hexene-3-ol	2.616	1.31	1.484	–0.174
2-hexene-4-ol	2.575	1.31	1.455	–0.145
2-methyl-4-penten-3-ol	2.507	1.11	1.407	–0.297
n-heptanol	3.302	2.34	1.967	0.373
2-methyl-2-hexanol	3.132	1.87	1.847	0.023
3-methyl-3-hexanol	3.204	1.87	1.898	–0.028
2,3-dimethyl-2-pentanol	3.006	1.67	1.758	–0.088
2,4-dimethyl-2-pentanol	2.931	1.67	1.705	–0.035
2,2-dimethyl-3-pentanol	3.092	1.69	1.819	–0.129
2,3-dimethyl-3-pentanol	3.071	1.67	1.804	–0.134
2,4-dimethyl-3-pentanol	3.130	1.71	1.846	–0.136
3-ethyl-3-pentanol	3.273	1.87	1.946	–0.076
benzyl alcohol	1.983	1.10	1.038	0.062
n-octanol	3.802	2.84	2.319	0.521
2-phenylethanol	2.415	1.36	1.342	0.018
2,2,3-trimethyl-3-pentanol	3.379	1.99	2.021	–0.031
n-nonanol	4.544	3.15	2.841	0.309
2-phenyl–1-propanol	2.794	1.88	1.609	0.271
diphenylcarbinol	3.818	2.67	2.330	0.340

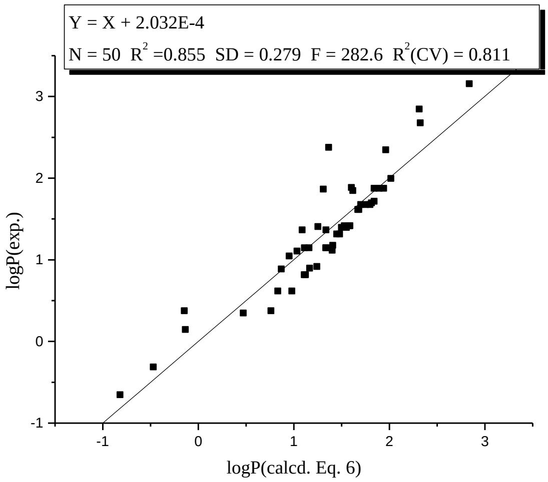


Fig. 3. logP (calculated, Equation 6) vs logP (exp.) for 50 alcohols (Table 3)

3.2.2. Amines

The same Eq. (3) was applied for 37 amines with available experimental logP values.

$$\log P = 0.696(\pm 0.034)\mathrm{HLB} + 0.113 \qquad (7)$$

$$N = 37, \quad R^2 = 0.922, \quad SD = 0.333, \quad F = 413.5, \quad R^2(CV) = 0.875$$

The results of these calculations are presented in Table 5, which according to Fig. 4 validates the accuracy of ($R^2 = 0.922$) estimates.

Table 5. Values of parameters involved in Equation (3) for amines and for logP experimental [30-34]

Compound	*A*logP	*MSA*	*D*	*P*	*HySA*	*SA*	*ST*	*SF*	HLB	*logP* (exp.)
methylamine	–0.648	53.60	16.60	8.055	0	3.912	18.4	–1	–1.648	–0.58
ethylamine	–0.299	72.40	16.55	6.021	2.133	5.264	21.6	–1	–0.809	–0.13
dimethylamine	–0.216	73.68	14.10	3.416	0	5.319	15.5	–1	–1.216	–0.38
propylamine	0.225	90.84	16.98	4.940	3.083	6.617	23.8	0	0.797	0.48
iso-propylamine	0.079	89.08	16.22	4.946	4.268	6.617	22	–1	–0.124	0.26
cyclopropylamine	–0.158	77.88	18.10	5.911	1.892	5.108	37	0	0.286	0.07
trimethylamine	0.320	89.01	13.99	8.743	6.647	6.721	18.6	–1	0.525	0.27
ethylmethylamine	0.133	91.08	14.56	2.733	2.133	6.672	18.2	–1	–0.452	0.15
butylamine	0.681	111.0	16.17	4.495	4.434	7.969	25.3	0	1.380	0.75
iso-butylamine	0.544	106.1	15.75	4.559	4.841	7.973	23.7	0	1.308	0.73
sec-butylamine	0.602	103.8	15.39	4.454	5.216	7.971	23.7	0	1.429	0.74
tert-butylamine	0.284	102.5	15.00	4.376	6.403	8.100	23	0	1.288	0.40
diethylamine	0.482	112.5	14.86	2.277	4.268	8.026	20.2	–1	0.182	0.57
pentylamine	1.137	130.2	16.35	3.863	5.787	9.323	26.4	0	1.927	1.49
methyl-n-butylamine	1.113	131.5	15.01	1.611	4.840	9.379	21.7	–1	0.805	1.33
ethyl-iso-propylamine	0.859	127.1	14.37	1.599	6.403	9.381	20.6	–1	0.783	0.93
piperidine	0.701	108.0	20.34	2.049	3.248	7.811	26.7	0	1.214	0.85
hexylamine	1.594	151.2	16.48	3.387	7.141	10.67	27.2	0	2.455	2.06
cyclohexylamine	1.211	110.4	17.41	3.125	5.954	9.113	31.4	0	2.033	1.49
dimethyl-n-butylamine	1.649	147.0	15.21	5.722	9.761	10.79	23.4	0	2.798	1.70
aniline	1.083	124.0	19.43	5.157	3.484	7.048	41.7	0	1.684	0.91
2-floroaniline	1.289	130.2	16.49	10.17	4.159	7.499	39.3	0	1.955	1.26
dipropylamine	1.529	150.9	15.33	1.424	6.973	10.73	23	0	2.406	1.67
heptylamine	2.050	169.0	16.58	3.015	8.493	12.03	27.9	0	2.967	2.57
n-propyl-n-butylamine	1.985	169.7	15.55	1.274	8.326	12.09	24	0	2.920	2.12
n-propyl-sec-butylamine	1.907	159.5	15.04	1.266	9.110	12.09	23	0	2.936	1.91
benzylamine	0.936	140.8	19.86	4.237	5.052	8.439	38.8	0	1.671	1.09

Compound	*A*logP	*MSA*	*D*	*P*	*HySA*	*SA*	*ST*	*SF*	HLB	*logP* (exp.)
N-methylaniline	1.639	145.0	18.9	2.286	4.898	8.467	35.6	0	2.371	1.71
N-ethylpiperidine	1.586	148.2	16.85	6.051	7.622	10.57	26.7	0	2.483	1.88
o-methylaniline	1.570	141.4	18.92	4.395	5.329	8.441	39.5	0	2.351	1.32
m-methylaniline	1.570	144.9	18.92	4.395	4.862	8.438	39.5	0	2.283	1.40
p-methylaniline	1.370	145.5	18.92	4.395	4.865	8.438	39.5	0	2.084	1.39
dibutylamine	2.442	189.6	15.72	1.152	9.679	13.44	24.8	0	3.425	2.68
tripropylamine	2.938	194.6	15.83	4.259	10.46	14.86	25.9	0	3.854	2.79
N,N-dimethylbenzylamine	1.904	174.0	17.93	5.451	9.484	11.25	32.7	0	2.955	1.98
diphenylamine	3.380	215.0	20.58	1.481	6.956	11.51	44	0	4.151	3.44
triphenylamine	5.163	292.0	21.47	3.849	10.43	16.34	47.2	1	6.962	5.74

Table 6. Experimental and calculated logP (Equation 7) and calculated HLB values (Equation 3) for amines

Compound	*HLB*	*logP* (exp.)	*logP* (calcd.)	Resid.
methylamine	–1.648	–0.58	–1.034	0.454
ethylamine	–0.809	–0.13	–0.450	0.320
dimethylamine	–1.216	–0.38	–0.733	0.353
propylamine	0.797	0.48	0.668	–0.188
iso-propylamine	–0.124	0.26	0.027	0.233
cyclopropylamine	0.286	0.07	0.312	–0.242
trimethylamine	0.525	0.27	0.478	–0.208
ethylmethylamine	–0.452	0.15	–0.202	0.352
butylamine	1.380	0.75	1.073	–0.323
iso-butylamine	1.308	0.73	1.023	–0.293
sec-butylamine	1.429	0.74	1.108	–0.368
tert-butylamine	1.288	0.40	1.009	–0.609
diethylamine	0.182	0.57	0.240	0.330
pentylamine	1.927	1.49	1.454	0.036
methyl-n-butylamine	0.805	1.33	0.673	0.657
ethyl-iso-propylamine	0.783	0.93	0.658	0.272
piperidine	1.214	0.85	0.958	–0.108
hexylamine	2.455	2.06	1.822	0.238
cyclohexylamine	2.033	1.49	1.528	–0.038
dimethyl-n-butylamine	2.798	1.70	2.060	–0.360
aniline	1.684	0.91	1.285	–0.375
2-floroaniline	1.955	1.26	1.474	–0.214
dipropylamine	2.406	1.67	1.788	–0.118
heptylamine	2.967	2.57	2.178	0.392
n-propyl-n-butylamine	2.920	2.12	2.145	–0.025
n-propyl-sec-butylamine	2.936	1.91	2.156	–0.246
benzylamine	1.671	1.09	1.276	–0.186
N-methylaniline	2.371	1.71	1.763	–0.053
N-ethylpiperidine	2.483	1.88	1.841	0.039
o-methylaniline	2.351	1.32	1.749	–0.429

Compound	*HLB*	*logP* (exp.)	*logP* (calcd.)	Resid.
m-methylaniline	2.283	1.40	1.702	–0.302
p-methylaniline	2.084	1.39	1.563	–0.173
dibutylamine	3.425	2.68	2.497	0.183
tripropylamine	3.854	2.79	2.795	–0.005
N,N-dimethylbenzylamine	2.955	1.98	2.170	–0.190
diphenylamine	4.151	3.44	3.002	0.438
triphenylamine	6.962	5.74	4.959	0.781

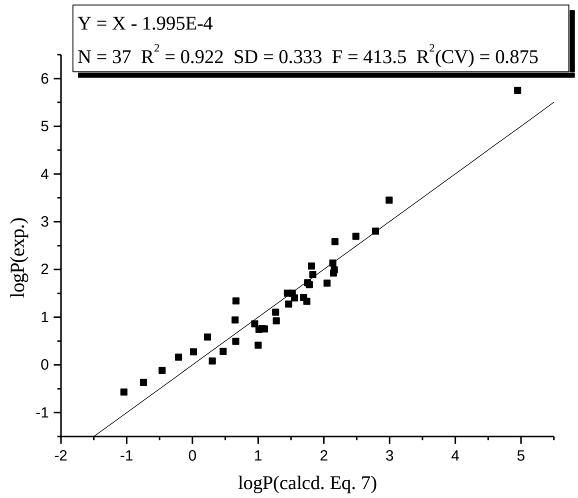


Fig. 4. logP (calculated, Equation 7) vs logP (exp.) for 37 amines (Table 5)

3.2.3. Ethers

Applying the same Eq. (3) the calculations strategy has been extended in the case of 15 ethers.

$$\log P = 0.824(\pm 0.079)HLB + 0.233 \qquad (8)$$

$$N = 15, \quad R^2 = 0.901, \quad SD = 0.231,$$
$$F = 108.4, \quad R^2(CV) = 0.871$$

The results of these calculations are presented in Table 7, which according to Fig. 5 validates the accuracy of ($R^2 = 0.901$) estimates.

Table 7. Values of parameters involved in Equation (3) for ethers and for logP experimental [30-34]

Compound	*A*logP	*MSA*	*D*	*P*	*HySA*	*SA*	*ST*	*SF*	HLB	*logP* (exp.)
dimethyl ether	0.051	71.01	13.62	4.353	4.449	5.036	14	–1	0.171	0.10
methyl n-propyl ether	0.923	107.9	14.85	3.001	6.203	7.737	19	–1	0.965	1.03
methyl iso-propyl ether	0.777	103.8	14.24	3.004	7.144	7.733	17.8	–1	0.986	0.73
methyl cyclopropyl ether	0.540	94.40	15.64	3.841	5.165	6.221	22.5	–1	0.589	1.24
diethyl ether	0.748	108.8	14.52	2.935	7.142	7.732	19	–1	0.956	1.03
ethyl n-propyl ether	1.272	127.1	15.07	2.572	7.551	9.085	20.7	–1	1.366	1.53
ethyl iso-propyl ether	1.126	126.0	14.55	2.575	8.492	9.082	19.6	–1	1.366	1.33
methyl butyl ether	1.379	127.1	15.19	2.594	7.557	9.091	20.7	–1	1.471	1.53
methyl iso-butyl ether	1.242	123.8	14.83	2.624	7.561	9.093	19.6	–1	1.338	1.33
methyl sec-butyl ether	1.301	120.5	14.55	2.574	8.499	9.088	19.6	–1	1.538	1.33
methyl tert-butyl ether	0.982	122.4	14.24	2.536	8.621	9.211	19.1	–1	1.229	1.06
dipropyl ether	1.796	146.9	15.49	2.289	7.958	10.44	22.1	–1	1.805	2.03
diisopropyl ether	1.503	140.1	14.57	2.293	9.839	10.43	20.1	–1	1.768	1.52
n-propyl iso-propyl ether	1.649	143.9	15.03	2.291	8.901	10.43	21.1	–1	1.786	1.83
dibutyl ether	2.708	186.6	15.86	1.847	9.673	13.14	24.1	0	3.697	3.21

As for alcohols and amines, on the basis of Eq. (8), logP values were calculated for ethers, finding that the results validated the assumption (Table 7, Fig. 5).

Table 8. Experimental and calculated logP (Eq. 8) and calculated HLB (Eq. 3) values for isomeric ethers

Compound	HLB	*logP* (exp.)	*logP* (calcd.)	Resid.
dimethyl ether	0.171	0.10	0.374	–0.274
methyl n-propyl ether	0.965	1.03	1.028	0.002
methyl iso-propyl ether	0.986	0.73	1.045	–0.315
methyl cyclopropyl ether	0.589	1.24	0.718	0.522
diethyl ether	0.956	1.03	1.021	0.009
ethyl n-propyl ether	1.366	1.53	1.359	0.171
ethyl iso-propyl ether	1.366	1.33	1.359	–0.029
methyl butyl ether	1.471	1.53	1.445	0.085
methyl iso-butyl ether	1.338	1.33	1.336	–0.006
methyl sec-butyl ether	1.538	1.33	1.500	–0.170
methyl tert-butyl ether	1.229	1.06	1.246	–0.186
dipropyl ether	1.805	2.03	1.720	0.310
diisopropyl ether	1.768	1.52	1.690	–0.170
n-propyl iso-propyl ether	1.786	1.83	1.705	0.125
dibutyl ether	3.697	3.21	3.279	–0.069

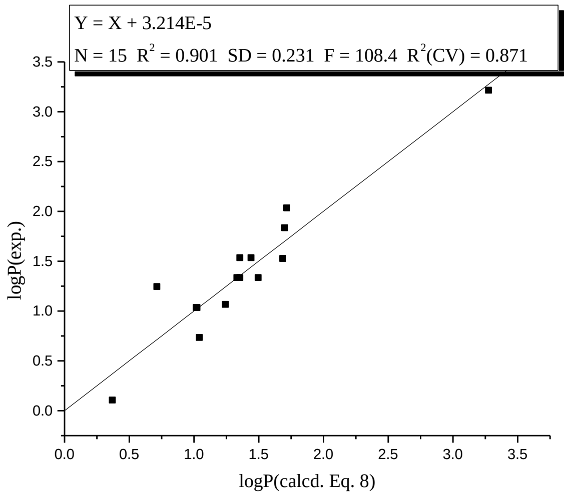


Fig. 5. logP (calculated, Equation 8) vs logP (exp.) for 15 ethers (Table 7)

4. Conclusions

The experimental values of the molecular hydrophobicity (R_{M0}) determined by RP-TLC for eight *bis*-dinitrophenyl-Kryptofix-22 derivatives (four isomeric pairs, (**1a, 1b**; **1c, 1d**; **1e, 1f**; and **1g, 1h**) were correlated with the hydrophilic-lipophilic balance (HLB) values calculated by a new method involving physico-chemical characteristics that influence this parameter. Through this strategy we obtained satisfactorey statistical parameters (R^2 > 0.95). This strategy applied to HLB calculation showed that an experimental parameter characterizing the hydrophobicity/lipophilicity (e.g. R_{M0}) can be successfully involved if calculations take into account structural features that can influence the HLB value, so that they can predict values for functional analogs in a series.

The same strategy involving HLB calculated values has been applied with good results for 50 alcohols, 37 amines and 15 ethers, and the results were checked by correlations with the experimental *logP* parameters.

This theoretical study proves that the approach of hidrophobicity/hydrophilic characteristics calculated through HLB values can lead to practical considerations involving these properties of chemical compounds.

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