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Article

QSPR Modeling using Catalan Solvent and Solute Parameters

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A área de correlação quantitativa entre estrutura e propriedade (QSPR) pode beneficiar-se de descritores moleculares que representam interações intermoleculares. Catalan desenvolveu um método de escalas solvatocrômicas para solventes que pode ser explorado para esta finalidade. Neste trabalho, escalas de solvente de Catalan foram usadas como descritores moleculares para o desenvolvimento de modelos QSPR, e para o cálculo de novos descritores de soluto para uso posterior em QSPR. As escalas Catalan para o solvente e os descritores de soluto derivados foram recentemente comparados com o método de descritores de Abraham, em termos da qualidade do QSPR desenvolvido. Os parâmetros Catalan para solventes, que mostraram uma correlação modesta com os correspondentes descritores de Abraham, mostraram-se bem sucedidos para modelar temperatura de fusão, temperatura de ebulição, ponto de ignição, índice de refração, tensão superficial, densidade e parâmetro de solubilidade dos solventes, com médias geométricas dos desvios relativos (GMRD) de 7,1, 6,6, 4,9, 3,8, 9,1, 6,0 e 4,2%, respectivamente. Os descritores do soluto foram obtidos a partir das equações de regressão entre a solubilidade de um soluto em diferentes solventes com um GMRD total de 30,0%. Os descritores de soluto obtidos desta maneira superam o modelo de solvatação geral de Abraham no cálculo de solubilidade em meio aquoso de 27 solutos de várias famílias químicas. Os descritores Catalan podem ser considerados como um recurso valioso para modelagem QSPR.

The field of quantitative structure-property relationship (QSPR) can greatly benefit from molecular descriptors that particularly represent the intermolecular interactions. Catalan has developed a set of solvatochromic scales for solvents, which could be exploited for this purpose. In this work, Catalan solvent scales were explored as molecular descriptors for the development of QSPR models, and for the calculation of new solute descriptors for further use in QSPR. Catalan solvent scales and the newly derived solute descriptors were compared with the commonly used set of Abraham descriptors in terms of the quality of the developed QSPRs. Catalan solvent parameters, which showed modest correlation with the corresponding Abraham descriptors, proved to be successful in modeling melting point, boiling point, flash point, refractive index, surface tension, density, and solubility parameter of the solvents with geometric mean relative deviations (GMRD) of 7.1, 6.6, 4.9, 3.8, 9.1, 6.0, and 4.2%, respectively. The solute descriptors were obtained from regression equations between a solute's solubility in different solvents with an overall GMRD of 30.0%. The solute descriptors obtained in this way outperformed Abraham general solvation model in the calculation of aqueous solubility for 27 solutes of broad chemical ranges. It was concluded that Catalan descriptors can be regarded as a valuable resource for QSPR modeling.

Keywords: Catalan, solvatochromic, solubility, modeling, QSPR

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Introduction

Solubility of a compound in different solvents such as water and 1-octanol can be used in quantitative structure-property relationships (QSPRs) as a measure of its property in phases similar to those solvents.[1] Solubility not only can be used directly as a molecular descriptor, but also other parameters can be derived from solubility and employed as molecular descriptors of QSPR. Examples of such solubility-related parameters include thermodynamic solubility parameter of Hildebrand,[1] and solvatochromic parameters.[2-8] A set of solvatochromic parameters was originally derived from spectroscopic methods of investigating the intermolecular interactions by Kamlet, Taft, and Abraham in 1970-1980.[2-5] The parameters included solvent polarity/polarizability scale, solvent basicity scale, and solvent acidity scale, which were then used in QSPR models to estimate properties and activities of solvents or solutes in the solutions.[2-5] The parameter set was later extended to the corresponding solute descriptors of hydrogen-bonding acidity (A) and basicity (B) scales, and polarity/polarizability (S) scale.[9,10] In addition to these parameters, the general solvation equation proposed by Abraham and co-workers[9,10] (equation 1) also includes excess molar refraction (E) and the one percent of McGowan molar volume (V).

$$PCP = c + eE + sS + aA + bB + vV \quad (1)$$

In equation 1, PCP is a property under study; c, e, s, a, b, and v are the coefficients of the model determined by multiple linear regression analysis. Abraham parameters have found many applications in chemistry and pharmacy-related fields, for example estimations of solubility,[6] partitioning,[11] chromatographic retention parameters,[12] toxicity,[13,14] and intestinal absorption.[15] Due to the experimental nature of A, B, and S parameters, several methods have been suggested for their determination from the experimental data.[16-18] Moreover, a method has been suggested for the back calculation of solute Abraham parameters recently, which employs the calculated E and V parameters along with the experimental solubility of solutes in several organic solvents and the previously determined solvent coefficients of equation 1 (c, e, s, a, b, and v) for partitioning in a large number of water/solvent systems, followed by fitting the appropriate values of S, A and B.[19]

Catalan has expanded another set of solvatochromic parameters for a generalized treatment of the effects of solvents.[7] Catalan parameters consist of solvent polarity/polarizability scale (SPP), solvent basicity scale (SB defined as cb in this work), and solvent acidity scale (SA defined as ca in this work),[8,20-23] which recently SPP parameter split into two separate scales: solvent dipolarity (SdP defined as cd in this work) and solvent polarizability (SP defined as cp in this work).[7] The approach for measuring these parameters is similar to those of Kamlet and Taft,[2,3] where a probe with specific interactions with solvent has been used and variances in spectroscopy data have been recorded and applied for the definition of the solvent scales.[2-4,8,20-23] In formulating the independent solvent scales, the choice of an appropriate probe for the experimental determination of the scales is the major challenge. The selected probe should measure the effect of a single solvent property, for example, hydrogen-bonding basicity, without the interference of any other solvent effects. Solvatochromic scales of Catalan have employed different probes to those used for the development of Kamlet and Taft's scales.

This investigation explored the suitability of Catalan solvent parameters for use in QSPR field and the possibility of drawing new solute parameters from original Catalan scale. Therefore, Abraham and Catalan solvent parameters were first compared by investigating the relationships between the two sets of parameters. Secondly, Catalan solvent parameters were used for the development of QSPR models for several solvent properties and the validity of the resulting QSPRs was investigated. The solvent properties included melting point, boiling point, flash point, refractive index, surface tension, viscosity, density, and solubility parameter. In the next step, Catalan solute parameters were derived based on the correlations between a solute solubility in several nonaqueous solvents and Catalan solvent scales for those solvents. Finally, the applicability of these newly defined solute parameters for the prediction of the molar aqueous solubility of some compounds was investigated and the resulting QSPR was compared with the QSPR models developed using Abraham parameters.

Experimental

Materials and methods

Solvent properties, Abraham and Catalan parameters were collected from the literature, as detailed below, and multiple linear regression analysis was used to investigate the relationships and to develop the QSPR models using Catalan and Abraham parameters (for more details see Table S1 of electronic supplementary information).

Inter-relationship between Catalan and Abraham solvent parameters: Catalan solvent parameters were obtained from a recent publication.[7] Abraham solvent parameters were collected from the literature.[24-42] Regression

analyses were performed to find the relationships between the corresponding polarity/polarizability, hydrogen-bonding basicity, and hydrogen-bonding acidity scales of Abraham and Catalan.

Development of QSPR models using Catalan solvent parameters: Melting point, boiling point, flash point, refractive index, surface tension, viscosity, density, and solubility parameter of 54 common solvents with known Catalan solvent parameters were obtained from the literature.[43] Catalan descriptors were used to develop regression models for the above-mentioned physicochemical properties.

Determination of Catalan solute descriptors: Mole fraction solubility of a large set of compounds in several nonaqueous solvents was obtained from Handbook of Solubility Data for Pharmaceuticals.[44] The inclusion criteria for the collected nonaqueous solubility data in this study were:

(*i*) Only the solubility values measured at room temperature (25 ± 1 °C) were included.

(*ii*) Only solubility values reported in mole fraction, mole *per* liter or those that were convertible to one of these units were used.

(*iii*) For inclusion in the analysis, solubility of a solute had to be available in a minimum of eleven nonaqueous solvents.

For each solute, the logarithm of solubility in different solvents was regressed against Catalan parameters of the solvents and the regression equations were collected as below.

$$\log X = i_{Solute} + CP\ cp + CD\ cd + CA\ cb + CB\ ca \quad (2)$$

In equation 2, logX is the solubility of a solute in different solvents in mole fraction unit, cp, cd, cb, and ca are Catalan polarizability, dipolarity, hydrogen-bonding basicity, and acidity scales for the solvents, i_{Solute} is the intercept, CP, DP, CA, and CB are coefficients of the regression equation. The coefficients of the regression equations for each solute were recorded to be used as the solute polarizability, dipolarity, hydrogen-bonding acidity, and basicity scales.

Application of Catalan and Abraham solute parameters in QSPR model development for aqueous solubility

Solute descriptors were calculated using Catalan solvent parameters (as explained above) for 27 solutes for which aqueous solubility and Abraham solute descriptors[24-42] were available through recent publications. For these solutes, the new solute parameters were compared with Abraham solute descriptors in terms of: the accuracy of the original equation used for the estimation of solute parameters; and the accuracy of the models developed for the estimation of aqueous solubility of 27 solutes. For this purpose, the Catalan model was:

$$\log S_w = i_W + \alpha_P\ CP + \alpha_D\ CD + \alpha_A\ CB + \alpha_B\ CA + i_{Solute} \quad (3)$$

By rearranging the equation as below, it allows one to perform a regression analysis:

$$\log S_w - i_{Solute} = i_W + \alpha_P\ CP + \alpha_D\ CD + \alpha_A\ CB + \alpha_B\ CA \quad (4)$$

where i_W is the intercept of regression of aqueous solubility data against Catalan solute parameters computed from equation 2; α_P, α_D, α_B, and α_A are the regression coefficients, which correspond to the calculated Catalan solvent scales of polarizability, dipolarity, basicity, and acidity for water.

The comparable Abraham solvation model[27] reported in the literature for aqueous solubility is:

$$\log S_w = 0.395 - 0.955E + 0.320S + 1.155A + 3.255B - 0.785AB - 3.330V \quad (5)$$

Equations 4 and 5 were compared in terms of the accuracy of the calculation of aqueous solubility. In the analyses of this study, relative deviation (RD), mean relative deviation (MRD), geometric MRD (GMRD) and absolute error (AE) were used as error criteria and defined as:

$$RD = \frac{100 \times \left| PCP_{Exp} - PCP_{Cal} \right|}{PCP_{Exp}} \quad MRD = \frac{100}{n} \sum \frac{\left| PCP_{Exp} - PCP_{Cal} \right|}{PCP_{Exp}}$$
$$GMRD = 10\text{^}\frac{100}{n} \sum \log\left(\frac{\left| PCP_{Exp} - PCP_{Cal} \right|}{PCP_{Exp}} \right) \quad AE = \left| \log PCP_{Exp} - \log PCP_{Cal} \right| \quad (6)$$

where n is the number of data points in each analysis, PCP_{Exp} and PCP_{Cal} are the experimental and calculated PCP.

Results and Discussion

Table S2 of electronic supplementary information (SI) tabulates 41 solvents for which Catalan solvent parameters and Abraham solvent parameters were available from the literature. The correlation parameters between Catalan and Abraham solvent parameters for 41 solvents showed modest correlation coefficients (Table 1).

Based on definition of the Catalan, the CP, CD, CB, and CA are polarizability, dipolarity, basicity, and acidity of the solvents, respectively.[7,18-23] The Abraham solvent parameters

Table 1. Correlation of Abraham solvent parameters *vs.* Catalan solvent parameters for 41 solvents

	r^2	SE	F	p value
s-CP	0.093	0.605	3.992	< 0.05
s-CD	0.526	0.437	43.212	< 0.0005
a-CB	0.872	0.620	266.354	< 0.0005
b-CA	0.704	0.363	92.768	< 0.0005

s, a, and b are the interaction terms of the solvents with S, A, and B of the solute, respectively. As the S, A, and B are indicators of the solute's polarity, acidity, and basicity, hence the s, a, and b are indicators of solvent polarity, basicity, and acidity, respectively.[45] All investigated correlations reported in Table 1 were statistically significant ($p < 0.05$).

Melting point, boiling point, flash point, refractive index, surface tension, viscosity, density, and solubility parameter of 54 common solvents with the known Catalan solvent parameters are listed in Table S3 in SI. The QSPRs developed using Catalan solvent scales for these physicochemical properties are reported in Table 2. Careful examinations of these results reveal very good models fit for melting point, boiling point, flash point, refractive index, surface tension, density, and solubility parameter of the solvents. However, viscosity did not fit well into the Catalan model. Figure 1 shows correlation between experimental and calculated solubility parameters for the studied solvents.

Table 3 presents, for each solute, the equations derived for the solubility in several nonaqueous solvents. Reported data in Table 3 are the coefficients of multiple linear regression (r^2) equations between the compounds' solubility in nonaqueous solvents and Catalan solvent parameters (data fitted into equation 2) for 37 different compounds in which the solutes solubility was expressed as mole fractions. Included in Table 3 are also the coefficients of determinations of the regression equations, number of solvents used for each solute, AE and MRD values.

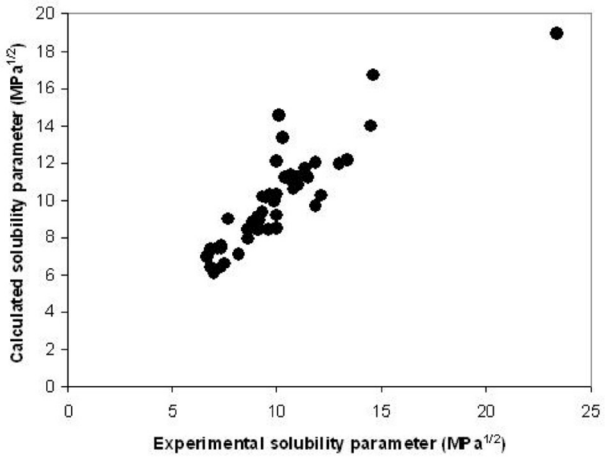

Figure 1. Correlation between experimental and calculated solubility parameters using Catalan solvent scales for the studied solvents.

We are proposing that the coefficients of these multiple regression equations are associated with the characteristics of the solutes and can be used as the corresponding solute parameters. It can be seen in Table 3 that the MRD values of the equations vary between 2.6% for methandienone solubility in 11 solvents and 776.9% for niflumic acid solubility in 23 solvents and the GMRD is 30.0%. Despite the low correlation coefficients of the models for some solutes such as niflumic acid, piroxicam and ibuprofen, the equations were statistically significant with p-values below 0.05 for the equation and p-values for the significant descriptors < 0.3. One explanation for the poor correlations observed for some solutes could be the dominant effect of crystal packing energy on the solubility of such solvents. These effects cannot be explained solely by simple parameters such as those used here, and are assumed to be related to the specific three-dimensional arrangements of molecules within the crystals. A similar pattern was observed for AE.

In assessing the resulted Catalan solute parameters, one must consider that: (*i*) the resulted acidic and basic scales

Table 2. Coefficients of PCP = α_1 cp + α_2 cd + α_3 ca + α_4 cb (Catalan model) for calculating some solvents' PCP

PCP	α_1	α_2	α_3	α_4	n	r^2	GMRD (%)
Melting point (K)	295.312	21.756	41.954	–37.478	53	0.972	7.1
Boiling point (K)	494.143	NS[a]	44.328	62.548	54	0.985	6.6
Flash point (K)	368.468	23.549	74.712	28.389	49	0.987	4.9
Refractive index	1.964	–0.182	0.215	0.118	54	0.995	3.8
Surface tension (dyn cm^{-1})	34.751	12.188	21.750	–12.534	53	0.938	9.1
Viscosity (cP)	NS[a]	NS[a]	3.300	11.230	53	0.238	89.2
Density (g cm^{-3})	1.273	0.196	NS[a]	–0.230	54	0.977	6.0
Solubility parameter ($MPa^{1/2}$)	10.350	2.725	8.665	NS[a]	48	0.984	4.2

[a]NS: Not significant.

are based on the behavior of solute in nonaqueous solvents. It means that an acid in water could act in a different way, *i.e.* as a neutral or basic compound, in the organic solvents; (*ii*) the coefficients of the Catalan solute parameters might indicate the effect of acidic or even basic functional groups of the compound on its solubility in organic solvents, therefore the numerical values of the coefficient could be a positive or negative sign.

In order to examine the suitability of the new Catalan solute parameters for QSPR modeling, the parameters were used for the estimation of aqueous solubility. Moreover, the model was compared with the model developed using Abraham solute parameters obtained using a similar back-calculation procedure,[24-42] and also Abraham aqueous solubility model reported in the literature.[27] Listed in Table 4 are molar aqueous solubility

Table 3. Catalan solute parameters for the studied solutes with mole fraction solubilities, coefficients of determination, mean relative deviation (MRD) and absolute error (AE) values

No.	Solute	CAS	n	i_{Solute}	CP	CD	CB	CA	r^2	MRD	AE
1	2-Hydroxybenzoic acid	69-72-7	33	–4.065	1.650	0.683	NS[a]	2.486	0.741	102.8	0.37
2	4-Aminobenzoic acid	150-13-0	28	–4.545	NS[a]	2.549	NS[a]	1.864	0.660	259.5	0.49
3	4-Hydroxybenzoic acid	99-96-7	26	–4.778	NS[a]	1.932	NS[a]	3.551	0.783	160.0	0.48
4	Acetylsalicylic acid	50-78-2	28	NS[a]	–3.196	0.872	NS[a]	0.342	0.934	75.6	0.26
5	Anthracene	120-12-7	30	–5.953	4.797	NS[a]	–3.025	0.623	0.842	32.0	0.13
6	Benzil	134-81-6	16	–6.351	6.535	1.080	–3.557	0.540	0.714	32.4	0.13
7	Benzoic acid	65-85-0	37	–2.992	1.747	0.625	NS[a]	0.935	0.750	55.8	0.21
8	Betulin	473-98-3	11	–8.031	5.681	1.267	–0.893	1.012	0.750	46.8	0.19
9	Diclofenac	15307-86-5	21	–3.532	NS[a]	1.594	–1.452	1.563	0.537	140.8	0.46
10	Diflunisal	22494-42-4	11	–8.609	5.757	1.863	0.776	2.124	0.999	7.1	0.03
11	Flubiprofen	5104-49-4	18	–9.135	9.372	1.882	–0.514	0.826	0.937	40.8	0.17
12	Haloperidol	52-86-8	15	–3.375	2.040	NS[a]	–1.056	NS[a]	0.362	86.9	0.33
13	Ibuprofen	15687-27-1	26	2.559	–5.117	NS[a]	NS[a]	NS[a]	0.345	169.5	0.36
14	Ketoprofen	22071-15-4	14	NS[a]	–2.070	0.346	–1.297	0.624	0.999	5.5	0.02
15	Lactose	63-42-3	16	–13.696	9.143	2.065	2.080	1.946	0.802	210.5	0.51
16	Mannitol	69-65-8	11	–9.063	5.761	1.727	0.895	NS[a]	0.952	31.5	0.13
17	Mestanolone	521-11-9	13	–7.289	5.567	–1.801	6.591	0.417	0.997	7.3	0.03
18	Methandienone	72-63-9	11	–6.111	4.010	–0.697	8.369	–0.163	0.999	2.6	0.01
19	Methyl *p*-hydroxybenzoate	99-76-3	32	–2.406	–2.680	2.663	–0.601	2.598	0.871	153.6	0.30
20	Methyltestosterone	58-18-4	13	–6.112	4.049	–1.148	7.487	0.218	0.999	3.6	0.02
21	Nandrolone	434-22-0	11	–6.131	4.192	0.306	9.483	–1.072	0.999	7.3	0.03
22	Naproxen	22204-53-1	36	–2.815	NS[a]	1.529	–1.132	0.513	0.436	105.5	0.32
23	Niflumic acid	4394-00-7	23	–3.375	NS[a]	NS[a]	NS[a]	2.225	0.223	776.9	0.76
24	Paracetamol	103-90-2	15	–6.411	1.928	2.635	0.773	2.399	0.957	61.8	0.26
25	Phenacetin	62-44-2	11	–9.073	7.148	2.798	–0.728	1.369	0.941	33.5	0.15
26	Phenothiazine	92-84-2	30	–4.438	2.120	0.739	–1.546	1.295	0.632	76.0	0.25
27	Pimozide	2062-78-4	14	–8.130	5.538	1.175	–2.020	2.051	0.679	88.6	0.27
28	Piroxicam	36322-90-4	22	–4.156	NS[a]	1.890	–1.503	NS[a]	0.291	307.9	0.70
29	Pyrene	129-00-0	19	–5.938	6.099	–0.393	–1.482	0.409	0.895	27.4	0.11
30	Saccharose	57-50-1	12	–16.613	9.138	3.979	NS[a]	1.566	0.935	62.7	0.24
31	Salicylamide	65-45-2	24	–6.272	7.076	1.240	NS[a]	–0.901	0.515	51.2	0.17
32	Sulfadiazine	68-35-9	21	–11.498	6.353	4.467	–2.710	1.253	0.806	122.3	0.43
33	Sulfamethoxypyridazine	80-35-3	26	–9.160	5.315	3.606	–1.766	0.958	0.808	78.2	0.31
34	Temazepam	846-50-4	25	–6.246	5.046	1.298	–2.086	0.473	0.796	57.3	0.23
35	Testosterone	58-22-0	11	–7.430	5.667	–1.507	8.968	0.212	0.999	4.0	0.02
36	Testosterone propionate	57-85-2	21	–5.290	5.184	1.772	NS[a]	–2.364	0.909	34.9	0.16
37	Xanthene	92-83-1	29	–4.231	4.354	–0.167	–1.163	NS[a]	0.828	25.7	0.11

[a]NS: Not significant.

and Abraham solute parameters from the literature, and Catalan solute parameters calculated in this study for 27 solutes.

It should be noted that when a model was trained using molar solubilities, it provides more accurate predictions in molar solubilities rather than other solubility expressions. Multiple linear regression analysis against Abraham descriptors and Catalan solute coefficients resulted in equations:

$$\log S_w = 0.395 - 0.551E + 0.528\,S - 0.145A + 5.41B - 4.790V \qquad r^2 = 0.939 \qquad (7)$$

$$\log S_w = -3.395 + i_{Solute} + 0.503CP + 1.726CD + 0.061CA + 0.847CB \qquad r^2 = 0.969 \qquad (8)$$

The coefficients in equation 8 might be related to the effects of the solvent used (in this case water). Catalan solvent parameters for water are cp = 0.681, cd = 0.997, cb = 0.025, and ca = 1.062, which show a similar trend in comparison with the coefficients of equation 8. This could indicate the validity and reliability of the suggested method for the calculation of Catalan solute parameters. Also it has been shown that aqueous solubility has indirect correlation with the molecular volume of the compounds.[46] Based on this fact, the following equation was proposed:

$$\log S_w = -0.902 + i_{Solute} + 0.521\,CP + 1.670\,CD + 0.289\,CA + 0.757\,CB - 1.851\,V \qquad r^2 = 0.986 \qquad (9)$$

The coefficients of the regression are similar to those of equation 8, and negative coefficient of the volume variable is meaningful.

Table 5 gives the calculated $\log S_w$ and relative deviations (RD) from equations 5, 7, 8 and 9 as well as the GMRD value.

It can be seen that Abraham's general solvation model (equation 5) gives the highest error of average 162.0%. This

Table 4. Abraham and Catalan solute parameters and logarithm of molar aqueous solubility data for 27 chemical and pharmaceutical compounds

No.	Solute	E	S	A	B	V	i_{Solute}	CP	CD	CB	CA	$\log S_w$
1	1,2,4,5-Tetramethylbenzene	0.739	0.600	0.000	0.190	1.280	2.565	–3.755	–0.780	–1.070	0.588	–4.59
2	1-Chloroanthraquinone	1.900	1.790	0.000	0.507	1.651	NS[a]	–3.128	1.227	–2.578	NS[a]	–5.54
3	1-Nitronaphthalene	1.600	1.590	0.000	0.290	1.260	–3.918	4.843	1.747	–3.130	NS[a]	–3.54
4	2-Chloro-5-nitrobenzoic acid	1.250	1.400	0.670	0.460	1.228	NS[a]	NS[a]	0.870	–0.604	–0.569	–2.59
5	2-Methoxybenzoic acid	0.899	1.410	0.450	0.620	1.131	–3.808	5.378	1.780	NS[a]	–1.479	–1.55
6	3,5-Dinitrobenzoic acid	1.280	1.630	0.700	0.590	1.280	–3.163	4.412	1.477	–0.383	–1.336	–2.42
7	3-Chlorobenzoic acid	0.840	0.950	0.630	0.320	1.054	–2.000	2.847	0.844	NS[a]	–0.584	–2.65
8	4-Aminobenzoic acid	1.075	1.650	0.940	0.600	1.032	–2.796	3.514	1.331	NS[a]	–1.189	–1.37
9	4-Chloro-3-nitrobenzoic acid	1.250	1.470	0.700	0.440	1.228	–4.304	5.856	1.495	–0.813	–1.030	–3.00
10	4-Methoxybenzoic acid	0.899	1.250	0.620	0.520	1.131	–4.465	5.523	1.452	–0.562	–1.148	–2.80
11	4-Nitrobenzoic acid	0.990	1.520	0.680	0.400	1.106	–3.493	4.323	1.369	–0.867	–1.245	–2.98
12	9-Fluorenone	1.600	1.490	0.000	0.350	1.372	–3.905	4.678	1.388	–1.995	NS[a]	–3.98
13	Acenaphthene	1.604	1.050	0.000	0.220	1.259	–2.152	2.759	0.598	–1.941	NS[a]	–4.54
14	Anthracene	2.290	1.340	0.000	0.280	1.454	–4.225	3.579	0.651	–2.032	NS[a]	–6.43
15	Benzil	1.445	1.590	0.000	0.620	1.637	–5.163	6.076	1.450	–0.675	–0.579	–4.05
16	Fluoranthene	2.377	1.550	0.000	0.240	1.585	–3.395	3.973	0.657	–2.555	0.256	–5.92
17	Fluorene	1.588	1.060	0.000	0.250	1.357	1.122	–2.715	–1.455	0.519	0.815	–5.00
18	Hexachlorobenzene	1.490	0.990	0.000	0.000	1.451	–3.785	3.247	–0.266	–1.088	NS[a]	–7.68
19	Ibuprofen	0.730	0.695	0.565	0.790	1.777	–1.375	NS[a]	0.867	NS[a]	1.191	–3.76
20	Naproxen	1.510	2.022	0.600	0.673	1.782	–4.009	5.901	1.049	–0.780	–1.494	–4.16
21	Phenanthrene	2.055	1.290	0.000	0.260	1.454	–2.383	2.882	0.678	–2.194	NS[a]	–5.17
22	Phenothiazine	1.890	1.560	0.310	0.300	1.479	–4.392	3.366	1.598	–1.817	0.878	–5.10
23	Pyrene	2.808	1.710	0.000	0.280	1.585	–3.682	4.040	0.544	–2.501	0.392	–6.15
24	Salicylamide	1.160	1.580	0.610	0.510	1.031	–6.486	8.024	2.042	NS[a]	–0.843	–1.75
25	Thianthrene	2.240	1.390	0.000	0.360	1.543	–3.344	2.783	NS[a]	–1.279	0.327	–5.95
26	*trans*-Stilbene	1.450	1.040	0.000	0.340	1.563	–4.173	4.728	0.510	–0.888	–0.206	–5.80
27	Xanthene	1.502	1.070	0.000	0.230	1.415	–3.053	3.814	0.335	–1.468	NS[a]	–5.21

[a]NS: Not significant.

Table 5. Relative deviations (RD) and absolute errors (AE) of calculated aqueous solubility using different equations

No.	Solute	$logS_w$	Calculated $logS_w$				Relative deviation (RD)				Absolute error (AE)			
			equation				equation				equation			
			5	7	8	9	5	7	8	9	5	7	8	9
1	1,2,4,5-Tetramethylbenzene	–4.59	–3.76	–4.80	–4.93	–4.61	571.9	38.5	54.6	3.5	0.83	0.21	0.34	0.02
2	1-Chloroanthraquinone	–5.54	–4.69	–4.88	–5.03	–5.49	600.0	362.0	220.4	11.8	0.85	0.66	0.51	0.05
3	1-Nitronaphthalene	–3.54	–3.87	–4.12	–4.51	–4.08	53.7	73.5	89.4	71.1	0.33	0.58	0.97	0.54
4	2-Chloro-5-nitrobenzoic acid	–2.59	–2.41	–3.05	–2.44	–2.34	50.0	65.1	40.7	75.4	0.18	0.46	0.15	0.24
5	2-Methoxybenzoic acid	–1.55	–1.46	–1.49	–1.52	–1.46	24.0	16.0	8.7	25.5	0.09	0.06	0.04	0.10
6	3,5-Dinitrobenzoic acid	–2.42	–2.16	–2.49	–2.20	–2.34	79.2	15.3	66.0	18.3	0.26	0.07	0.22	0.07
7	3-Chlorobenzoic acid	–2.65	–2.00	–2.98	–2.54	–2.13	344.3	52.9	27.9	232.2	0.65	0.33	0.11	0.52
8	4-Aminobenzoic acid	–1.37	–0.94	–1.16	–2.20	–1.90	167.6	61.9	85.2	70.3	0.43	0.21	0.83	0.53
9	4-Chloro-3-nitrobenzoic acid	–3.00	–2.42	–3.12	–2.93	–2.84	280.5	24.6	18.7	43.7	0.58	0.12	0.07	0.16
10	4-Methoxybenzoic acid	–2.80	–1.68	–2.14	–3.12	–2.91	1233.0	361.4	52.5	23.1	1.12	0.66	0.32	0.11
11	4-Nitrobenzoic acid	–2.98	–1.87	–2.58	–3.16	–2.92	1179.9	149.9	34.3	15.4	1.11	0.40	0.18	0.06
12	9-Fluorenone	–3.98	–4.09	–4.38	–4.24	–4.10	21.7	60.3	45.3	24.2	0.11	0.40	0.26	0.12
13	Acenaphthene	–4.54	–4.28	–4.78	–4.77	–4.42	83.2	42.2	41.4	32.6	0.26	0.24	0.23	0.12
14	Anthracene	–6.43	–5.29	–5.61	–6.42	–6.40	1269.1	556.8	2.9	6.4	1.14	0.82	0.01	0.03
15	Benzil	–4.05	–3.91	–4.05	–3.61	–4.18	37.8	0.3	177.1	26.7	0.14	0.00	0.44	0.13
16	Fluoranthene	–5.92	–5.88	–6.39	–5.81	–5.92	10.7	66.4	30.2	0.2	0.04	0.47	0.11	0.00
17	Fluorene	–5.00	–4.48	–5.07	–5.66	–5.51	226.8	15.1	78.1	68.9	0.52	0.07	0.66	0.51
18	Hexachlorobenzene	–7.68	–5.54	–6.86	–6.93	–6.95	13609.4	564.2	466.1	440.1	2.14	0.82	0.75	0.73
19	Ibuprofen	–3.76	–3.12	–3.96	–3.20	–3.77	332.7	37.2	263.4	3.1	0.64	0.20	0.56	0.01
20	Naproxen	–4.16	–3.77	–4.35	–3.38	–4.40	146.7	36.0	503.2	43.1	0.39	0.19	0.78	0.24
21	Phenanthrene	–5.17	–5.15	–5.62	–5.02	–5.00	4.6	64.3	42.6	47.5	0.02	0.45	0.15	0.17
22	Phenothiazine	–5.10	–4.57	–5.33	–4.82	–4.73	235.8	41.4	90.1	135.1	0.53	0.23	0.28	0.37
23	Pyrene	–6.15	–6.11	–6.33	–6.20	–6.28	10.6	34.0	10.9	26.3	0.04	0.18	0.05	0.13
24	Salicylamide	–1.75	–1.52	–1.68	–2.37	–1.95	70.8	17.7	76.0	35.9	0.23	0.07	0.62	0.19
25	Thianthrene	–5.95	–5.26	–5.55	–6.40	–6.52	384.8	150.0	64.7	73.3	0.69	0.40	0.45	0.57
26	*trans*-Stilbene	–5.80	–4.76	–5.51	–5.08	–5.38	1009.1	97.1	430.3	160.6	1.04	0.29	0.72	0.42
27	Xanthene	–5.21	–4.66	–5.4	–5.19	–5.14	254.0	36.1	3.6	18.2	0.55	0.19	0.02	0.07
						Mean	825.6	112.6	112.0	64.2	0.55	0.32	0.36	0.23
		Number of solutes with RD > 100 (or AE > 1)					16	6	6	4	5	0	0	0

high error could be due to the chemicals falling outside the applicability domain of equation 5. Therefore, to provide a nonbiased comparison, a new QSPR was drawn from Abraham descriptors (equation 7), as mentioned above. Equation 7 derived from five Abraham solute descriptors, and equation 8 which employs four solute descriptors derived from Catalan solvent scales, show similar error in correlation. By adding volume term to the equation 8 and correlating it with aqueous solubility data, equation 9 was derived. This equation shows better correlation in comparison with equations 5, 7, and 8. The highest deviations of the calculated solubilities from the measured values are observed for hexachlorobenzene in all estimation methods, with equation 5 showing the maximum relative deviation for this compound. The number of high error solutes with relative deviations greater than 100% is 6 and 4 for equations 8 and 9, respectively. The corresponding values for Abraham models are 16 and 6 using equations 5 and 7, respectively.

Conclusions

In this study, we showed that Catalan and Abraham solvent parameters are rather different solvatochromic scales of solvents although similar procedures are employed for their experimental determination. The applicability of both solvent parameters in QSPR analyses was evident from the results obtained for solvents and solutes. A methodology was introduced for the calculation of new solvatochromic solute parameters based on Catalan solvent parameters.

The method takes advantage of the coefficients of Catalan solvent parameters in multiple linear regression models of solute solubility in several nonaqueous solvents. The new solute parameters compared well with Abraham solute parameters for the estimation of aqueous solubility of compounds. The back-calculated Catalan parameters for water (coefficients of the model developed for aqueous solubility) were close to the experimental Catalan water parameters in their trend, which might confirm the suitability of the suggested method for the calculation of solute and solvent parameters.

The results of this study suggest that Catalan solvent parameters and the new solute parameters can be regarded as a valuable resource for applications in QSPR modeling. A further advantage of exploitation of Catalan parameters is the vast number of the solvents for which these parameters have already been measured which amounts to more than 150 solvents to date. For example, propylene glycol, among these solvents, is an important pharmaceutically interested solvent.

Supplementary Information

List of parameters used in this work and supplementary data are available free of charge at http://jbcs.sbq.org.br as PDF file.

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Supplementary Information

QSPR Modeling Using Catalan Solvent and Solute Parameters

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Table S1. List of parameters used in this study

Parameter	Definition	Parameter	Definition
A	Abraham' hydrogen bonding acidity parameter for the solute	SPP	Catalan polarity/polarizability parameter for the solvent
B	Abraham' hydrogen bonding basicity parameter for the solute	SP (cp)	Catalan polarizability parameter for the solvent
S	Abraham' polarity/polarizability parameter for the solute	SdP (cd)	Catalan dipolarity parameter for the solvent
E	Excess molar refraction of the solute	SB (cb)	Catalan basicity parameter for the solvent
V	One percent of McGowan volume of the solute	SA (ca)	Catalan acidity parameter for the solvent
c	Abraham' constant value for the solvent	i_{Solute}	Catalan constant value for the solute*
a	Abraham' interaction term of the solvent with acidity of the solute (solvent basicity)	CP	Catalan polarizability parameter for the solute*
b	Abraham' interaction term of the solvent with basicity of the solute (solvent acidity)	CD	Catalan dipolarity parameter for the solute*
s	Abraham' interaction term of the solvent with polarity/polarizability of the solute	CB	Catalan basicity parameter for the solute*
e	Abraham' interaction term of the solvent with molar refraction of the solute	CA	Catalan acidity parameter for the solute*
v	Abraham' interaction term of the solvent with molar volume of the solute	i_W	Intercept of the aqueous solubility prediction equation*

*These parameters were resulted from this study.

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Table S2. Abraham solvent parameters (c, e, s, a, b, and v) for available solvents and their related Catalan solvent parameters (cp, cd, cb, and ca)

No.	Solvent	c	e	s	a	b	v	cp	cd	ca	cb
1	1,2-Dichloroethane	0.227	0.278	–0.167	–2.816	–4.324	4.205	0.771	0.742	0.030	0.126
2	1,4-Dioxane	0.098	0.350	–0.083	–0.556	–4.826	4.172	0.737	0.312	0.000	0.444
3	Butan-1-ol	0.152	0.437	–1.175	0.098	–3.914	4.119	0.674	0.655	0.341	0.809
4	Decan-1-ol	–0.062	0.754	–1.461	0.063	–4.053	4.293	0.722	0.383	0.259	0.912
5	Heptan-1-ol	–0.026	0.491	–1.258	0.035	–4.155	4.415	0.706	0.499	0.302	0.912
6	Hexan-1-ol	0.044	0.470	–1.153	0.083	–4.057	4.249	0.698	0.552	0.315	0.879
7	Octan-1-ol	–0.034	0.490	–1.048	–0.028	–4.229	4.219	0.713	0.454	0.299	0.923
8	Pentan-1-ol	0.080	0.521	–1.294	0.208	–3.908	4.208	0.687	0.587	0.319	0.860
9	Propan-1-ol	0.148	0.436	–1.098	0.389	–3.893	4.036	0.658	0.748	0.367	0.782
10	Butan-2-ol	0.106	0.272	–0.988	0.196	–3.805	4.110	0.656	0.706	0.221	0.888
11	2-Methyl propan-1-ol	0.177	0.335	–1.099	0.069	–3.570	3.990	0.657	0.684	0.311	0.828
12	2-Methyl propan-2-ol	0.197	0.136	–0.916	0.318	–4.031	4.113	0.632	0.732	0.145	0.928
13	Propan-2-ol	0.063	0.320	–1.024	0.445	–3.824	4.067	0.633	0.808	0.283	0.830
14	Propan-2-one	0.335	0.349	–0.231	–0.411	–4.793	3.963	0.651	0.907	0.000	0.475
15	Acetonitrile	0.413	0.077	0.326	–1.566	–4.391	3.364	0.645	0.974	0.044	0.286
16	Benzene	0.142	0.464	–0.588	–3.099	–4.625	4.491	0.793	0.270	0.000	0.124
17	Carbon disulfide	0.047	0.686	–0.943	–3.603	–5.818	4.921	1.000	0.000	0.000	0.104
18	Carbone tetrachloride	0.260	0.573	–1.254	–3.558	–4.558	4.589	0.768	0.000	0.000	0.044
19	Chlorobenzene	0.040	0.246	–0.462	–3.038	–4.769	4.640	0.833	0.537	0.000	0.182
20	Chloroform	0.327	0.157	–0.391	–3.191	–3.437	4.191	0.783	0.614	0.047	0.071
21	Cyclohexane	0.159	0.784	–1.678	–3.740	–4.929	4.577	0.683	0.000	0.000	0.073
22	Dibutyl ether	0.203	0.369	–0.954	–1.488	–5.426	4.508	0.672	0.175	0.000	0.637
23	Dichloromethane	0.314	0.001	0.022	–3.238	–4.137	4.259	0.761	0.769	0.040	0.178
24	Diethyl ether	0.308	0.377	–0.813	–0.468	–5.012	4.379	0.617	0.385	0.000	0.562
25	Dimethylformamide	–0.438	–0.099	0.670	0.878	–4.970	4.552	0.759	0.977	0.031	0.613
26	Dodecane	0.114	0.668	–1.644	–3.545	–5.006	4.459	0.683	0.000	0.000	0.086
27	Ethanol	0.208	0.409	–0.959	0.186	–3.645	3.928	0.633	0.783	0.400	0.658
28	Ethyl acetate	0.358	0.362	–0.449	–0.668	–5.016	4.155	0.656	0.603	0.000	0.542
29	Ethylene glycol	0.243	0.695	–0.670	0.726	–2.399	2.670	0.777	0.910	0.717	0.534
30	Heptane	0.325	0.670	–2.061	–3.317	–4.733	4.543	0.635	0.000	0.000	0.083
31	Hexadecane	0.087	0.667	–1.617	–3.587	–4.869	4.433	0.704	0.000	0.000	0.086
32	Hexane	0.361	0.579	–1.723	–3.599	–4.764	4.344	0.616	0.000	0.000	0.056
33	Isooctane	0.288	0.382	–1.668	–3.639	–5.000	4.461	0.618	0.000	0.000	0.044
34	Methanol	0.329	0.299	–0.671	0.080	–3.389	3.512	0.608	0.904	0.605	0.545
35	Methylcyclohexane	0.246	0.782	–1.982	–3.517	–4.293	4.528	0.675	0.000	0.000	0.069
36	Methy-*tert*-butyl ether	0.376	0.264	–0.788	–1.078	–5.030	4.410	0.622	0.422	0.000	0.567
37	Nonane	0.240	0.619	–1.713	–3.532	–4.921	4.482	0.660	0.000	0.000	0.053
38	Octane	0.223	0.642	–1.647	–3.480	–5.067	4.526	0.650	0.000	0.000	0.079
39	Tetrahydrofuran	0.207	0.372	–0.392	–0.236	–4.934	4.447	0.714	0.634	0.000	0.591
40	Toluene	0.143	0.527	–0.720	–3.010	–4.824	4.545	0.782	0.284	0.000	0.128
41	Undecane	0.058	0.603	–1.661	–3.421	–5.120	4.619	0.678	0.000	0.000	0.080

Table S3. Melting point (mp), boiling point (bp), flash point (fp), refractive index (*n*), surface tension (γ), viscosity (η), density (ρ), and solubility parameter (SP) data of 54 common solvents[a]

No.	Solvent	mp (K)	bp (K)	fp (K)	*n*	γ (dyn cm^{-1})	η (cP)	ρ (g cm^{-3})	SP
1	1,1,1-Tricloroethane	243	347		1.438	30	0.65	1.338	7.7
2	1,2-Dichloroethane	237	356.5	286	1.444	32.2	0.9	1.253	9.8
3	1,2-Propanediol	213	460	372	1.431	72	54	1.0362	
4	1,4-Dioxane	285	374	285	1.42	40	1.3	1.034	10
5	2,2,4-Trimethyl pentane	166	372	261	1.389	18.33	0.477	0.692	7.4
6	Acetic Acid	290	391	313	1.37	27.4	1.13	1.051	10.1
7	Acetone	178	329	255	1.357	23.3	0.33	0.79	10
8	Acetonitrile	229	354.6	279	1.342	29.1	0.38	0.782	11.9
9	Acetophenone	292.6	475	355	1.532	12	1.74	1.024	
10	Aniline	267	457	349	1.583	45.5	4.4	1.022	10.3
11	Benzene	278.5	353	262	1.498	28.9	0.65	0.879	9.2
12	Carbon disulphide	162	319	243	1.628	32	0.36	1.26	10
13	Carbon tetrachloride	250	349		1.459	27	0.97	1.58	8.6
14	Chloroform	250	334		1.444	27.16	0.57	1.48	9.3
15	Cyclohexane	279.5	354	256	1.424	24.98	0.98	0.778	8.2
16	Cyclohexanone	241	429	316	1.448	34.5	2.2	0.948	9.9
17	Dibutyl ether	178	415	298	1.397	22.4[a]	0.63	0.769	7.2
18	Diethyl ether	157	307.5	228	1.352	17	0.24	0.715	7.4
19	Diisopropyl ether	187	341	245	1.367	18	0.33	0.724	6.9
20	Dimethylacetamide	253	439	343	1.436	34	0.92	0.945	11
21	Dimethylformamide	212	426	335	1.427	35	0.82	0.945	12.1
22	Dimethylsulphoxide	291.5	462	368	1.476	43.7	2	1.101	13
23	Ethanediol	260	471	384	1.429	46.5	20	1.115	14.6
24	Ethanol	159	351	286	1.359	22.3	1.08	0.789	13.4
25	Ethyl acetate	189	350	269	1.37	24	0.46	0.895	9.1
26	Ethylbenzene	179	409	288	1.493	29.2	0.72	0.867	8.9
27	*i*-Butanol	165	381	298	1.394	22.8	3.96	0.802	10.7
28	*i*-Propanol	185	355	285	1.375	21.7	2	0.786	11.5
29	Methanol	175	337	288	1.326	22.6	0.6	0.792	14.5
30	Methyl acetate	175	330	263	1.36	24	0.37	0.927	9.6
31	Methyl ethyl ketone	186	353	267	1.377	24.6	0.41	0.805	9.3
32	Methy-*tert*-butyl ether	164	328	239	1.369	18.3	0.35	0.741	7.4
33	Methylene chloride	178	313		1.4211	28.1	0.44	1.326	9.7
34	Monochlorobenzene	227	405	302	1.523	33	0.8	1.106	9.5
35	*n*-Amyl alcohol	195	411	321	1.408	25.6	4	0.815	
36	*n*-Butanol	193	391	308	1.397	24.6	3	0.81	11.4
37	*n*-Butyl acetate	200	399	295	1.392	25.1	0.73	0.876	8.6
38	*n*-Decane	243	447	317	1.408			0.73	6.7
39	*n*-Heptane	182	371	269	1.385	19.3	0.41	0.664	7.5
40	*n*-Hexane	178	342	251	1.372	18.4	0.31	0.659	6.9
41	Nitrobenzene	279	484	361	1.55	43.9	1.8	1.204	10
42	*n*-Methyl-2-pyrrolidone	249	475	368	1.468	40.7	1.8	1.03	11
43	*n*-Nonane	220	424	304	1.403	22.9	0.67	0.718	
44	*n*-Octane	216	399	286.3	1.395	21.7	0.5	0.703	
45	*n*-Octanol	257	467	354	1.427	27.5	7.5	0.827	10.4
46	*n*-Pentane	144	309	233	1.358	16	0.235	0.626	7
47	*n*-Propanol	146	370	298	1.383	23.7	1.72	0.804	11.9
48	Pyridine	231	388	293	1.507	36.6	0.88	0.983	10.7
49	2-Butanol	158	372.5	294	1.395	23	3.7	0.807	10.8
50	Sulfolane	300.4	558	450	1.471	35.5	10.3	1.26	
51	Tetrahydrofuran	164	339	258	1.404	28	0.55	0.888	9.1
52	Toluene	178	383.6	277	1.494	28.5	0.59	0.867	8.9
53	Water	273	373		1.332	72.75	0.89	0.998	23.4
54	Xylenes (mixed isomers)		409	296	1.496	28.6	0.7	0.87	8.9

[a] http://www.springerlink.com/content/r364t1631p53p436/, accessed in September 2009.