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Polarity study of Ionic Liquids with the solvatochromic dye Nile Red: a QSPR approach using *in silico* VolSurf+ descriptors

Alessio Paterno'^a, Francesca D'Anna^b, Cosimo G. Fortuna^a, and Giuseppe Musumarra^a*

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^a Dipartimento di Scienze Chimiche, Università di Catania, Viale A. Doria 6, I-95125 Catania, Italy. ^b Dipartimento STEBICEF, Università di Palermo, Viale delle Scienze - Parco d'Orleans II, Ed.17, 90128 Palermo, Italy.

Abstract

The *in silico* VolSurf+ descriptors, accounting for both cationic and anionic structural features of ionic liquids (ILs). were used to develop a Partial Least Squares (PLS) model able to establish a Quantitative Structure Property Relationship (QSPR) correlation with their solvatochromic dye Nile Red polarity. The PLS model allowed prediction of E_{NR} values for 116 ILs providing an *in silico* ILs polarity database.

Keywords

Ionic liquids; Polarity; Nile Red; QSPR

*gmusumarra@unict.it

1. Introduction

Ionic liquids (ILs), organic salts formed of an organic cation and an inorganic or organic anion, are nowadays a very popular class of compounds due to their versatility in applications which, from their original use as reaction media, soon expanded to many others.¹ Their low melting point made them widely adopted as reaction media originally considered as "green" solvents due to their low volatility, as well as to their high chemical and thermal stability.

As reaction media, they can exert very different effects. Indeed, ILs can affect reaction mechanisms inducing different pathways with respect to conventional organic solvents^{2,3} or, alternatively, they can exert a kinetic effect giving products with higher yields in significantly lower reaction times and/or temperatures.⁴

Given the huge number of cation/anion combinations, a large variety of solvent systems having different properties can be obtained. This may simultaneously represent an advantage and a detriment. Although a wide range of solvents would be in principle available for the same process, the lack of knowledge of solvent properties and the effort required to perform experimental investigations makes the selection of a suitable solvent for a given process or reaction a hard task. Hence the need to predict solvent properties by Quantitative Structure Property Relationships (QSPR) models based on *in silico* structural descriptors. In this context a new opportunity is provided by the VolSurf+ approach,^{5,6} which uses information coded into 3D GRID Molecular Interaction Fields (MIFs)⁷⁻¹⁰ to derive physicochemical molecular descriptors such as molecular size and shape, hydrophilic and hydrophobic properties, hydrogen bonding, amphiphilic moments, critical packing parameters and pharmacokinetic descriptors related to solubility, metabolic stability and cell permeability.

The VolSurf+ procedure has been successfully applied in QSAR studies to predict a wide variety of biological properties such as structure–permeation relationships,⁵ antitumour activities,¹¹⁻¹³ phospholipidosis induction^{14,15} and more recently the aquatic toxicity of ionic liquids.¹⁶

In the ionic liquids field VolSurf+ descriptors take into account several cationic ILs structural features such as heterocyclic aromatic and non-aromatic cores, alkyl chain length, presence of oxygen atoms in the substituents as well as physicochemical properties of various inorganic and organic anions.

In this study we wish to verify if VolSurf+ descriptors, designed for *in silico* modelling of biological activities, could be suitable for the prediction of an important ILs property such as solvent polarity. A recent review, examining several approaches to computational chemistry used with ILs¹⁷ and pointing out the utility of combining computational and experimental approaches,

confirms that the proposed methodology, widely adopted in medicinal chemistry and industrial experimental design, has not been previously applied for modelling ILs physico-chemical properties.

Among solvent properties, polarity is one of the most widely used and different empirical scales known. In general, both neutral and charged probes have been used, for example the Kosower¹⁸ and Reichardt^{19,20} scales adopt pyridinium betaine dyes as polarity probes, while a neutral "sensor" dye Nile Red (NR) exhibits bathocromic shifts above 100 nm.

As far as ILs are concerned, interesting experimental studies on the determination of ILs dielectric constants have been carried out by Weingaertner and coworkers.²¹⁻²⁴

The use of empirical scales to evaluate their polarity has been the object of an intense debate. Indeed, the response of the probe to the solvent is determined by all possible solvent-solute interactions, and in the case of ionic solvents media, some can play a more significant role than others. Polarity of ILs has been determined using single-molecules as spectroscopic probes, taking advantage of the effects they are able to exert on electronic absorption, fluorescence and vibrational spectra, as well as on paramagnetic resonance signals.²⁵

In the case of UV-Vis active probes, both charged and neutral "sensors" have been used. Consequently, the polarity of ILs has been evaluated using pyridinium betaine dyes, transitionmetal complexes such as $[Cu(acac)(tmen)]^+$, merocyanine probes and Nile Red (NR). In particular, NR has been used not only to evaluate the polarity of ILs by means of the E_{NR} parameter, but also to have information about their 3-dimensional organization as neat solvents or in combination with other ILs or conventional organic solvents to give binary mixtures.^{26,27} More than a decade ago, Seddon *et al.* reported a pioneering study on NR polarity of 1-alkyl-3-methylimidazolium ILs²⁸ and showed that their polarity is comparable with that of the lower alcohols. This paper points out "a paucity of good reproducible data" and the need "to create a reliable database".

Studies relating different ILs structures²⁹ and structural variations in both cationic and anionic moieties to ILs polarity³⁰ using the empirical Kamlet–Taft solvent parameters have been reported. In this context we here report the polarity of 18 ILs with different aromatic and non-aromatic cationic scaffolds, different alkyl chain length and different anions and develop a Quantitative Structure Property Relationships (QSPR) model based on VolSurf+ descriptors with the aim to predict E_{NR} values for a large number of commonly used ILs.

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Scheme 1. Structure of ILs and of the solvatochromic probe used.

2. Results and Discussion

In Table 1 we report both literature³¹⁻³³ and experimental E_{NR} values for 18 ILs (see Scheme 1) with different cationic and anionic structural features: mainly imidazolium cationic scaffolds (plus one piperidinium and one pyrrolidinium), different length alkyl side chains (up to 8 carbon atoms), and 8 anions ranging from tetrafluoroborate to oxygenated anions.

The PLS analysis was carried out using a 18x176 descriptor matrix including 18 ILs (Table 1) and 176 variables (128 cation and 48 anion VolSurf+ descriptors)¹⁶ and the E_{NR} polarity as the response. The analysis provided a 3 PLS components model (see Table 2) explaining 93.2% of y variance ($Q^2 = 0.770$) where the 1st and the 2nd PLS components explain already 88.1% of y variance ($Q^2 = 0.728$). The plot of predicted *vs*. experimental data (Fig. 1) shows a good agreement between experimental and predicted E_{NR} values.

Table 1. Experimental E_{NR} values for ILs used as learning and test set and PLS predictions.

	Ionic Liquids	ENR (Kcal/mol)	ENR ^a (Kcal/ mol)	PLS pred.	DModX⁵	Name
1	IM1-(1Ph) (CF3SO2)2N	216.2 ^c		216.3	1.54	1-Benzyl-3-methylimidazolium 1,1,1-trifluoro-N- [(trifluoromethyl)sulfonyl]methanesulfonamide
2	IM12 (CF3SO2)2N	217.9 ^d		217.8	1.07	1-Ethyl-3-methylimidazolium 1,1,1-trifluoro-N- [(trifluoromethyl)sulfonyl]methanesulfonamide
3	IM14 (10)2PO2	218.0 ^e		217.8	0.63	1-Butyl-3-methylimidazolium dimethyl phosphate
4	IM14 N(CN)2	215.7 ^f		215.6	0.74	1-Butyl-3-methylimidazolium N-cyanocyanamide
5	IM14 PF6	217.7 ^f	218.5	217.5	0.79	1-Butyl-3-methylimidazolium hexafluorophosphate
6	IM14 (CF3SO2)2N	218.2 ^f	218.0	217.8	0.85	1-Butyl-3-methylimidazolium 1,1,1-trifluoro-N- [(trifluoromethyl)sulfonyl]methanesulfonamide
7	IM14 BF4	217.3 ^d	217.2	217.2	0.86	1-Butyl-3-methylimidazolium tetrafluoroborate
8	IM14 CF3COO	216.6 ^e		216.9	1.01	1-Butyl-3-Methylimidazolium trifluoroacetate
9	IM14 1COO	217.2 ^e		217.3	1.57	1-Butyl-3-methylimidazolium acetate
10	IM14-2Me (CF3SO2)2N	217.7 ^d		218.0	0.92	1-Butyl-2,3-dimethylimidazolium 1,1,1-trifluoro-N- [(trifluoromethyl)sulfonyl]methanesulfonamide
11	IM16 N(CN)2	215.3 ^f		215.1	0.70	1-Hexyl-3-methylimidazolium dicyanamide
12	IM16 (CF3SO2)2N	217.9 ^d		217.3	0.84	1-Hexyl-3-methylimidazolium 1,1,1-trifluoro-N- [(trifluoromethyl)sulfonyl]methanesulfonamide
13	IM16 SbF6	216.1 ^d		216.8	1.03	1-Hexyl-3-methylimidazolium hexafluoridoantimonate
14	IM18 (CF3SO2)2N	217.9 ^d		217.7	0.61	1-Methyl-3-octylimidazolium 1,1,1-trifluoro-N- [(trifluoromethyl)sulfonyl]methanesulfonamide
15	IM18 N(CN)2	215.7 ^f		215.5	1.07	1-Methyl-3-octylimidazolium dicyanamide
16	IM4-(1Ph) (CF3SO2)2N	216.1 ^c		216.4	1.41	1-Benzyl-3-butylimidazolium 1,1,1-trifluoro-N- [(trifluoromethyl)sulfonyl]methanesulfonamide
17	Pip14 (CF3SO2)2N	219.0 ^d		219.5	0.87	1-Butyl-1-methylpiperidinium 1,1,1-trifluoro-N- [(trifluoromethyl)sulfonyl]methanesulfonamide
18	Pyr14 (CF3SO2)2N	219.9 ^d		219.6	0.77	1-Butyl-1-methylpyrrolidinium 1,1,1-trifluoro-N- [(trifluoromethyl)sulfonyl]methanesulfonamide
19	IM1-10 BF4		219.2	216.9	1.40	1-Decyl-3-methylimidazolium tetrafluoroborate
20	IM16 PF6		216.8	217.0	0.87	1-Hexyl-3-methylimidazolium hexafluorophosphate
21	IM16 BF4		216.8	216.7	0.96	1-Hexyl-3-methylimidazolium tetrafluoroborate
22	IM18 PF6		217.6	217.4	0.86	1-Methyl-3-octylimidazolium hexafluorophosphate
23	IM18 BF4		217.7	217.1	1.01	1-Methyl-3-octylimidazolium tetrafluoroborate
N ₁	IM14 NO3		215.3	212.3	35.32	1-Butyl-3-methylimidazolium nitrate
N ₂	IM16 NO3		216.3	211.8	35.28	1-Hexyl-3-methylimidazolium nitrate
N ₃	IM18 NO3		217.4	212.2	35.29	1-Methyl-3-octylimidazolium nitrate

^a Ref. 28; ^b DModX values indicate the distance of the observations to the X-model hyperplane.³⁴ Predictions for ILs with DModX > 1.32 should be considered with caution; ^cRef. 31; ^dRef. 32; ^eThis work; ^fRef. 33.

Table 2. PLS model	parameters for the	3 extracted	principal	components ((PCs)).
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РС	R ² X	R ² X(cum)	R ² Y	R ² Y(cum)	Q²	Q ² (cum)
1	0.295	0.295	0.756	0.756	0.603	0.603
2	0.234	0.529	0.126	0.881	0.315	0.728
3	0.128	0.657	0.051	0.932	0.153	0.770

SIMCA (Soft Independent Modelling of Class Analogy)³⁴ models are soft models applicable within the experimental space covered by the observations (in the present case ILs) considered in the analyzed data matrix. Therefore the prediction affordability for each single IL depends on its structural similarity with the structures of the ILs considered in the model derivation. The PLS model predictions are reported in Table 1 together with DModX values, the model residuals in the X matrix, providing an estimate of the similarity of a new observation (IL) to the training set observations. Predictions for ILs exhibiting DModX values higher than 1.32 should be considered with some caution,³⁴ the higher the DModX value, the lower the prediction reliability.



Figure 1. PLS correlation plot reporting the experimental and the corresponding predicted E_{NR} values for ILs 1-18.

In order to check the experimental reliability of the model predictions, the E_{NR} values reported by Seddon²⁸ are also reported as a test set in Table 1. It has been noted³⁵ that although the Kamlet–Taft parameters are well established for traditional solvents, for ILs they are very sensitive to impurities.³⁶ However, in the present case, the E_{NR} values used as a learning set were determined in the presence of 1,4-dioxane. As previously reported, the comparison with literature values outline that the co-solvent presence has a negligible effect.³² This statement is further supported by the agreement between the E_{NR} values measured by us with literature ones²⁸ for three ILs (Table 1) which indicates a remarkable inter-laboratory reproducibility.

The PLS model predictions for the test set are in agreement with the experimental data in Table 1. Predictions for objects with high DModX values, such as ILs with nitrate anions absent in the learning set, are definitely unreliable. A possible interpretation of this result might rely on both anion geometry and size. Anions used in this study exhibit different geometries, as well as different ionic radii, comparable for $[BF_4^-]$ and $[PF_6^-]$ anions (232 and 240 pm, respectively) but significantly lower for $[NO_3^-]$ (179 pm) which determines a different charge distribution. Anyway, a specific

effect which renders nitrate modelling more difficult might be responsible for their peculiar behaviour.

As far as 1-decyl-3-methylimidazolium tetrafluoroborate is concerned, the poor agreement between experimental and predicted values could be ascribed to segregation effects, which heavily depend on the alkyl chain length.^{37,38} On the grounds of the above effects, the fluorescent probe could feel different polar and apolar microenvironments, more evident for decylimidazolium, than for octylimidazolium tetrafluoroborate.

The PLS model predictions were extended to E_{NR} values for a higher number of ILs (up to 116) exhibiting DModX values lower than 2.0 in Table S2.

In addition to its prediction potentiality, the PLS model allows us to evaluate quantitatively the importance of the VolSurf+ descriptors (Table S1 in ESI) in determining the E_{NR} values by means of their VIP (Variables Importance for the Projection) values.

Table 3 reports the VIP values for the top 75 descriptors, together with the coefficients referring to the 1st PLS component (the most relevant one) providing information on the sign of the descriptor contribution.

Table 3. VIP values for the top 75 descriptors together with the coefficients of the 1st PLS component. VIP values describe the importance of each X-variable both in modeling the objects and in relation to the Y response. The coefficients values express the sign and the magnitude of the contribution between the Xs and the Y.

	Var ID	VIP values	Coeff. Values
1	D3_Cat	1.80	-0.022
2	CP_Cat	1.80	-0.022
3	D5_Cat	1.78	-0.022
4	VD_Cat	1.78	-0.022
5	D4_Cat	1.78	-0.022
6	D6_Cat	1.77	-0.022
7	CD1_Cat	1.77	-0.022
8	CD2_Cat	1.77	-0.022
9	CD3_Cat	1.74	-0.021
10	CACO2_Cat	1.73	0.021
11	CD4_Cat	1.71	-0.021
12	D7_Cat	1.70	-0.021
13	D2_Cat	1.69	-0.021
14	CD7_Cat	1.66	-0.021
15	CD8_Cat	1.64	-0.021
16	CW2_Cat	1.62	-0.020
17	CD6_Cat	1.62	-0.020
18	CD5_Cat	1.61	-0.020
19	PSA_Cat	1.60	-0.019

20	D8_Cat	1.60	-0.020	
21	D1_Cat	1.58	-0.019	
22	D8_An	1.58	-0.019	
23	CD8_An	1.58	-0.019	
24	CD6_An	1.55	-0.018	
25	CD7_An	1.55	-0.018	
26	W2_Cat	1.54	-0.019	
27	D6_An	1.53	-0.018	
28	D7_An	1.52	-0.018	
29	CD5_An	1.51	-0.018	
30	CW1_Cat	1.48	-0.018	
31	CD4_An	1.47	-0.017	
32	D5_An	1.45	-0.017	
33	W3_Cat	1.39	-0.018	
34	D4_An	1.35	-0.016	
35	CW3_An	1.35	-0.016	
36	S_An	1.35	0.016	
37	V_An	1.34	0.016	
38	G_An	1.33	0.015	
39	CW3_Cat	1.32	-0.016	
40	W1_Cat	1.32	-0.015	
41	CW2_An	1.32	-0.015	
42	IW4_An	1.32	-0.015	
43	CW5_An	1.30	-0.015	
44	ID4_Cat	1.29	-0.014	
45	W5_An	1.26	-0.015	
46	R_An	1.25	0.014	
47	DD1_Cat	1.24	-0.012	
48	FLEX_Cat	1.24	-0.013	
49	W1_An	1.21	0.014	7
50	SOLY_Cat	1.20	0.013	7
51	LgS3_Cat	1.20	0.013	
52	LgS4_Cat	1.20	0.013	
53	LgS5_Cat	1.20	0.013	
54	LgS6_Cat	1.20	0.013	
55	LgS7_Cat	1.20	0.013	
56	LgS7,5_Cat	1.20	0.013	
57 F0	LgS8_Cat	1.20	0.013	
50	Lg39_Cat	1.20	0.013	
59 60	LgS10_Cat	1.20	0.013	
61		1.20	0.013	
62	LULGJ_COL	1.20	0.015	
62	G Cat	1.19	-0.012	
64		1 16	-0.013	
65	DD2 Cat	1 15	-0 011	
66	FLEX RR Cat	1 11	-0 013	
00			0.010	

67	CW4_An	1.11	-0.013
68	DD3_Cat	1.10	-0.009
69	A_An	1.10	0.013
70	S_Cat	1.10	-0.011
71	HSA_Cat	1.09	-0.011
72	MW_Cat	1.09	-0.012
73	CW1_An	1.06	-0.012
74	V_Cat	1.05	-0.010
75	DIFF_Cat	1.01	0.009

VIP values give an indication (in absolute values) of what variables in the X block (VolSurf+ descriptors) are relevant to determine the dependent variable (polarity of ILs). Table 3 shows that the major influence on the response is provided by cation descriptors, especially by those related to their hydrophobic character (hydrophobic volumes D_n and hydrophobic capacity factors CD_n at different energy levels). A lower contribution is given by cationic descriptors referring to a general hydrophilic character (hydrophilic volumes indicating polarizability W1-W4 and hydrophilic capacity factors CW1-CW3) and water solubility (intrinsic solubility SOLY and solubility at various pH LgSs). The latter descriptors show a positive contribution to the E_{NR} values (as expressed by the relative coefficients), whereas the former are inversely correlated to the responses, indicating that molecular polarizability (expressed by W1-W3) in ILs contribute to decrease the response, whereas ILs able to be dissolved in water have higher E_{NR} values. Similar considerations can be done for the corresponding anionic hydrophobic character (D4-D8 and CD4-CD8) and hydrophilic (W1,W5 and CW1-CW5) character descriptors. In particular, a positive contribution is found for anionic size descriptors (molecular globularity G, molecular volume V, molecular surface S and volume/surface ratio R), in agreement with the considerations made to rationalize the peculiarity of [NO₃⁻]-based ionic liquids.

In Fig. 2 we report the PC1 vs. PC2 scores plot displaying in the same chemical space the 18 ILs and E_{NR} (the y response). In the upper right quadrant ILs with a non-aromatic heterocyclic scaffold are located very close to E_{NR} showing that they positively influence the response (*i.e.* exhibit higher E_{NR} values). Moreover the shorter the side chain (*i.e.* more water soluble ILs located in the lower right part of the plot) the higher the E_{NR} values. When considering different ILs with the same cation (IM14) the anions size plays a relevant role evidenced by the second component, in agreement with the positive contribution of the anionic size descriptors: the higher the PC2 score, the higher the E_{NR} value.



Figure 2. PC1 vs. PC2 scores plot reporting the ILs 1-18 together with y-response: this plot can show similarities and dissimilarities among the objects (ILs) and allows to interpret how they are related to the response (E_{NR} variable) along the 1st and the 2nd PLS components.

The above considerations show that the present QSPR approach, considering simultaneous variations in both the cation (heterocyclic core and side chain length) and the anion structural features by means of 176 ILs descriptors is able to provide an estimate of their importance and a tentative interpretation of their physico-chemical significance in relation to the polarity of ILs. It is perhaps worth mentioning here that attempted correlations with Kosower and Reichardt empirical solvent parameters were not satisfactory probably due to the ionic structure of the solvatochromic dyes which in solution with ILs implies the presence of two cations and two anions, a condition quite difficult to be modelled. A neutral "sensor" such as Nile Red simplifies the above picture rendering *in silico* modelling possible.

3. Conclusions

VolSurf+ descriptors, accounting for both cationic and anionic structural features of ILs were used to develop a PLS model able to establish a QSPR correlation with their solvatochromic dye Nile Red polarity. The PLS model allowing prediction of E_{NR} values provided an *in silico* ILs polarity database for over 100 ILs. The above database including structurally different ILs with similar polarity provides the possibility to select an optimal IL according not only to its polarity but also to other properties such as synthetic affordability, environmental sustainability in its life cycle and economic considerations. The same approach, using readily available descriptors and an accessible statistical procedure such as PLS, could be extended to develop QSPR models for other relevant ILs physico-chemical properties.

4. Experimental

4.1 Synthesis and characterization of ILs

[IM14][(1O)2PO2], was purchased and used without any other purification. [IM14][CF3COO] and [IM14][1COO] were obtained by anion exchange on resin starting from corresponding halide as following reported. All ionic liquids were dried on a vacuum line at 60 °C for at least 2 h before use, then stored in a dryer under argon and over calcium chloride. In all cases, the silver nitrate test performed to verify the presence of residual halide anion, gave a negative result.

4.1.1 General procedure for anion exchange on resin. The Amberlite resin IRA-400 (16 g) was converted from chloride form to hydroxide form by eluting an aqueous solution of NaOH (10 mL, 10% w/v) within a column. Subsequently the resin was washed with water until the eluate was neutral. The halide salt (10 mmol), dissolved in methanol/water (70/30, v/v), was eluted, and the eluate collected into a flask containing a solution of the corresponding acid in stoichiometric amount, until neutralization. The resulting solution was concentrated *in vacuo*, then treated with activated charcoal in ethanol. Filtration and removal of the solvent afforded the ionic liquids as viscous oils in high to quantitative yields.

1-Butyl-3-methylimidazolium trifluoroacetate ([IM14][CF3COO]).

Pale yellow oil. Yield: 94%.

v_{MAX} (Nujol) 3150, 3095, 2970, 2880, 1700 cm⁻¹

¹H NMR (300 MHz, d₆-DMSO): δ=9.34 (s, 1 H), 7.91 (d, *J*=24 Hz, 2 H), 4.33 (t, *J*=8 Hz, 2 H), 4.01 (s, 3H), 1.93 (quint, *J*=7.6 Hz, 2 H), 1.40 (quint, *J*=7.6 Hz, 2 H), 1.07 (t, *J*=7.6 Hz, 3 H) ppm. ¹³C NMR (300 MHz, d₆-DMSO): δ = 158.0, 139.4, 125.3, 122.1, 50.4, 37.1, 30.9, 30.2, 22.4, 17.6 ppm. 1-Butyl-3-methylimidazolium acetate. ([IM14][1COO]).

Pale yellow oil. Yield: 99%.

v_{MAX} (Nujol) 3150, 3095, 2970, 2880, 1700 cm⁻¹

¹H NMR (300 MHz, d₆-DMSO): δ=9.73 (s, 1 H), 7.88 (d, *J*=21 Hz, 2 H), 4.24 (t, *J*= 7.6 Hz, 2 H), 3.92 (s, 3 H), 1.82 (quint, *J*=7.5 Hz, 2 H), 1.64 (s, 3 H), 1.29 (quint, *J*=7 Hz, 2 H), 0.95 (t, *J*=7 Hz, 3 H) ppm. ¹³C NMR (300 MHz, d₆-DMSO) δ = 172.9, 137.4, 123.7, 122.4, 59.2, 48.5, 35.7, 25.9, 18.9, 13.4 ppm.

4.2 E_{NR} measurements

The determination of polarity parameter E_{NR} was carried out by mixing into a quartz cuvette (optical path 0.2 cm), 500 µL of IL and 75 µL of a concentrated solution of spectroscopic probe in 1,4-dioxane. The concentration of the probe was equal to $2.0 \cdot 10^{-4}$ M. The obtained solution was thermostated at 298 K.

4.3 Computational Methods

In VolSurf+, the GRID⁷ force field was chosen to characterize potential polar and hydrophobic interaction sites around target molecules by the water (OH2), the hydrophobic (DRY), the carbonyl oxygen (O) and amide nitrogen (N1) probes. The information contained in the resulting MIFs is transformed into a quantitative scale by calculating the volume or the surface of the interaction contours. In particular, the VolSurf+ procedure consists of the generation of the 3D molecular fields from the interactions of the OH2, DRY, O and N1 probes around a target molecule, next the calculation of descriptors from the 3D maps obtained in the first step. The definition of all 128 VolSurf+ descriptors is given in case studies^{5,14,15,39-45} and with the previous versions of VolSurf.⁴⁶⁻⁴⁹ By adopting the procedure already reported in a recent QSAR work¹⁶ 176 *in silico* molecular descriptors for cations and anions (128 and 48 respectively) were calculated and here used as the X-matrix in a correlation model in which the E_{NR} values are used as the Y-responses by means of partial least squares model.

The Partial Least Squares Projections to Latent Structures" (PLS)⁵⁰ chemometric tool, available in the SIMCA Software package,³⁴ was adopted.

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