Chemical Engineering Journal 175 (2011) 17–23

Contents lists available at SciVerse ScienceDirect

Chemical Engineering Journal

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

Theoretical descriptor for the correlation of aquatic toxicity of ionic liquids by quantitative structure–toxicity relationships

S. Bruzzone[a,*], C. Chiappe[a], S.E. Focardi[b], C. Pretti[c], M. Renzi[d]

[a] Dipartimento di Chimica e Chimica Industriale, Università di Pisa, Via Bonanno 33, 56126 Pisa, Italy
[b] Dipartimento di Scienze Ambientali, Università di Siena, Via Mattioli 4, 53100 Siena, Italy
[c] Dipartimento di Patologia Animale, Profilassi ed Igiene degli Alimenti, Università di Pisa, Viale delle Piagge 2, 56127 Pisa, Italy
[d] Centro Ricerche di Ecologia Lagunare Pesca ed Acquacoltura, Polo Universitario Grossetano, via lungolago dei pescatori sn, Orbetello, GR, Italy

ARTICLE INFO

Article history:
Received 25 February 2011
Received in revised form 22 July 2011
Accepted 24 August 2011

Keywords:
Ionic liquid
Toxicity
Vibrio fischeri
QSAR
Polarizable continuum model

ABSTRACT

Quantitative structure–toxicity relationships were developed for the prediction of toxicity to *Vibrio fischeri* using the CODESSA treatment. A four-parameter correlation was found for a class of ionic liquids based on halide. All the descriptors utilized are calculated only from the structures of the molecules, which makes it possible to predict unavailable or unknown ILs, in gas phase and in water (PCM treatment). Satisfactory correlations with the same descriptors were found for both cases but the employment of descriptors calculated in solvent assure a better correlation and a bigger reliability on the foresight.

1. Introduction

Ionic liquids (ILs) represent a heterogeneous class of compounds liquid at or near room temperature which are generally composed by an organic cation and a polyatomic anion (inorganic or organic). Today ionic liquids constitute one of the hottest areas in chemistry as a promising field for the development of environmental friendly technologies. The interesting features of ILs include a negligible vapour pressure, excellent and adjustable solvation power for organic, inorganic and polymeric compounds, non-flammability, high thermal and electrochemical stability [39,44,15,17]. Also, the physical properties of ILs can be tailored to a specific task by a variation in the anion–cation combination, or, often, in a partial variation of cation structure [6,16]. This characteristic makes them "designer solvents", versatile as reaction media for synthesis, separation and electrochemical processes, catalysis and biocatalysis [42,26,32,31]. Although ILs are considered as "green solvent" in virtue of their negligible vapour pressure, which resets the risk of air pollution, they have significant solubility in water [30,37,11,12,35] and then are potentially pollutants through degradation or persistence in the environment. For this reason, before a wide use in industrial applications can be realized, the evaluation of the risks arising by possible (eco)toxicity is necessary in order to evaluate the environmental sustainability. Due to the extremely large number of possible ionic liquids [23], it would be highly desirable to develop computational schemes able to forecast with sufficient precision the environmental impact of new (or not yet synthesized) liquids [45,20], with no or reduced need for laboratory testing on living organisms; such development has been devised not only by scientific purposes, but even by environmental policy European laws such as the REACH [7]. Toxicity estimation of chemical species, as any effect of molecular species on complex living beings, is usually afforded with the help of multivariable statistical analysis, through the so-called quantitative structure–activity relationships (QSAR) [9,24,1,43]. The QSAR model is able to establish mathematically a quantitative connection between the chemical, physicochemical or biological activity of a given molecule and a limited set of molecular properties (structural, electronic, thermochemical, etc.), said descriptors, which can be obtained observing the molecular structure or using *ab initio* or semiempirical quantum-mechanical calculations; in this way, the model has a twofold utility. First, it allows the prediction of activity for molecules not already synthesized, or for which no (toxic) effect data are available. Second, it helps in understanding the mechanisms regulating the toxicity of a given molecular set or on a given biological sample, by expressing the same toxicity in terms of well-defined molecular properties, giving thus a powerful and intuitive tool for the rational synthetic design of low toxicity molecules. For what concerns ionic liquids, QSAR have been extensively used to predict physical properties such as partition coefficients of organic compounds in

* Corresponding author.
E-mail address: sama@dcci.unipi.it (S. Bruzzone).

1385-8947/$ – see front matter © 2011 Elsevier B.V. All rights reserved.
doi:10.1016/j.cej.2011.08.073

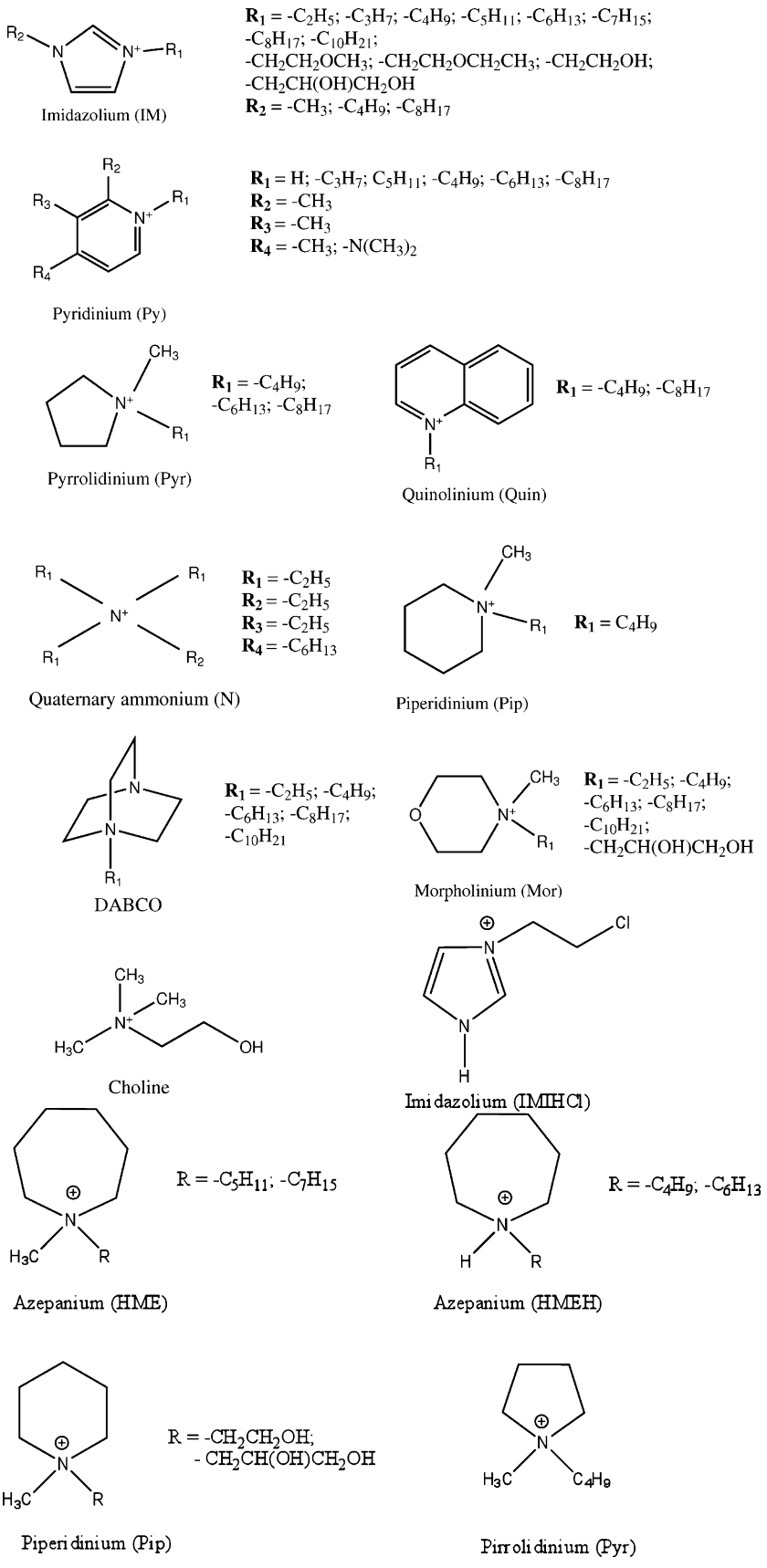

Fig. 1. Cationic structures as reported in Tables 3 and 5.

ILs [36], boiling [23] or melting point [27,46], vapour pressure [14], solubilities in various solvents [35] and viscosity and conductivity [4]. In the field of biological activity, an increasing number of experimental works have been developed in last years relating the biological action on enzyme, bacteria, algae, invertebrates, vertebrates and cells of ILs [43,8,21,29,28]. Concerning ionic liquids, few papers have faced the amount of experimental data on *V. fischeri* using QSAR model. Luis et al. [29,28] brought a group contribution method that considers three main groups of descriptors in the ionic liquid structure: the anion, the cation and the substitutions (carbon chains linked to the cation). Each group is represented by boolean contribution related to the molecular structure. In this work we proposed a QSAR model, performed using the CODESSA software package, based on descriptors calculated for the cations only, previous optimized *ab initio* in gas phase (i.e. as isolated molecule) and in water. The aim is to understand the mechanism of toxicity of ILs to a model organism, assuming that anions play a secondary role in determining toxicity [8] (Fig. 1).

2. Materials and methods

In order to develop the QSAR, a database of EC_{50} (μM Log_{10}-transformed data) for ionic liquids has been obtained from experiments and literature [34,29,40,8]. As showed by [22], the different commercial assays ToxAlert10® luminometer system (Merck), Microtox® acute toxicity system, (Strategic Diagnostics Inc.) and LUMIStox Acute Toxicity system (Dr. B. Lange) give almost identical results. Also, [38] recalled that the EC_{50} values for a specific chemical usually does not exhibit significant differences with exposure time. For these reasons, the QSAR training set includes 15- and 30-min incubation EC_{50} values without respect to the method. All data are referred to ILs with chloride or bromide anion, since it is possible to consider the contribution to toxicity of these anions almost negligible and however comparable. Experimental data were obtained for 5 1,4-diazabicyclooctane- (DABCO)- and 6 morpholinium-based ILs having bromide as counter anion, prepared using a standard procedure [5,3] alkylation of DABCO and methylmorpholine was performed using the proper alkyl bromide in ethyl acetate. In the case of DABCO-derivatives, temperature and DABCO-alkyl bromide ratio were carefully controlled to avoid the formation of the dialkylation product. The hazard assessment on aquatic environment of the all ILs was estimated using the standard Microtox® Acute Toxicity test system, determining the effective concentration at 50% to the *V. fischeri*.

The Microtox® Test was performed according to standard operating procedure using the Basic protocol (Azur Environmental, 1995), based on the ISO procedures [18]. The bacteria (*V. fischeri*) were obtained from Ecotox LDS (Pregnana Milanese, MI, Italy) as freeze-lyophilized cells. Bacteria were exposed to a dilution series of the sample and their light emission was determined after incubation. The light emission of the bacteria in the samples was measured after 5, 15 and 30 min and compared to an aqueous control. The tests were performed at 15° (pH 6–8,operative range) and with three replicates and four controls. All measurements were performed by using the M500 luminometer equipped with the appropriate cells. The instrument is interfaced with PC operating with the Microtox® Omni 1.16 software, for acquisition and data handling. Phenol was used as the positive toxicity control for the Microtox assay. EC_{50} values, expressed as Log_{10} ($EC_{50}/\mu M$) were reported as the means of three replicate determinations ± standard deviation.

2.1. Calculations

The molecular structure of the cations in the data set (Table 3) have been optimized and their electronic, geometric, and energetic parameters as isolated molecules and in water have been calculated *ab initio* with Gaussian 03 package [19]. The cations were optimized and their vibrational frequencies calculated at the DFT level relying on the B3LYP functional. Partial atomic charges were calculated using the Natural Bond Orbital method as implemented in Gaussian. After optimization, the CODESSA program was used to calculate five types of molecular descriptors (constitutional, topological, geometrical, electrostatic, and quantum chemical) and to derive correlations between each descriptor and the toxicity data. The determination of the descriptors has been carried out both in gas phase and in solution. In this latter case, the surrounding effects have been included by means of the well-recognized polarizable continuum model (IEF-PCM), in which the solute part (the cation) is lying inside a cavity, and the solvent is represented as a structureless material, characterized by its macroscopic properties. The heuristic procedure was used to obtain quantitative structure–property relationship. Before derivation of QSPRs, the method selects descriptors that correlate poorly with the property data, ill-defined descriptors for some compounds and descriptors intercorrelating with other descriptors; these selected descriptors are discarded for the calculations of QSPRs. Up to 342 descriptors, depending on the nature of the molecule, were calculated for each structure in the set. With the heuristic method, elimination of ill-defined, inter-correlated and poorly correlated descriptors led to a set of about 120 descriptors. For each QSPR the correlation coefficient (R^2), the Fisher significance parameter (F), the crossvalidated correlation coefficient calculated using a leave-one-out method (R^2_{cv}) and the corrected mean square error ($s2$) were determined.

3. Results and discussion

The property analysed is the toxicity towards *V. fischeri* of 33 ILs which joins 18 ILs for which the EC_{50} value have been determinated in our laboratory. The training set is composed by almost all the ILs (33 structures), based on halide as anion, for which the *V. fischeri* EC_{50} is available in literature. Some data for others ILs with halide anion are not considered in this paper due to the relative structural complexity of the cations: a too long alkyl chain makes problematic the *ab initio* optimization in solvent. Instead, between the ILs considered, there are imidazolium and pyridinium cations bearing not only linear alkyl chains (until 10 C atoms) but different functional group (alcohol and ethers) too and, in general, the whole set of 33 ILs is composed by ILs based on imidazolium (12), pyridinium (6), morpholinium (6), DABCO (5), pyrrolidinium and piperidinium (1), ammonium (1) and cholinium (1) salts. The set variety can be afforded because the correlation method tries to combine the toxicity, which is expression of molecular mechanisms and not a macroscopical behaviour, with some molecular properties. Also, in the calculation, it is not made a prior choice of descriptors, as in some papers on the argument [8,29], but the mathematical method performs an analysis on several intrinsic molecular properties available from the Gaussian output. We performed correlations for a growing number of descriptors in the range from 1 to 8. Plots of R2 values against the number of descriptors (Fig. 3), together with analysis of the relative importance of further descriptors in the QSPRs (Tables 1 and 2), can provide some indications about the number of descriptors adequate to describe the model. The main correlations of toxicity are reported in Tables 1 and 2 with descriptors calculated from optimizations of cations respectively in gas phase and in water. The models based on the same number of descriptors in the two cases, gas phase and in solvent, present almost the same descriptors too. Then, it is evident that the PCM *ab initio* optimizations in water are not necessary in order to understand the molecular properties

Table 1
Correlations of toxicity to *V. fischeri* by the heuristic method. In gas phase.

♯P	R^2	R^2_{cv}	F	X+DX	t-Test	Descriptors
1	0.7454	0.7168	90.89	8.6720e+00 5.9092e−01	14.6755	Intercept
				−8.8446e−02 9.2770e−03	−9.5339	XY Shadow
				−1.6513e−02 1.3189e−03	−12.5207	WPSA-1
				6.2290e−01 1.1676e−01	5.3350	LUMO+1 energy
				−2.4603e−03 1.9354e−04	−12.7122	WPSA-2
				5.9354e−01 1.1757e−01	5.0483	LUMO+1 energy
				1.2532e+00 4.9629e−01	2.5252	Max atomic+orbital electronic population
				−1.6956e−02 1.1766e−03	−14.4105	WPSA-1 [Zefirov's PC]
				4.9811e−01 1.0459e−01	4.7626	LUMO+1 energy
				1.9882e+00 5.3019e−01	3.7500	Max at. orb. elec. pop.
				−3.7889e+00 1.2662e+00	−2.9923	Min net at. charge for a C atom

influencing the toxicity, but, as will be explained later, taking into account the solvent presence in the *ab initio* calculation provides a better correlation and, as a consequence, bigger reliability on the foresight (Table 3). The most efficient correlation have been further cross-validated by dividing the dataset of experimental toxicities into three groups, based on their chemical nature. Recombining two of the subsets and calculating the toxicity for the third subset gave a correlation coefficient of 0.9123, 0.9034 and 0.9118, respectively.

In the four descriptors models, summary in Tables 1 and 2, the most important descriptor is the minimum net atomic charge for a C atom: this represent the electrostatic interactions and plays a key role in the solvation. Actually, the relative coefficient of this descriptor calculated in water is slightly bigger than the one obtained in gas phase. In both cases, the minimum net atomic charge for all the structures of chemicals considered is localized on the terminal methyl carbon of lateral chain. A similar meaning is related to surface weighted charged partial positive surface area WPSA-1 (Zefirof's PC), descriptor equal to atomic charge weighted partial positive surface area (PPSA1) multiplied by total molecular surface area (TMSA). These two descriptors all have negative coefficient in the linear model, which indicates that the EC_{50} is inversely proportional to them and, consequently, there is a direct proportionality with the toxicity. Because the values of both descriptors are strongly related to the branched chain length, our result fits with the frequent observation [40,8,10,25,33,13,41] that ionic liquid toxicity to *V. fischeri* is linked with the cation branching. In particular, it has been repeatedly observed that lipophilic part of the molecules can be intercalated into the membrane, whereas their ionic head group is at least partially solvated in the aqueous solution [2]. Thus, it appears physically reasonable that a minor (absolute) negative charge on the terminal carbon lateral chain, lowering the dipole moment, lowers the overall polarity of the cation also. The lower is the polarity, the greater is the affinity for the lipidic cellular membrane and the possibility to intercalate and get in the cell. So, the lower the absolute charge, the higher is the toxicity (Fig. 2). It has to be underlined that the importance of positive accessible surface area such as PPSA and DPSA has been already recognized in recent years [8] despite in this work electronic calculation were performed at a semiempirical level (Fig. 3).

The others descriptors have quantum mechanical nature: the maximum atomic orbital electronic population, which reflects the concentration of the electron density at a particular atom and the *LUMO*+1 energy, which parameterize the affinity for electrons. The maximum atomic orbital electronic population is a simplified index to describe the nucleophilicity of the molecule and could be interpreted as its ability to undergo oxidation and start degenerative metabolic processes. The virtual orbital energy as calculated by density functional theory may not be a good measure of the electron affinity because the orbital is not occupied; it is well known that a virtual orbital relaxes to a lower energy level when it is occupied and a new, self-consistent wavefunction is calculated. Employment of virtual orbital energies in QSARs may be successful because the amount of orbital relaxation is similar for chemically similar species. The positive coefficients obtained for energy LUMO+1 (i.e. toxicity increases as energy LUMO+1 decreases) are

Table 2
Correlations of toxicity to *V. fischeri* by the heuristic method. In solvent.

♯P	R^2	R^2_{cv}	F	X+DX	t-Test	Descriptors
1	0.7648	0.7386	100.8	8.7566e+00 5.6967e−01	15.3713	Intercept
				−9.0135e−02 8.9773e−03	−10.0404	XY Shadow
				−1.5971e−02 1.2748e−03	−12.5275	WPSA-1
				6.7882e−01 1.2393e−01	5.4777	LUMO+1 energy
				−1.5573e−01 1.2726e−02	−12.2372	WPSA-3
				8.8189e+00 1.3402e+00	6.5803	FPSA-2
				−5.9261e+01 1.8957e+01	−3.1261	Min part. charge for a C atom [Zefirov's PC]
				−1.6720e−02 1.0432e−03	−16.0282	WPSA-1 [Zefirov's PC]
				5.3667e−01 1.0166e−01	5.2792	LUMO+1 energy
				2.0912e+00 4.5463e−01	4.5997	Max at. orb. elec. pop.
				−4.3925e+00 1.1325e+00	−3.8785	Min net at. charge for a C atom

Table 3
Toxicity of ILs to *V. fischeri*.

Compound	$Log_{10}EC_{50}$ (μM)		
	Experimental	Calc. in gas phase	Calc. in water
IM12	4.55[a]	4.3117	4.3998
IM14	3.71[b]	3.5373	3.4765
IM16	1.94[a]	2.5198	2.4935
IM18	0.63[b]	1.1461	1.1869
IM1-10	0.50[c]	0.1033	0.0896
IM11O2	4.01[d]	4.5324	4.6395
IM12O1	4.18[d]	3.5822	3.6125
IM12O2	4.28[d]	3.9784	4.2331
IM12OH	3.89[e]	4.1719	4.1404
IM1GLY	4.69[e]	3.8052	3.9637
IM4GLY	4.52[e]	3.4843	3.5346
IM8GLY	0.49[e]	1.2165	0.9271
Py4	3.41[b]	3.2673	3.3078
Py4-3Me	2.75[b]	3.0485	2.9961
Py4-35Me	2.69[b]	2.7044	2.6713
Py4-4NMe2	2.52[d]	2.7845	2.6300
Py6-3Me	2.06[b]	2.1048	2.0648
Py8-3Me	0.79[b]	0.8341	0.7766
Pyr16	2.99[a]	3.0684	3.0069
Mor12	5.20[e]	5.6140	5.6714
Mor14	4.70[e]	4.6715	4.6732
Mor16	3.95[e]	3.7221	3.7419
Mor18	2.40[e]	2.4186	2.4306
Mor1-10	1.35[e]	1.1020	1.2154
Mor1GLY	3.23[e]	4.4703	4.3575
Pip14	4.27[d]	3.8762	3.7721
DABCO12	5.60[x]	5.3905	5.4653
DABCO14	4.85[e]	4.4754	4.4706
DABCO16	3.70[e]	3.5234	3.5303
DABCO18	2.30[e]	2.4814	2.4555
DABCO1-10	1.30[e]	1.2049	1.2382
N2226	2.46[b]	2.8013	2.6048
Choline	5.00[b]	5.1539	5.1227
IM13	–	3.9170	3.9931
IM15	–	2.8232	2.9248
IM17	–	1.7121	1.8912
IM13O1	–	3.4818	3.4285
IM13OH	–	4.2569	4.2255
Py	–	3.1017	3.1988
Py2	–	3.9061	3.9514
Py3	–	3.5021	3.5705
Py5	–	2.7679	2.8354
Py6	–	2.2920	2.2811
Py8	–	1.1552	1.1882
Py4-2Me	–	3.1974	3.1357
Py6-4Me	–	2.1229	1.8520
Py8-4Me	–	0.7804	0.6719
Pyr14	–	4.0147	3.9411
Pyr18	–	2.0354	1.9526
Quin4	–	3.0962	2.8913
Quin8	–	1.1953	0.9813

[a] Ref. [29].
[b] Ref. [8].
[c] Ref. [34].
[d] Ref. [40].
[e] From this work.

consistent with the notion that electrophilicity is an important factor determining the relative ease at which molecules undergo reductive metabolic transformation and free radical generation. Both these quantum mechanical descriptors could be considered as representations of mechanisms through which to express the toxic action. The main differences between the four descriptors models obtained starting by *ab initio* calculations in gas phase and in water concerns the correlation coefficients R^2, which, as reported in Tables 1 and 2, are respectively 0.9017 and 0.9209. Both the correlations are satisfying (Fig. 4). Indeed, the calculated values of EC_{50}, presented in Table 3, are well in agreement with the experimental data, mostly for ILs slightly toxic. The same behaviour shown by R^2, such as the value in gas phase is less than the one in

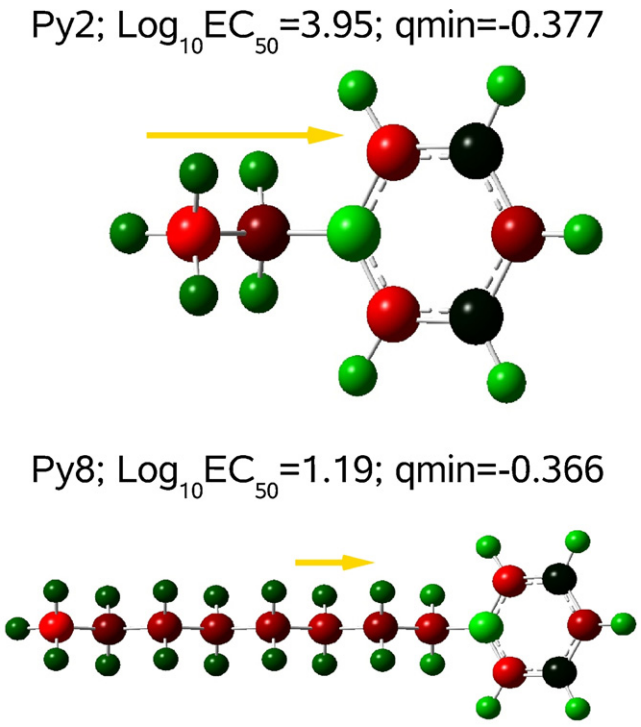

Fig. 2. Graphical representation of "minimum net atomic charge" descriptor: longer alkyl chain corresponds to a lower (in absolute value) charge on the terminal methyl group and subsequentially in a lower dipole moment $\vec{p}$. Green nuclei have positive charge while red nuclei have negative charge; a lighter color corresponds to a higher absolute value of the charge. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

solvent, is followed by R^2CV (0.8563 versus 0.8842), the cross-validated correlation coefficient, a characteristic of the predictive power of the correlation equation. The differences between the values of EC_{50} calculated (in gas phase and in water) and experimental are reported in Table 4 and graphically shown in Fig. 5. Our conclusion is that, in order to quantitatively predict the toxicity of ILs not yet synthesized or not studied, the present method requires preliminary calculations carried out taking into account the solvent effect. The correlations obtained were tested in order to assess their predictive power towards new or untested ionic liquids. A new data set comprising 10 structures (none of which present in the training data set) was built, their structures calculated both in vacuo

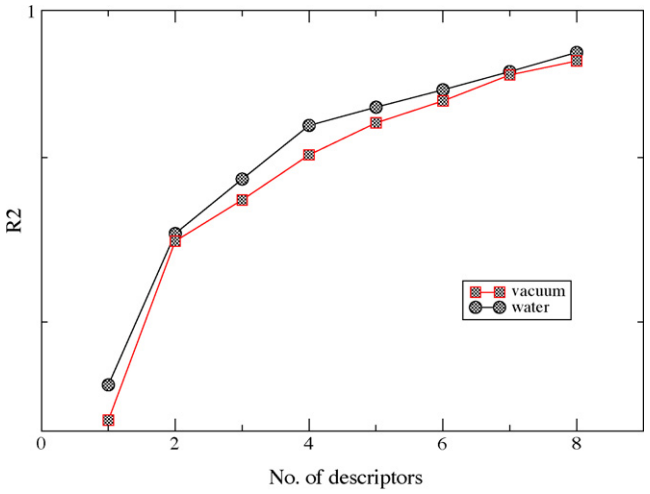

Fig. 3. Plot of R2 in gas phase (squares) and in water (circles) against the number of descriptors for $Log_{10}EC_{50}$ QSPR analysis.

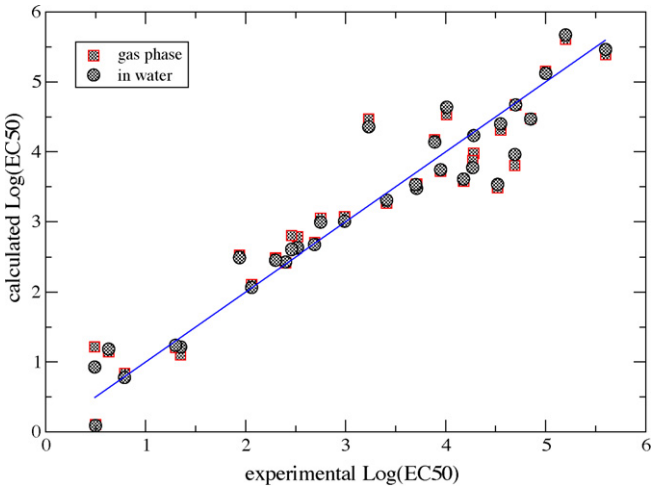

Fig. 4. Calculated versus experimental $Log_{10}EC_{50}$ in the four descriptors models. Descriptors calculated in gas phase (squares) and in water (circles).

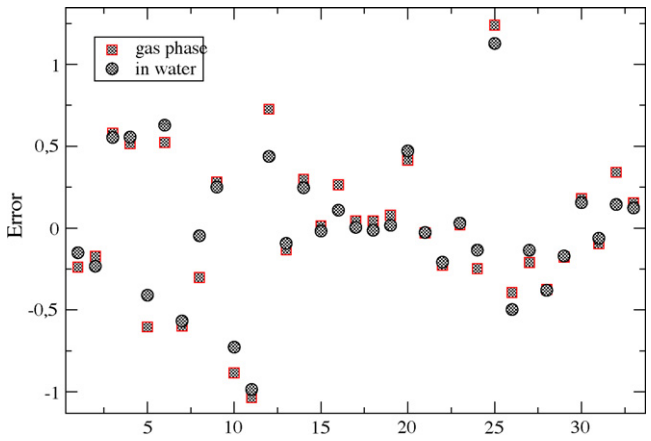

Fig. 5. Differences between $Log_{10}EC_{50}$ calculated by QSPR analysis according to correlation 4 and $Log_{10}EC_{50}$ experimental as reported in Table 4. Descriptors calculated in gas phase (squares) and in water (circles). In abscissa, the compound identity number is reported.

Table 4
Calculated error on toxicity of ILs to *V. fischeri*.

Compound	Error	
	In gas phase	In water
IM12	−0.2383	−0.1502
IM14	−0.1727	−0.2335
IM16	0.5798	0.5535
IM18	0.5161	0.5569
IM1-10	−0.6033	−0.4104
IM11O2	0.5224	0.6295
IM12O1	−0.5978	−0.5675
IM12O2	−0.3016	−0.0469
IM12OH	0.2819	0.2504
IM1GLY	−0.8848	−0.7263
IM4GLY	−1.0357	−0.9854
IM8GLY	0.7265	0.4371
Py4	−0.1327	−0.0922
Py4-3Me	0.2985	0.2461
Py4-35Me	0.0144	−0.0187
Py4-NMe2	0.2645	0.1100
Py6-3Me	0.0448	0.0048
Py8-3Me	0.0441	−0.0134
Pyr16	0.0784	0.0169
Mor12	0.4140	0.4714
Mor14	−0.0285	−0.0268
Mor16	−0.2279	−0.2081
Mor18	0.0186	0.0306
Mor1-10	−0.2480	−0.1346
Mor1GLY	1.2403	1.1275
Pip14	−0.3938	−0.4979
DABCO12	−0.2095	−0.1347
DABCO14	−0.3746	−0.3794
DABCO16	−0.1766	−0.1697
DABCO18	0.1814	0.1555
DABCO1-10	−0.0951	−0.0618
N2226	0.3413	0.1448
Choline	0.1539	0.1227

Table 5
Toxicity of external set ILs to *V. fischeri*.

Compound	$Log_{10}EC_{50}$ (μM)		
	Experimental	Calc. in gas phase	Calc. in water
HME15	3.2000	3.738	2.634
HME17	2.1200	1.542	1.507
HMEH4	3.9400	3.335	3.500
HMEH6	2.6900	2.291	2.519
IMHCL	4.6200	4.525	4.546
PIP1E	4.3300	4.637	4.503
PIP1G	4.4200	4.683	4.540
PYR14	4.3800	4.014	4.522
PYR1G	4.0600	4.912	4.803

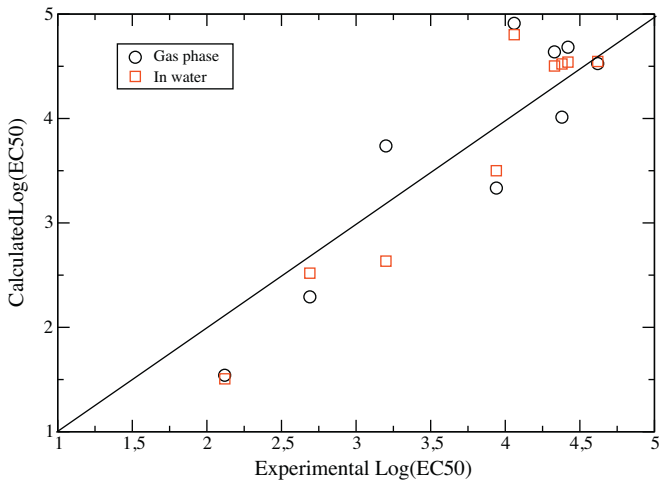

Fig. 6. Calculated versus experimental $Log_{10}EC_{50}$ in the four descriptors models for the external set used for validation. Descriptors calculated in gas phase (circles) and in water (squares).

and in solution, and their descriptors used to set up the correlation. The results obtained are shown in Table 5. The EC_{50} values have been predicted with an average error of 11.63% when using the correlation obtained from gas-phase calculations, while an average error of 9.41% is obtained from the correlation obtained by the solution calculations. Such result is remarkable, due to the fact that the external set of ionic liquids is composed by species that are not belonging to chemical families present already in the training set. This test shows that, even for an external dataset, the model is able to predict the correct order of magnitude for the toxicity (Fig. 6).

4. Conclusions

We have presented QSAR for the aquatic toxicity of a broad set of ILs, where the cations always are accompanied by a halide anion (Cl or Br). The studied cations belong to several family of ILs, so that the developed correlations can be applied to large number of ILs. Also, according to the literature, ionic liquids with the same cation and different anions do not show any statistical difference in toxicity [34]; thereby our model could in principle be applied to a still

broader range of ILs with different anions. The method employed requires the optimization and the calculation of vibrational frequencies and partial atomic charges for each cation considered. All these properties are searched at *ab initio* DFT level, for a single isolated molecule in gas phase and in water solution. The correlations obtained building up more than 300 descriptors by these *ab initio* calculations are satisfactory, but the model based on the properties in water gives an higher correlation coefficient R^2 and ensures a better predictive power. The most important descriptors founded in both correlations are a measurement of interaction between ions, solvent and biological cell membrane and appear physically sound.

Acknowledgement

University of Pisa is gratefully acknowledged for financial support for this work.

References

[1] J. Arning, S. Stolte, A. Baschen, F. Stock, W.R. Pitner, U. Welz-Biermann, B. Jastorff, J. Ranke, Qualitative and quantitative structure activity relationships for the inhibitory effects of cationic head groups, functionalised side chains and anions of ionic liquids on acetylcholinesterase, Green Chem. 10 (2008) 47–58.
[2] R.P. Austin, P. Barton, A.M. Davis, C.N. Manners, M.C. Stansfield, The effect of ionic strength on liposome-buffer and 1-octanol-buffer distribution coefficients, J. Pharm. Sci. 87 (1998) 599–607.
[3] R. Bini, O. Bortolini, C. Chiappe, D. Pieraccini, T. Siciliano, Development of cation/anion "interaction" scales for ionic liquids through esi-ms measurements, J. Phys. Chem. B 111 (2007) 598–604.
[4] R. Bini, M. Malvaldi, W.R. Pitner, C. Chiappe, Qspr correlation for conductivities and viscosities of low-temperature melting ionic liquids, J. Phys. Org. Chem. 21 (2008) 622–629.
[5] C. Chiappe, B. Melai, A. Sanzone, G. Valentini, Basic ionic liquids based on monoquaternized 1,4-diazobicyclo[2.2.2]octane (dabco) and dicyanamide anion: physicochemical and solvent properties, Pure Appl. Chem. 81 (2009) 2035–2043.
[6] C. Chiappe, D. Pieraccini, Ionic liquids: solvent properties and organic reactivity, J. Phys. Org. Chem. 18 (2005) 275–287.
[7] European Community, European Community Regulation on Registration, Evaluation, Authorisation and Restriction of Chemicals.
[8] D.J. Couling, R.J. Bernot, K.M. Docherty, J.K. Dixon, E.J. Maginn, Effects of different head groups and functionalised side chains on the aquatic toxicity of ionic liquids, Green Chem. 8 (2006) 82–90.
[9] J. Devillers, P. Chambon, Acute toxicity and qsar of chlorophenols on daphnia magna, Bull. Environ. Contam. Toxicol. 37 (1986) 599–605.
[10] K.M. Docherty, C.F. Kulpa Jr., Toxicity and antimicrobial activity of imidazolium and pyridinium ionic liquids, Green Chem. 7 (2005) 185–189.
[11] U. Domanska, A. Rekawek, A. Marciniak, Solubility of 1-alkyl-3-ethylimidazolium-based ionic liquids in water and 1-octanol, J. Chem. Eng. Data 53 (2008) 1126–1132.
[12] M.G. Freire, P.J. Carvalho, A.M.S. Silva, L.M.N.B.F. Santos, L.P.N. Rebelo, I.M. Marrucho, J.A.P. Coutinho, Ion specific effects on the mutual solubilities of water and hydrophobic ionic liquids, J. Phys. Chem. B 113 (2009) 202–211.
[13] M.T. Garcia, N. Gathergood, P.J. Scammells, Biodegradable ionic liquids part ii. effect of the anion and toxicology, Green Chem. 7 (2005) 9–14.
[14] R.L. Gardas, J.A.P. Coutinho, Applying a qspr correlation to the prediction of surface tensions of ionic liquids, Fluid Phase Equilib. 265 (2008) 57–65.
[15] A. Heintz, Recent developments in thermodynamics and thermophysics of non-aqueous mixtures containing ionic liquids. A review, J. Chem. Thermodyn. 37 (2005) 525–536.
[16] J.G. Huddleston, A.E. Visser, W.M. Reichert, H.D. Willauer, G.A. Broker, R.D. Rogers, Characterization and comparison of hydrophilic and hydrophobic room temperature ionic liquids incorporating the imidazolium cation, Green Chem. 3 (2001) 156–164.
[17] C.L. Hussey, Room temperature haloaluminate ionic liquids. Novel solvents for transition metal solution chemistry, Pure Appl. Chem. 60 (1988) 1763–1772.
[18] ISO11348-3, 2007. Water quality. determination of the inhibitory effect of water samples on the light emission of *Vibrio fischeri* (luminescent bacteria test). Part 3: method using freeze-dried bacteria.
[19] M.J. Frisch, et al., in: Gaussian 03 (Revision A.1), Gaussian, Inc., Pittsburgh, PA, 2003.
[20] B. Jastorff, K. Molter, P. Behrend, U. Bottin-Weber, J. Filser, A. Heimers, B. Ondruschka, J. Ranke, M. Schaefer, H. Schroder, A. Stark, P. Stepnowski, F. Stock, R. Stormann, S. Stolte, U. Welz-Biermann, S. Ziegerta, J. Thominga, Progress in evaluation of risk potential of ionic liquids basis for an eco-design of sustainable products, Green Chem. 7 (2005) 362–372.
[21] B. Jastorff, R. Stormann, J. Ranke, K. Molter, F. Stock, B. Oberheitmann, W. Hoffmann, J. Hoffmann, M. Nuchter, B. Ondruschka, J. Filser, How hazardous are ionic liquids? Structure–activity relationships and biological testing as important elements for sustainability evaluation, Green Chem. 5 (2003) 136–142.
[22] V.L.K. Jennings, M.H. Rayner-Brandes, D.J. Bird, Assensing chemical toxicity with the bioluminescent photobacterium (*Vibrio fischeri*): a comparison of three commercial systems, Water Res. 35 (2001) 3448–3456.
[23] A.R. Katritzky, R. Jain, A. Lomaka, R. Petrukhin, M. Karelson, A.E. Visser, R.D. Rogers, Correlation of the melting points of potential ionic liquids (imidazolium bromides and benzimidazolium bromides) using the codessa program, J. Chem. Inf. Comput. Sci. 42 (2002) 225–231.
[24] A.R. Katritzky, D.B. Tatham, Theoretical descriptors for the correlation of aquatic toxicity of environmental pollutants by quantitative structure–toxicity relationships, J. Chem. Inf. Comput. Sci. 41 (2001) 1162–1176.
[25] A. Latala, P. Stepnowski, M. Nedzi, W. Mrozik, Marine toxicity assessment of imidazolium ionic liquids: acute effects on the baltic algae *Oocystis submarina* and *Cyclotella meneghiniana*, Aquat. Toxicol. 73 (2005) 91–98.
[26] H. Liu, Y. Liu, J. Li, Ionic liquids in surface electrochemistry, Phys. Chem. Chem. Phys. 12 (2010) 1685–1697.
[27] I. Lopez-Martin, E. Burello, P.N. Davey, K.R. Seddon, G. Rothenberg, Anion and cation effects on imidazolium salt melting points: a descriptor modelling study, ChemPhysChem 8 (2007) 690–695.
[28] P. Luis, A. Garea, A. Irabien, Quantitative structure–activity relationships (qsars) to estimate ionic liquids ecotoxicity ec50 (*Vibrio fischeri*), J. Mol. Liq. 152 (2010) 28–33.
[29] P. Luis, I. Ortiz, R. Aldaco, A. Irabien, A novel group contribution method in the development of a qsar for predicting the toxicity (*Vibrio fischeri* ec50) of ionic liquids, Ecotoxicol. Environ. Saf. 67 (2007) 423–429.
[30] J. McFarlane, W.B. Ridenour, H. Lou, R.D. Hunt, D.W. Depaoli, R.X. Ren, Room temperature ionic liquids for separating organics from produced water, Sep. Sci. Technol. 40 (2005) 1245–1265.
[31] M. Moniruzzaman, K. Nakashima, N. Kamiya, M. Goto, Recent advances of enzymatic reactions in ionic liquids, Biochem. Eng. J. 48 (2010) 295–314.
[32] S.V. Muginova, A.Z. Galimova, A.E. Polyakov, T.N. Shekhovtsova, Ionic liquids in enzymatic catalysis and biochemical methods of analysis: capabilities and prospects, J. Anal. Chem. 65 (2010) 331–351.
[33] J. Pernak, K. Sobaszkiewicz, I. Mirska, Anti-microbial activities of ionic liquids, Green Chem. 5 (2003) 52–56.
[34] J. Ranke, K. Molter, F. Stock, U. Bottin-Weber, J. Poczobutt, J. Hoffmann, B. Ondruschka, J. Filser, B. Jastorff, Biological effects of imidazolium ionic liquids with varying chain lengths in acute *Vibrio fischeri* and wst-1 cell viability assays, Ecotoxicol. Environ. Saf. 58 (2004) 396–404.
[35] J. Ranke, A. Othman, P. Fan, A. Muller, Explaining ionic liquid water solubility in terms of cation and anion hydrophobicity, Int. J. Mol. Sci. 10 (2009) 1271–1289.
[36] A.L. Revelli, F. Mutelet, J.N. Jaubert, Prediction of partition coefficients of organic compounds in ionic liquids: use of a linear solvation energy relationship with parameters calculated through a group contribution method, Ind. Eng. Chem. Res. 49 (2010) 3883–3892.
[37] L. Ropel, L.S. Belvèze, S.N.V.K. Aki, M.A. Stadtherr, J.F. Brennecke, Octanol–water partition coefficients of imidazolium-based ionic liquids, Green Chem. 7 (2005) 83–90.
[38] T.W. Schultz, M.T.D. Cronin, T.I. Netzeva, The present status of qsar in toxicology, J. Mol. Struct. Theochem. 622 (2003) 23–38.
[39] R.A. Sheldon, Green solvents for sustainable organic synthesis: state of the art, Green Chem. 7 (2005) 267–278.
[40] S. Stolte, M. Matzke, J. Arning, A. Boschen, W.R. Pitner, U. Welz-Biermann, B. Jastorff, J. Ranke, Effects of different head groups and functionalised side chains on the aquatic toxicity of ionic liquids, Green Chem. 9 (2007) 1170–1179.
[41] R.P. Swatloski, J.D. Holbrey, S.B. Memon, G.A. Caldwell, K.A. Caldwell, R.D. Rogers, Using *Caenorhabditis elegans* to probe toxicity of 1-alkyl-3-methylimidazolium chloride based ionic liquids, Chem. Commun. 6 (2004) 668–669.
[42] T. Torimoto, T. Tsuda, K. Okazaki, S. Kuwabata, New frontiers in materials science opened by ionic liquids, Adv. Mater. 22 (2010) 1196–1221.
[43] J.S. Torrecilla, J. Garcia, E. Rojo, F. Rodriguez, Estimation of toxicity of ionic liquids in leukemia rat cell line and acetylcholinesterase enzyme by principal component analysis, neural networks and multiple lineal regressions, J. Hazard. Mater. 164 (2009) 182–194.
[44] T. Welton, Room-temperature ionic liquids. Solvents for synthesis and catalysis, Chem. Rev. 99 (1999) 2071–2084.
[45] N. Wood, G. Stephens, Accelerating the discovery of biocompatible ionic liquids, Phys. Chem. Chem. Phys. 12 (2010) 1670–1674.
[46] C.Q. Yan, M.J. Han, H. Wan, G.F. Guan, Qsar correlation of the melting points for imidazolium bromides and imidazolium chlorides ionic liquids, Fluid Phase Equilib. 292 (2010) 104–109.