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# Physico-Chemical Properties of Task-Specific Ionic Liquids

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## 1. Introduction

Ionic liquids (ILs) are currently defined as organic salts that melt at or below 100 $^{o}$C. Even though, they have been first described as early as the 1910s[1], only in the last 20 years the interest from both academia and industry has been gained significant impact. This recent interest is mainly due of their environmental friendly characteristics as green alternative for traditional volatile organic solvents (VOCs) and because of their wide range of physicochemical properties. There are a large number of organic cations and anions that can be combined to form different ionic liquids, and this is one of the most important features of these compounds.

ILs have been also described with some peculiar properties such as their high conductivity, variable range of density and viscosity values, tuneable polarity and solubility as well as their high thermal and chemical stability.[2]

In this chapter will be discussed some relevant physico-chemical properties of ILs particularly melting point, density, viscosity and toxicity.

The number of different cations readily obtained is very large only by modification of the substituents of these families of organic cations particularly for imidazolium, pyridinium, ammonium, phosphonium and guanidinium units. In last decades, ILs based on methylimidazolium cations have been the most studied and applied in several research topics. Anions, on the other hand, can be of either organic or inorganic nature. Overall, the number of possible ionic liquids is estimated around $10^{18}$, whereas the number of traditional solvents widely used in industry accounts for a few hundred.

The reported experimental procedures in order to synthesize and purify different types of methylimidazolium ILs is significantly higher compared with other cation families.

Depending of cation/anion combinations, the physico-chemical properties of ILs will be changed. Looking for the large number of possible combinations the development of novel

functional compounds designated as Task-Specific Ionic Liquids (TSILs) has been a remarkable issue.[3]

The purification process of ILs is a relevant step of synthetic methodologies because all of the physico-chemical properties reported in this chapter are moderate to high sensitive to the presence of impurities.

The presence of water or halogen ions (e.g. chloride, bromide or iodide) impurities are frequently considered as the reason of remarkable discrepancies of some properties in particular viscosity, density or conductivity.[4]

In the literature is frequent to find differences of viscosity or density for the same ionic liquid measured in similar experimental conditions. This fact is mainly observed for ILs more hygroscopic.

The possibility to develop alternative synthetic methods that can avoid the presence of some impurities have been recently described.[5] In the same line several greener methodologies using for example no-solvent reaction media, microwave and ultra-sonification systems have been reported.[6] Different purification methods are also described on the literature according the type of impurities and their desired applications.

It´s already possible to develop TSILs with at least one peculiar physico-chemical property such as high-dense ILs[7], high thermal ILs[8], large conductivity ILs[9, high or low-viscous ILs[10] and non-toxic or biodegradable ILs.[11] For example, high-dense ILs have been prepared on the lab by introduction of heavy elements (e.g. iodo, bromo or fluor) in the cation combined with fluoride based anions. These TSILs are relevant as energetic materials.[12] High to low-viscous ILs can be useful depending the further applications. For some organic or bioorganic transformations and chemical engineering applications the viscosity values of ILs is a crucial parameter. Large conductivity allows that ILs can be used as alternative electrolytes or relevant materials for electrochemical processes.[13] Non-toxic and biodegradable ILs have been recently applied in biological and pharmaceutical research areas.[14]

In experimental point of view is difficult to design novel functional materials as task-specific ionic liquids without any additional help from prediction or theoretical methods. These methods can orientated the synthetic strategies and avoid the long and expensive ILs synthesis.

ILs can be considered complex molecules containing cation and anion units with polar and apolar domains, which allow their use in a high range of tasks but at the same time restrict the physico-chemical properties prediction, simply by looking to the structure of the compounds. In order to circumvent this problem, the construction of models more or less complex and specific is required.

The **melting point** is the primal property in the definition of an ionic liquid, establishing the lowest temperature from it can be obtained the liquid state. Because the importance of this property several models were constructed such as computational, chemoinformatic linear and non-linear, group contribution equation, physico-chemical equations based and empirical methods. Melting point has been described as a complex property based not only in the intermolecular forces but also in the arrangement of the crystal lattice. Considering the attempts made so far, when more general models are required two different situations might happen, or there is a decrease of the predictive ability or more complex models are required considering the number of parameters involved and the complexity of the algorithm. Despite some limitations of current models is possible to discover new room

temperature ionic liquids with relatively simple models. The most studied families of ILs are based on imidazolium, pyridinium, ammonium and guanidinium cations.

**Density** is another important physico-chemical property based essentially in the mass of the elements of the compound and their inter-molecular forces. The complexity of this property is lower than the melting point, but in order to have quantitative values, several models were constructed using empirical, group contribution, linear and quantum mechanic methods. The obtained predictions are generally accurate.

Some recent efforts to predict the polarity of ionic liquids were performed.[15] This property illustrates the complexity of ionic liquids.

Other properties as viscosity and toxicity are also focused in this chapter. The prediction of these properties is important in order to obtain ionic liquids for specific applications. Because of the reliability of the experimental data, standardization of conditions and time of establishment of the property limited their predictions.

Modelling ionic liquids lacks behind experimental measures, since for a model to be built, reliable experimental data are needed. Stringent protocols need to be implemented in order to obtain sound physicochemical data. Only then robust models can be developed.

## 2. Melting point

Despite the description of the first ionic liquid (ethylammonium nitrate) by Walden in 1914, the field of low temperature melting salts remained a rarity for decades.[16] In the 1970s and 1980s the moisture sensitive chloroaluminate imidazolium ionic liquids attracted the interest of electrochemists.[17] The most important features for this new class of ionic liquids becoming common use were their air and moisture stabilities.

For many important applications of ILs a low melting temperature is desirable. It is known that large non-symmetric ions with a high degree of conformational freedom and diffused univalent charge drop the melting point. Yet, this rule-of-thumb falls short for the rational design of ionic liquids.

The main reasons for developing tools to predict ILs properties are their tuneable nature, this is to say, the prospect of finding an IL exhibiting certain physical-chemical-biological property. And then the enormous number of possible cation-anion combinations, which makes unrealistic synthesising all of them to check for their properties.

Nevertheless, modelling the melting temperature, $T_m$ of ionic liquids faces some difficulties. First, the reliability of available experimental data related with the discrepancies in the publication of melting point values for the same ILs. Moreover, conformational freedom can lead to glass formation and polymorphism.[18] These downsides probably account for the limit of accuracy attained when predicting the melting points of ILs.

There are two main ways of modelling ILs.

i. Quantitative Structure-Property Relationships (QSPR)
ii. Theoretical quantum chemical calculations.

Pros, cons, and examples of these two different approaches will be discussed herein.

### 2.1 Quantitative Structure-Property Relationships

QSPR modelling is based on the idea that all the information related to a molecule can be derived from its chemical nature by means of parameters that encode or describe different molecular features, and these parameters, or descriptors, can be correlated to a particular property (QSPR) or activity (QSAR) chemical or biochemical, the so-called figure of merit.

In other words the goal of a QSPR is to find a function that predicts any molecular property/activity, using information solely derived from the chemical structure.[19]

$$\text{Property} = F(\text{structure}) = F(\cdot)$$

$$F(\cdot) = g\{f_E[f_R(\cdot)]\} \quad (1)$$

Where $f_R$ is the molecular representation; $f_E$ contains the structural encoding descriptors; and $g$ represents the mapping function. The input domain of $F$ is then the global information that characterises the molecules, and the output domain is typically a set of numbers quantifying the property of interest.

$f_R$: the molecular representation can be substantiated by means of SMILES notation, H-depleted graphs, geometrical representations, and by quantum-mechanical optimised structures.

$f_E$: to encode the structure, descriptors can be produced in different ways, in particular:

a. based on molecular properties using experimental quantities as descriptors. In this approach the feature representation of the molecule is realised through several characteristic experimental properties (solvatochromic parameters). In this case the limitation lies mainly on the fact that a given set of experimental values is required for each compound. This is the method employed to derive Kamlet-Taft parameters (Linear Solvation Energy Relationship, LSER).
b. Based on group contributions. Relies on the idea that a molecule acts as a number of fragments (atoms, bonds, moieties,…) independently contributing to the investigated property, usually by an additive scheme. Yet, many of these methods are of questionable accuracy and have limited applicability due to the oversimplification of the molecular structure representation.[2]
c. Based on structural molecular descriptors. Molecular descriptors such as topological indices, quantum-chemical, geometrical, and electrostatic descriptors and so forth, are used to encode molecular features. This approach can take advantage of full, realistic representation of the molecules if descriptors are derived from quantum chemical geometry optimisations, especially those carried out at *ab initio* level.

$g$: The mapping function can be based on linear or non-linear methods, such as multivariate statistics, standard regression analyses, genetic algorithm regression models and artificial neural networks. Linear methods are more easily interpretable, and conclusions on the mechanisms of action can eventually be derived. Non-linear methods, on the other hand, yield more accurate models, yet difficult to understand in physical terms.

### 2.2 Theoretical quantum chemical calculations

In this approach, the thermodynamic parameters associated to the fusion process are computed, for an appropriate Born-Fajans-Haber cycle, using quantum-mechanical calculations. Unlike the QSPR models, this methodology requires little or no experimental data.[21]

### 2.3 Reports on modelling melting point for ionic liquids

The first models to predict the $T_m$ of ionic liquids were developed by Katritzky *et al.* in 2002. Two separate studies were reported for pyridinium,[22] and benzylimidazolium bromides.[23] Melting point data were withdrawn from the Beilstein database and ranged

from 30 to 370 ºC. A total of 126 pyridiniums and 149 benzylimidazoliums were modelled, respectively.

For the pyridinium cations, a six-descriptor equation with a reasonably good correlation is developed for the prediction of the melting temperatures by means of a CODESSA built-in heuristic regression model.

The descriptors most significant to the model are related to the coordination ability of the cation, to electrostatic intermolecular interactions, and to the conformational and rotational degrees of freedom in solid and liquid phases.

For the benzylimidazolium cations, best multi-linear regression yielded a five-parameter correlation able to predict the melting point of this class of compounds. The descriptors involved in the correlations reflect directly both the intermolecular interactions and the influence of intramolecular electronic effects on those interactions. Prediction studies using the same type of methodology have been reported for other families of potential ILs. Trohalaki *et al.* built separate models for thirteen bromides, thirteen nitrates, and seven nitrocyanamide salts of 1,2,4-triazolium cations.[24] Novelty is related with the application of Quantum-Chemical RHF/6-31G** theory for computing the optimised structures of the melts in the gas phase. Then CODESSA was used to derive the model by best multi-linear regression or heuristic method. These authors pointed out the necessity for designing specific descriptors for ILs. Similarly, using CODESSA and semi-empirical AM1 calculations in order to optimise the geometries, Zhang *et al.* estimated the $T_m$ for two separate families of dialkylimidazolium (nineteen tetrafluoroborate anions and twenty nine hexafluorophosphate anions) cations.[25] They concluded that the descriptors involved in the models (three and five, respectively) reflect both intermolecular and intramolecular interactions.

Eike, Brennecke, and Maginn[26] applied a genetic function with the Cerius2 package to model the same pyridinimium bromides previously reported,[22] and 109 ammonium or choline-based bromides. In all cases, five-descriptor correlations were calculated, showing that asymmetry due to one or two moderately long chains (e.g. n-octyl chains) with two or three shorter chains (e.g. n-butyl) should be favourable. In addition, branching on the longer chains is predicted to be beneficial as long as two or more bonds separate branch points.

In 2005, Aires-de-Sousa and Carrera[27] reported the use of non-linear methods, namely decision trees and neural networks, for the modelling of the set of 126 pyridinium bromides first modelled by Katritzky group. Descriptors were calculated with DRAGON[28] (since then the program has been updated, and the webpage has moved to http://www.talete.mi.it/products/dragon_description.htm) and PETRA[29] programs on 3D models computed with CORINA.[3] These non-linear methods are highly flexible and capable of accounting for multiple mechanisms of action, whereas linear methods are more rigid. Thus, in comparison with previous studies, comparable $R^2$ (as high as 0.933) and RMS (as low as 12.61 ºC) were attained. Furthermore, the quality of the predictions can be improved by using an ensemble of trees, i.e. a decision forest. Decision trees and neural networks thus constitute suitable methodologies for modelling purposes.

In 2007 Varnek *et al.*[31] published a comprehensive study testing the performance of different linear and non-linear machine learning methods in performing QSPR modelling. A large set of 717 nitrogen-containing cations, all paired with bromide anions, was studied, as well as subsets of it. Descriptors were used from different types such as molecular fragments, E-state indices, and various molecular features. The authors concluded that the most efficient method-descriptors combination depends on the data set used. Overall, there

is a slight preference of non-linear SVM (support vector machines), AsNN (associative neural networks), and BPNN (back propagation neural networks) over other methods, such as modified partial least-squares analysis and multiple linear regression analysis, no matter what descriptors, of those tested, are used.

In 2009, Liu *et al.* modelled, once again, the groups of melts previously studied by different groups, in which the influence of the anion is ignored, it being the same (bromide) in all cases. Descriptors were calculated with CODESSA, and the sole novelty of this piece of work is the use of a Projection Pursuit Regression (PPR) to derive the model, along with CODESSA built-in Heuristic Method (HM), preceded by Principal Component Analysis (PCA). The authors concluded that PPR performed better than HM.

In 2010, Yan *et al.*[32] reported models for small sets of thirty imidazolium bromides, of 20 imidazolium chlorides, and for the merger of both. Only cationic structures of these ILs were optimised, by means of Hyperchem[33] software and MOPAC program.[34] QSAR module of Materials Studio software and Genetic Algorithm (GA) programs[35] were employed to calculate and select the structure descriptors of ILs. Then, the prediction models correlating the selected structure descriptors and melting points of ILs were set up by using the multiple linear regressions (MLR) method and the back-propagation artificial neural network (BP ANN) method, separately. The authors concluded that ANN shows higher prediction precision than MLR, and that this might denote a non-linear relationship between the cationic structure and the melting point.

A different way of encoding the structure consists of using chemical graphs as input for a recursive neural network (RNN). The RNN automatically encodes the structural information depending on the computational problem at hand.[36] Again, the influence of the anion was overlooked, for this methodology was applied to a set of ILs based on pyridinium bromide.

López-Martin *et al.*[37] reported the first study in which both ions were taken into account to build up a model for predicting the melting point of ILs. Their unique approach consists of optimising the geometries of both ions separately, by means of semi-empirical AM1 calculations; then descriptors are derived with CODESSA for each ion, and finally ion descriptors are paired up for each ionic liquid to develop a model by means of partial least squares analysis. Advantage was taken from the fact that CODESSA provides a variety of constitutional, topological, geometrical, electrostatic, thermodynamic, and quantum-chemical descriptors. The correlation was high for a group of 62 different imidazolium units, encompassing 22 different cations and 11 different anions. Interestingly, the model selects three descriptors related to the structural regions in the imidazolium cation that are important for determining the melting point: the charge-rich region, at 4 Å, localised on the imidazolium ring; the symmetry-breaking region, at 5.5 Å, that decreases the melting point; and from 12 Å onwards the hydrophobic region that increases $T_m$ due to Van der Waals interactions.

Subsequently, Torrecilla et al.[38] extended the scope of this approach to a larger and more diverse group of imidazolium cations. Moreover, the methodology was improved by introducing *ab initio* Hartree-Fock calculations to obtain the minimised ion geometries, and optimising an artificial neural network to build up the prediction model, that rendered a regression coefficient of 0.99 and a mean *P*-value of 0.92 (with a mean prediction error of 1.3 %). Sifting a pool of *ca.* 700 descriptors for each ionic liquid by means of linear statistics analyses produced a pool of nine descriptors for the cations and five descriptors for the

anions as being most influential. These are the sole descriptors that were subsequently used in the modelling.

Interestingly, Carrera *et al.*[39] developed a QSPR for the $T_m$ of 101 guanidinium salts, which encompassed four different anions ($Cl^-$, $Br^-$, $I^-$, and $BPh_4^-$), by means of counter-propagation neural networks, and then synthesised and successfully checked the melting point of six suitable low-melting ILs according to the model. Furthermore, the authors included twelve new descriptors, among a total of 92, purposely designed to encode certain features of the guanidinium cations. Typical absolute errors of 20 ºC do not change if anionic families are considered individually.

Molecular dynamics and Monte Carlo simulations have been used in the last decade to model ionic liquids.[4] Most of these simulations are classical as opposed to quantum mechanical; the interactions between chemical species are modelled by empirical force fields, hence, the quality of these simulations is strongly dependent on the intermolecular potential employed. It has been proven that it is possible to find force fields accurate enough to describe ILs.[41] Long and large simulations using *ab initio* are impractical, however, *ab initio* molecular dynamics (AIMD) are somewhat less computer demanding and provide an accurate picture of ion-ion interactions of the liquid state, by combining electronic structure calculations with conventional Molecular Dynamic (MD) methods.

Several reviews have been published that can help to gain insight into the details of molecular modelling.[42]

Thompson and Alavi studied the melting of ILs [emim][$PF_6$],[43] and 1-*n*-butyl-4-amino-1,2,4-triazolium bromide[44] by means of molecular dynamics simulations using the force field of Lopes *et al.*[45] If homogeneous nucleation is the sole mechanism to initiate melting, superheating will occur, and direct heating MD simulations of a solid without an interface also show this effect, yielding values for $T_m$ 20 to 30% larger than the experimental melting points. The superheating effect can be eliminated by simulating a system with a solid-liquid interface, and void defects are introduced in the lattice in order to eliminate the free-energy barrier for the interface formation. Calculated $T_m$ values were 10% higher than experimental ones. However, the downside of this procedure is that it requires more than 500 molecules and long simulation times.

Maginn and Jayaraman computed the melting point of two polymorph crystals of the IL [bmim][Cl] using a thermodynamic integration-based atomistic simulation method[46] (The absolute errors were in the range of 30 to 50 ºC).[47]

As early as 2003, Singer *et al.* applied *ab initio* calculations to investigate the relationship between the computed structure and the melting point of three dialkylimidazolium halides.[48] Two levels of computation implemented in Gaussian98 (HF and MP2) with a variety of basis sets, including diffuse functions were used in order to optimise several stable conformers for each cation. Gross trends relating interaction energy and melting point were found, suggesting that more than one factor contributes to the melting point behaviour of these ILs. Interaction energy is defined as the difference between the energy of the ionic system ($E_{AX}$) and the sum of the energies of purely cationic ($E_{A^+}$) and anionic ($E_{X^+}$) species.

$$E(kJ \cdot mol^{-1}) = 2625.5\left[E_{AX}(au) - E_{A^+}(au) + E_{X^-}(au)\right] \quad (2)$$

Moreover, optimised structures have been well-correlated with solid X-ray geometries. Recently, Li *et al.*[49] reported a similar study on the correlation between the interaction

energy and the melting point of thirty aminoacid based ILs. A density functional theory (DFT) method with 6-3111++G(d,p) basis set was used with Gaussian 03 package.
In previous report Katsyuba *et al.*[50] applied DFT methods alongside vibrational spectroscopy for the study of several imidazolium ILs molecular structure. Unlike Li *et al.* showed a correlation between molecular structure and the melting point, without involving the energy of interaction.
Another way of prediction of the melting point of ILs is employed by Krossing *et al.*[21] where they used an appropriate Born-Fajans-Cycle, $\Delta_{fus}G$ is estimated applying the principles of Volume-Based Thermodynamics (VBT) and simple quantum chemical calculations in combination with available experimental data. Each ion geometry was optimised in the gas phase at the (RI)-BP86/SV(P) level using TURBOMOLE.[51] The free energies of solvation were calculated using COSMO.[52]

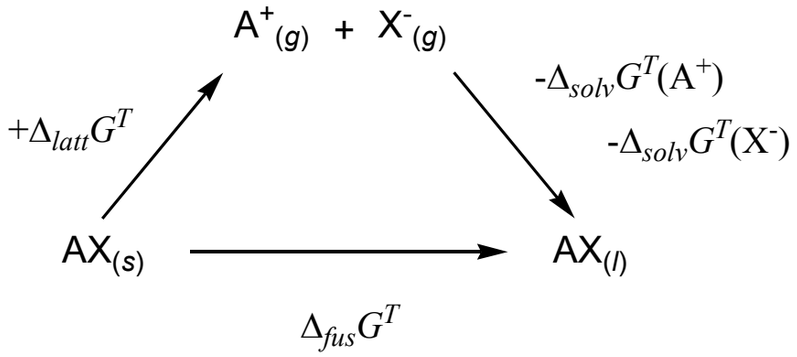



Fig. 1. Born-Fajans-Haber cycle for the assessment of the melting (fusion) of a binary salt (at T) from lattice (latt) and solvation (solv) energies.

Fourteen salts were investigated, and $T_m$ could be predicted with good accuracy in most cases. It is possible to obtain a clear indication whether a given ion pair is suitable as an IL within 2 to 4 h. However, this approach is difficult to use for purely theoretical predictions, since for an exact estimation of the free energy of fusion, both its intercept and slope have to be known with great accuracy.
Krossing *et al.*[53] present another methodology for predicting $T_m$ that needs no experimental data. Moreover, only single ions are used as input, thus avoiding lengthy, computer demanding calculation of ion pairs. Average error is 36.4 °C. Implementing the methodology by using COSMO-RS interaction enthalpies reduces the error to 24.5 °C. Optimisations were carried out with TURBOMOLE v5.10[54] and then COSMO. This methodology is an adaptation and refinement of Yalkowsky and Zhao method for neutral organic molecules.[55] Interestingly, the model includes the influence of both ions in the salt and needs only three 'descriptors' to achieve similar results to existing QSPR studies.

### 2.4 Measuring melting point of ionic liquids

The knowledge of the $T_m$ of an ionic liquid is important to determine its low-end operating range. Modelling the melting point of ILs faces some problems. It is necessary to know some experimental values in order to develop QSPR models, but for some ILs several $T_m$ values are reported.[31] This can have to do with the occurrence of polymorphs or, sometimes, with poor quality measurements due to, by instance, the presence of impurities.

Furthermore, in some cases only glass transition temperatures have been determined, and these values should be avoided for the model.
The NIST ionic liquid database provide with accurate, reliable data, yet only a small number of values are available so far.[56]
Test samples must be, as pure as possible and, in any case, parameters of purity should be measured and reported, such as water content, halide impurity, and other arising typically from the synthetic procedure.
In the recent years, several reports on determination of $T_m$ of ionic liquids have appeared. Yet abundant other values have been measured earlier, sometimes only for in-house use, some other available in databases.[57]
Brennecke *et al.* measured the melting points of several ILs, including pyridinium, imidazolium, and ammonium cations. Melting points were measured by Differential Scanning Calorimetry (DSC). Commercial samples (>98 % purity) and some synthesised on purpose were dried *in situ* several times, if needed, until result remained constant. For some of the ILs studied, only $T_g$ was detected.[58]
Xu *et al* reported $T_m$ or $T_g$ of chiral-amine functionalised ILs. DSC showed that all compounds studied had melting points of glass transitions between -49 to 145 $^{o}$C. Samples were cooled to -70 to -100 $^{o}$C, then heated at a 10 $^{o}$C/min rate. Compounds were synthesised in 95 to 97 % purity and characterised by usual $^{1}$H, and $^{13}$C NMR, FTIR and HRMS techniques, yet no means of further purification were reported.[59]
ILs based on aminoacid derivative anions have been studied by different groups, and their $T_m$ or $T_g$ were reported.[6] Typically, these samples were dried under vacuum at moderate to high temperatures (40 to 80 $^{o}$C) for 24-48h, and purity were checked by $^{1}$H and $^{13}$C NMR.
In the report of Hardacre *et al.* water contents, as determined by Karl-Fischer titration, were reported. These authors also reported the DSC heating and cooling cycle rates of 10 and 5 K·min$^{-1}$, respectively. Heating and cooling cycles were repeated during four cycles to ensure reproducibility (uncertainty was determined to be 0.01 K).
Physical-chemical properties of pyrrolidinium ILs have been reviewed by Domańska[61] while new hydrophobic pyridinium-based ILs have been reported by Papaiconomou *et al.*[62] (for some ILs both $T_g$ and $T_m$ could be determined by DSC, 10 $^{o}$C/min rate).
A pool of 53 amidinium based potential ILs were synthesised by Dechambenoit *et al.* For some of them the melting point was reported, and it was found that only a few of them qualified as ILs.[63]
Gores *et al.* studied nine different ILs (pyrrolidinium and imidazolium) and they gave a clear report of the purification and experimental measurement of the transition points at very low heating and cooling temperatures. All ILs were dried under high vacuum ($10^{-3}$ Pa) and, if necessary, high temperature (up to 333 K). They were checked by $^{1}$H, $^{13}$C, $^{11}$B, and $^{19}$F NMR. Water content was determined by Karl-Fischer titration. Every sample was cooled down and heated up for at least seven to twenty times for reproducibility, at cooling and heating rates ranging from 2.5 to 30 K·h$^{-1}$.

## 3. Density

Density (ρ) is a fundamental property in all the materials and is defined by the mass per volume unit:

$$\rho = \frac{m}{v} \tag{3}$$

Density values are currently expressed in $Kg.m^{-3}$ (or $g.cm^{-3}$) as S.I. units. This property reflects the interactions and the distance between the chemical structures defining the applicability of a substance in daily life situations as permitting that an iceberg or a ship floats.

The relevance of this property have been reported in different correlation studies between the structure of a compound with its density. In n-alkanes, it was observed that density increases with the increment of the number of carbon atoms in the alkyl chain, other observation concerns to the higher density of cyclic n-alkanes comparing with linear equivalents.[64] In the case of more complex molecules is more complicated to obtain a direct correlation between the structure of the compound and the density. ILs are examples of very complex molecules with a wide range of applications. Looking for the high number of possible combinations between cation and anions, it's important to develop prediction or estimation methodologies for density parameters instead the experimental preparation of the IL (with the required density simply by trial an error, sparing time and money).

### 3.1 Relationship between structure and density

In order to establish relationships between the structure of the ionic liquid and density, several attempts were performed with differential degrees of complexity, range of applicability and methodology used. Experimental studies regarding specific classes of ILs are important in order to create detailed databases as well as to establish some relationships and validate other methodologies.

Water and halides are important contaminants for experimental measurements of the density, it's already known that the presence of these impurities generally leads to a decrease of the measured value of density.[65]

The most studied family of ILs is based on imidazolium[66] cation. Ammonium[67], phosphonium[68] and guanidinium[69] based ILs were also studied. It was observed that the increase of alkyl chain in 1-alkyl-3-methylimidazolium provokes a correspondent decrease on density values as described by Esperança et al[68] and Gardas[70] et al. Both independent studies reported a constant augment of the molar volume of the salt per each two $-CH_2-$ groups (34.4 $cm^3.mol^{-1}$ and 33.88 $cm^3.mol^{-1}$, respectively). This progressive augment of molar volume leads to the decrease of density. In another study was observed that the presence of fluorine in the structure of the IL (as cation or anion) provokes an increment of density.[71] Other halogens (e.g. iodine and bromide) increases significantly the density values [72] The presence of pentafluorosulfane ($-SF_5$) in the cation structure will lead to an increase of density and a reduced melting point.[73] An additional observation is related with the higher densities for aromatic cations than aliphatic ones mainly due their π-π interactions which can reduce the inter-molecular distances. The presence of nitrile[74] and hydroxyl[75] groups in the cation normally increase the density. The symmetry and the presence of cyclic units are characteristics that increase the density values which have been related with the reduction of conformational and rotational degrees of freedom and consequent reducing of the free volume between structures. The presence of alkyl ether functional groups for imidazolium based ILs provokes higher densities than n-alkyl substituted equivalents.[76] Many studies have reported that the anion also influences significantly the value of density, the increment of the number of fluorine atoms in the anion generally will lead to higher densities: $[CH_3SO_3]^- \approx [BF_4]^- < [CF_3CO_2]^- < [CF_3SO_3]^- < [PF_6]^- < [NTf_2]^-$. The presence of heavy elements on the anion structure increases significantly the

density (e.g. oxypentafluorotungstate anion , $[WOF_5]^-$).[77] With the support of experimental studies is possible to find the density value of a certain compound. But the accurate quantitative prediction of density is only determine using predictive tools.

One of the first attempts about ILs density predictions was performed by Deetlefs et al.[78] They described two different methods: a) one is based on the equation proposed by Macleod[79] that correlate the density and the surface tension (Equation 3); b) the other is based in the value of refractive index $R_I$, molar refractivity $R_M$ and molar mass of the compound M through the relationship of Lorentz-Lorenz (Equation 4):

$$R_M = \frac{M}{\rho}\left(\frac{{R_I}^2 - 1}{{R_I}^2 + 2}\right) \tag{4}$$

The molar refractivity $R_M$ is obtained by the addition of tabulated values of structural fragments. With both methods was possible to attain $R^2$ of 0.999 and 0.998, respectively, for a set of nine ILs.

Differently Ye and Shreeve[80] determine the volume of ILs through the tabulated volumes of cation and anion, crystallographic data and simplified relation between the volume of the salt and the volume of cation and anion:

$$V_{salt} = V_{cation} + V_{anion} \tag{5}$$

This method permitted the density prediction of 35 RTILs based on imidazolium cation with a medium absolute error (MAE) of 0.02 $g.cm^{-3}$. More recently the same authors[81] propose a correction (to the previous method[81]) of -8 $Å^3$ to $-NH_2$ groups in certain chemical environments in order to predict the density of energetic materials.

Gardas et al[82] extended the method of Ye and Shreeve[81] by the introduction of a range of temperatures and pressures using the following equation:

$$\rho = \frac{W}{NV_0\left(a + bT + cP\right)} \tag{6}$$

where $V_0$ is the molecular volume at the reference temperature ($T_0$) and pressure ($P_0$). The coefficients *a*, *b* and *c* can be obtained by fitting this equation to experimental data. *N* is the Avogadro number and *W* the molecular weight.

In a different study, Trohalaki et al[83] used heuristic methods based in several linear regressions to obtain the density of triazolium bromides, the descriptors were used in order to represent the degree of electrostatic interaction and the relation between the surface charge associated to hydrogen bridges and the total surface.

Valderrama et al[84] reported a semi-empirical linear model based on empirical parameters and boiling points that can help for the determination of ILs density values at different temperatures. This model permits that the obtained prediction has 98% of probability with a deviation lower than 10%.

The same author[85] used artificial neural-networks and group contribution method (based on the mass of selected fragments) to calculate the density of several families of the ILs at several temperatures. With this model was obtained an absolute average deviation of 0.26% for a prediction set of 83 points.

Qiao et al[86] used group contribution method based on the addition of selected fragments with the value associated to a specific fragment depending on the localization of the group. All the fragments are accounted in a linear fashion. The method is able to estimate densities of several families of ILs at different temperatures and pressures (the average relative error obtained is 0.88%).

Lazzús[87] predicted the density of several families of ionic ILs using 11 descriptors and polynomial equation. The value of density is predicted at several temperatures and pressures.

The same author[88], obtained a model based on artificial neural network with particle swarm optimization using as input the molar mass and the structure of the compound, represented by the abundance of defined fragments. This method was valid for imidazolium based ILs over a wide range of pressures and temperatures. Using a back propagation neural-network Lazzús[89] estimated the density of several families of ILs using as input the frequency or specific fragments, temperature, pressure and molar mass.

Wang et al[90] used a group contribution equation of state that embodies hard-sphere repulsion, dispersive attraction and ionic electrostatic interaction energy. According to the method each ionic liquid is divided into several groups representing the cation, anion and alkyl group substituents. The method was used to predict the density of imidazolium based ILs over a wide range of temperatures and pressures. The model was found to estimate accurately the densities of the different ILs with an average relative deviation of 0.63% for prediction set.

Palomar et al[91] using a more sophisticated methodology (quantum chemistry methodology called COSMO) were able to optimize the geometry of the salt and determined the different interactions between cation and anion and consequently the volume of the analysed salts. With this method was obtained the density of 40 imidazolium salts with a correlation of 0.995 as $R^2$ comparing predicted and experimental values. This method is able to determine the distribution of sigma charges. In this distribution is found a zone of polar interactions and other zone of apolar interactions, and according of this distribution the observed densities were interpreted.

The same author[92] used back-propagation neural network associated to distribution of sigma charges determined by COSMO-RS in order to determine accurately the density of imidazolium salts. More recently,[93] the same group used a complex methodology to search the cation/anion pair that can lead to required values of the selected properties, including density. In the first step, the properties of interest are calculated based on back-propagation-neural network model associated to sigma charge distribution. In the second step, the calculated properties are used as input to determine the correspondent sigma distribution charge using an inverse neural network.

Preiss et al[94] used COSMO software to construct a cavity based on the optimized radius of each element of the salt. The volume of the cavity is the calculated volume of the structure from it can be easily determined the molar volume $V_m$ and also the value of density. The value of $V_m$ is used to determine relevant properties.

In Table 1 are represented the predicted and experimental densities of reference ILs illustrating the accuracy of one of the first methods[81] developed to predict densities at atmospheric pressure and at room temperature. This table can also be used as reference to find an ionic liquid with the target density.

| Cation | Anion | Predicted ρ g.cm$^{-3}$ | Experimental ρ g.cm$^{-3}$ |
|---|---|---|---|
| **Imidazolium** | | | |
| MMIM | $NTf_2$ | 1.558 | 1.559 |
| EMIM | $BF_4$ | 1.289 | 1.279 |
| | $NTf_2$ | 1.511 | 1.518 |
| | OTf | 1.389 | 1.390 |
| | $CF_3CO_2$ | 1.284 | 1.285 |
| | DCA | 1.098 | 1.08 |
| BMIM | $BF_4$ | 1.207 | 1.208 |
| | $PF_6$ | 1.367 | 1.37 |
| | $NTf_2$ | 1.433 | 1.429 |
| | OTf | 1.304 | 1.30 |
| | $CF_3CO_2$ | 1.211 | 1.209 |
| | DCA | 1.052 | 1.06 |
| HMIM | $BF_4$ | 1.149 | 1.148 |
| | $PF_6$ | 1.293 | 1.293 |
| | $NTf_2$ | 1.371 | 1.37 |
| | OTf | 1.242 | 1.24 |
| OMIM | $BF_4$ | 1.108 | 1.109 |
| | $PF_6$ | 1.236 | 1.237 |
| | $NTf_2$ | 1.320 | 1.32 |
| | OTf | 1.194 | 1.12 |
| | DCA | 0.995 | 1.0 |
| $C_{10}MIM$ | BF4 | 1.075 | 1.072[95] |
| **Phosphonium** | | | |
| $P_{6,6,6,14}$ | $BF_4$ | 0.929 | 0.94 |
| | $NTf_2$ | 1.062 | 1.07 |
| | Cl | 0.867 | 0.883 |
| **Ammonium** | | | |
| $N_{1,8,8,8}$ | $NTf_2$ | 1.109 | 1.11 |
| | $CF_3CO_2$ | 0.961 | 0.97 |
| $N_{1,1,2,3}$ | $NTf_2$ | 1.406 | 1.41 |
| **Pyridinium** | | | |
| *N*-$C_4$Pyr | $BF_4$ | 1.222 | 1.22 |
| *N*-$C_6$Pyr | $BF_4$ | 1.161 | 1.16 |
| **Pyrrolidinium** | | | |
| $C_1C_4$Pyrr | $NTf_2$ | 1.400 | 1.40 |
| | OTf | 1.266 | 1.25 |
| | DCA | 1.020 | 1.02 |
| $C_6C_6$Pyrr | $NTf_2$ | 1.240 | 1.25 |
| $C_1C_8$Pyrr | $NTf_2$ | 1.296 | 1.29 |

Table 1. Predicted versus experimental density of reference ionic liquids, the predicted and experimental values were extracted from reference[81] unless otherwise stated.

### 3.2 Applications of task-specific ionic liquids based on density property

The range of applications where density plays a fundamental role is vast. Density is fundamental in several design problems in industry such as design of condensers, reboilers, liquid/liquid mixer settler units, determination of tower heights and dimensions of storage vessels. This property is also important in the context of inertial fluids used in navigation instruments as accelerometers and gyroscopes.[73]

Density values can also help for the determination of several thermodynamic and physico-chemical properties.

This property is useful to determine the efficiency of an energetic material, as explosives which are dependent of the pressure and velocity of detonation as well as of the specific density. With the density parameters is possible to determine the enthalpy of formation of a compound $\Delta H^o$:

$$\Delta H^o = \Delta H_{cation}{}^o + \Delta H_{anion}{}^o + \Delta H_{crysatl_lattice} \tag{7}$$

With $\Delta H_{crystal_lattice}$ being dependent on the value of density:

$$\Delta H_{crystal_lattice} = 1981.2.\left(\sqrt[3]{\frac{M}{\rho}}\right) + 108.8 \tag{8}$$

where $M$ is the molar mass. Other properties can be calculated with $V_m$ as for example the standard entropy $S^o$ according Glasser's theory[96]:

$$S^o = 1246.5.V_m + 29.5 \tag{9}$$

The coefficient of thermal expansion $\alpha_P$ can also be determined with the knowledge of the variation of the volume with temperature according the equation 10:

$$\alpha_P = \left(\frac{1}{V}\right)\left(\frac{\partial V}{\partial T}\right)_P \tag{10}$$

Finally, the isothermic compressibility $k_T$ can be obtained according equation 11:

$$k_T = -\frac{1}{V}.\left(\frac{\partial V}{\partial P}\right) \tag{11}$$

This section described the relevance to establish a structure-property relationship between the structure of an ionic liquid and the value of density. According this relationship can be possible to find in straightforward manner the target ionic liquid for a given application.

## 4. Viscosity

Viscosity is a measure of a fluid's internal resistance to flow and may be thought of as a measure of fluid friction. Two different viscosity coefficients have been described, dynamic viscosity, the more usual one which is defined in Pascal-second (Pa.s, SI unit) or centipoises (cP, where 1 cP = 0.001 Pa.s) and kinematic viscosity that is the dynamic viscosity divided by the density (normally in $m^2.s^{-1}$ or centistokes).

The viscosity parameters of fluids can be measured using viscosimeters when one flow condition is observed or rheometers for liquids with viscosities which vary with flow conditions.
It's already known that in the case of liquids, the additional forces between molecules become important. In liquids, viscosity is independent of pressure (except at very high pressure); and tends to change depending of variation of the temperature.[96] The dynamic viscosities of liquids are typically several orders of magnitude higher than dynamic viscosities of gases.
Viscosity is an important physical property of ionic liquids (ILs).
High viscosity values are useful for applications as lubricants[97] or engineering systems while low viscosity values is generally desired in order to use ILs as a solvent[98] (to minimize pumping costs and increase mass transfer rates). The viscosities of ILs are relatively high compared to those of common organic solvents. Organic solvents typically have room temperature viscosities ranging from 0.2 to 10 cP[99] whereas ILs display a broad range of room temperature viscosities, from 10 to greater than $10^5$ cP.[100] The viscosities of ILs vary widely depending on the selection of organic cation and inorganic or organic anions.
In this context, in the case of ILs can be possible to tune the viscosity parameters according our desired application.

### 4.1 Experimental viscosity ILs studies

Experimental data for viscosity of ILs is still narrow and limited to a few classes of well-researched ILs mainly based on metylimidazolium, ammonium, phosphonium, guanidinium, pyrrolidinium and pyridinium cations, among others. More viscosity data and better understanding of this property are required for developing ILs for a specific purpose, and if experimentally measured viscosity data are not available, theoretical or empirical methods must be used in order to establish if the viscosity are within acceptable limiting values defined in the design specifications.
Viscosity of an ionic liquid is dictated by a combination of electrostatics, van der Waals interactions, hydrogen bonding, and ion size and also polarizability, several studies of viscosity can provide information on its fundamental chemical characteristics. ILs based on methylimidazolium cations have been reported with values of viscosity larger according the increase of the length of substituted alkyl cation unit.[101] The ramifications in the alkyl chain seem to reduce the viscosity values of IL. The anion is focused as an important factor where the presence of polyfluor units is favorable in order to reduce the viscosities because the van der waals interactions are also reduced.[102] In this context, anions based on trifluoroacetate, tetrafluoroborate, trifluoromethanesulfonate and bistrifluoromethanesulfonylimide have been described as anions of ILs that promote lower viscosities.[103]
Another relevant factor that influence the viscosity values is related with the size and symmetry of the anion, for example in the case of imidazolium ILs was described that the increase of viscosity is: $Cl^- > PF_6^- > BF_4^- > NTf_2^-$.[104]
The viscosity frequently exhibits a pronounced temperature dependence, however, with values falling significantly upon modest increases in temperature.
Recently, Sanchez and co-workers[105] reported a detailed study about several physical properties of ILs such as viscosity, density and surface tension measured at atmospheric

pressure and at temperatures between (293 and 363) K. For viscosity studies were selected 13 commercial available RTILs based on imidazolium, pyridinium, and pyrrolidinium cations combined with dicyanamide, thiocynanate, methylsulfate, or tetrafluoroborate anions.

The viscosities of [BMIM][$BF_4$], [OMIM][$BF_4$], [BMIM][DCA], [BMPy][$BF_4$], and [BMPy][DCA] decrease rapidly when the temperature is increased. The measured viscosities were higher for the liquids with pyridinium cation than those obtained for the imidazolium-based ILs. The reported viscosities are strongly influenced by the purity of ILs such as water or organic solvents content and halogen impurities. The different purity grade of ILs is one of the reasons about the significant discrepancies of viscosity values observed for the same ILs.

Marsh and co-workers[106] reported the first systematic study of the effect of impurities and additives (e.g., water, chloride, and co-solvents) on the physical properties of Room Temperature Ionic Liquids (RTILs). They concluded that the viscosity of mixtures was dependent mainly on the mole fraction of added molecular solvents and only to a lesser extent upon their identity, allowing viscosity changes during the course of a reaction to be entirely predictable. While the presence of chloride impurities, arising from the preparation of the ILs, increase viscosity dramatically. In general, the addition of co-solvents particularly reduces the viscosity, with the effect being stronger according the higher co-solvent dielectric constant.

Torrecilla et al[107] described the effect of relative humidity (RH) of air on the water content, density, apparent molar volume, dynamic viscosity, and surface tension of the ionic liquid 1-ethyl-3-methylimidazolium ethylsulfate, [EMIM][$EtSO_4$]. Viscosity measurements were conducted at a temperature of 298.15 K, at atmospheric pressure, and in a RH range of (0 to 100) %. As expected, the absorption of atmospheric moisture by the IL affects its chemical structure. Of the studied physical properties, viscosity exhibits the greatest sensitivity which decreases with increasing RH and water content of the IL.

The relevance of purity of the ILs is clearly observed in the case of halogen contamination (e.g. chloride). In order to illustrate the magnitude of the increase in viscosity with chloride content, known quantities of [$C_n$mim]Cl were deliberately added to [$C_{4-6}$mim][$BF_4$] and to [$C_{4-6}$mim][$PF_6$]. In all cases, the viscosity increased dramatically with the concentration of chloride.

Takada et al[108] described the effect of adding an inorganic salt, lithium chloride, and water on the viscosity of an ionic liquid, 1-n-butyl-3-methylimidazolium chloride [BMIM][Cl], which was studied by shear stress measurements with a rheometer. The shear rate dependence of the viscosity showed shear thinning behavior, which implies that some structure should exist in the liquid and the structure should change at high shear rates. Addition of LiCl enhances the viscosity of [BMIM][Cl]. The increasing rate of the viscosity by addition of LiCl was about 10 times larger than in aqueous solution of LiCl. When water was added into [BMIM][Cl], the correspondent viscosity value decreased. The increasing rate of the viscosity by addition of LiCl for [BMIM][Cl] with about 5 wt % of water was almost the same as that for [BMIM][Cl], without addition of water.

Several studies have been reported in the literature about the viscosity behavior of methylimidazolium, pyridinium and pyrrolidinium as pure ILs or in binary mixture using water or organic solvents (IL + water or IL + organic solvent) at different temperatures and pressure values.[109]

A number of research groups have examined the introduction of an ether oxygen atom into the cations to lower viscosity for the resulting IL.[110]

Wu et al[111] described the preparation of tetraalkylammonium-based aminoacid ionic liquids that showed lower viscosity values compared with other ammonium ILs or examples of ILs with aminoacids as anions. It seems that in the case of combination of tetraethylammonium alanine is found the lowest viscosity of 81 mPa.s (alfa-alanine) and 132 mPa.s (beta-alanine). Anouti et al[112] also described examples of alkylammonium cation based protic acid ILs which were developed through a simple neutralization reaction between an amine (such as di-isopropylmethylamine, and di-isopropylethylamine) and a Brønsted acid, HX, where X is $HCOO^-$, $CH_3COO^-$, or $HF_2^-$. Particularly relevant, the very low viscosities measured in the case of N-ethyl di-isopropyl formate (18 cP) and N-methyl di-isopropyl formate (24 cP) at 25 °C. More recent, Bond et al[113] reported a novel series of ILs based on S-alkyl thiolonium, S-alkyl thiotetrazolium and S-alkyl thiobenzolium cations combined with $NTf_2$, TfO, alkyl phosphate, Cl and $PF_6$ as anions. The most part of these novel ILs are liquid at RT and have been presented as examples of low viscous RTILs (viscosity values between 36.9 to 222 mPa.s). Other examples of low viscous ILs have been recently reported by Matsumoto and co-workers[114] using perfluoroalkylborate with ether-oxygen units such as $[CF_3OCF_2CF_2BF_3]^-$. According the authors the viscosity of $[CF_3OCF_2CF_2BF_3]^-$ based ILs was much lower than those of the corresponding $[C_nF2_{n+1}BF_3]^-$ (n=3, 4) based ILs even though the size and the shape of the three borate anions were close to each other.

### 4.2 Prediction viscosity ILs studies

The development of prediction methods for viscosity of ILs have been reported.[115]
While much work has been devoted to the wide range of applications of ILs, the basic understanding and study of their structure–property relationships is of equivalent importance but has lagged behind. More specifically, studies on how the structure of the ions in the IL influences their physical properties are rare. Knowledge of the structure–property relationship is important for assessing the suitability of ILs for specific applications as well as the design of new ILs. Very few works have systematically studied the qualitative and/or quantitative relationships between the structures of ILs and their fundamental properties[116], such as melting point, viscosity, density, surface tension, thermal and electrochemical stability, solvent properties, and speed of sound. At present, however, data for many other physico-chemical properties of ionic liquids are in short supply, or too unreliable to allow similar structure–property relationship studies.[117]
In this context is relevant the Hunt publication[118] about the viscosity study of 1-Butyl-2,3-dimethyl-imidazolium-based ILs. Substitution for a methyl group at the 2-position of the imidazolium cation in order to form 1-butyl-2,3-dimethyl-imidazolium ($[BDMIM]^+$) eliminates the main hydrogen-bonding interaction between the chloride anion and the imidazolium cation. Loss of this hydrogen bonding interaction could be expected to lead to a reduction in melting point and a decrease in viscosity; however the opposite is observed experimentally; melting points and viscosity both increased.
The prediction of the physico-chemical properties of an unknown ionic liquid will depend on understanding the fundamental molecular-level interactions that give rise to the observed physical and chemical properties. To obtain a deeper understanding of these interactions, the authors investigated the gas-phase ion pairs of a variety of ILs.[119] To give explanation why does a reduction in hydrogen bonding lead to an increase in viscosity values, they performed a study using *ab initio* quantum-chemical methods. The structure and hydrogen bonding of ion pairs ($[BDMIM]^+$ and $Cl^-$) were compared with those obtained

for the unsubstituted analogue [BMIM]Cl. After studies the authors hypothesized that the effects due to a loss in hydrogen bonding are outweighed by those due to a loss in entropy. The amount of disorder in the system can be reduced in two different ways: elimination of ion-pair conformers, which are stable for [BMIM]Cl but not in the case of IL [BDMIM]Cl, and an increase in the rotational barrier of the butyl chain, which limits free rotation as well as facilitates alkyl chain association. The reduction in entropy leads to greater ordering within the liquid increasing viscosity.

Many estimation methods for the viscosity of pure components and mixtures are available in recent literature.[119] The most useful viscosity estimation methods for complex molecules have been reported based on group contributions (e.g., the Orrick–Erbar method,[120] the Sastry–Rao method,[121] and the UNIFAC-VISCO method[122]), the corresponding states concept (e.g., Przezdziecki and Sridhar,[123] Chatterjee and Vasant,[124] Teja and Rice,[125] and Queimada et al.[126]) or the corresponding-states group-contribution (CSGC) method (e.g., Yinghua et al.[127]). Group contribution methods for the estimation of liquid viscosity usually employ some variation of temperature dependence proposed by de Guzman,[128] known as the Andrade equation.[129]

Coutinho et al[116] described the use of a group contribution method in order to estimate the viscosity of imidazolium, pyridinium, and pyrrolidinium based ILs containing hexafluorophosphate [$PF_6$], tetrafluoroborate [$BF_4$], bis(trifluoromethanesulfonyl) imide [$Tf_2N$], chloride [Cl], acetate [$CH_3COO$], methyl sulfate [$MeSO_4$], ethyl sulfate [$EtSO_4$], and trifluoromethanesulfonate [$CF_3SO_3$] anions, covering wide ranges of temperatures (293 to 393K) and viscosity values (4 to 21.000 cP). This method uses a group contribution technique[121] to estimate the A and B parameters in the following equation:

$$\ln \eta/\rho M = A + B/T \tag{12}$$

where $\eta$ and $\rho$ are the viscosity in cP units and density in $g.cm^{-3}$ units, respectively. M is the molecular weight and T is the absolute temperature.

For circa 500 data points of 29 ILs studied, an average percent deviation (MPD) of 7.7% with a maximum deviation smaller than 28% was observed (71.1% of the estimated viscosities presented deviations smaller than 10% of the experimental values while only 6.4% have deviations larger than 20%). The group contribution method allowed to evaluate the viscosity of new ILs in wide ranges of temperatures at atmospheric pressure and, as data for new groups of cations and anions became available, can be extended to a larger range of ILs.

Zhao and co-workers[130] described two prediction methods for shear viscosity of the pure IL [bmim][$PF_6$] at 300 K based on reverse non-equilibrium molecular dynamics and equilibrium molecular dynamics simulations respectively. The reverse non-equilibrium molecular dynamics approach has been suitable in order to study the shear viscosity of an ionic liquid of high viscosity. For the case of IL [bmim][$PF_6$], the results are in agreement with computationally more demanding equilibrium MD simulations. The force field used produces a good agreement with experimental results, although the calculated viscosity is lower than the experimental value (25 to 40% depending on which experimental value selected as reference). However, these results are an improvement comparing with previous force fields methods which typically overestimated the viscosities of ILs by more than one order of magnitude.

Ghatee et al.[131] described a correlation study with two linear relations of viscosities of ILs. The first one presents the temperature dependence of imidazolium, pyridinium,

pyrrolidinium, quaternary ammonium, and nicotinium-based ILs with high accuracy. From the non-linear behaviour of fluidity, the following linear equation can fit the viscosity of different ILs:

$$(1/\eta)^{\phi} = a + bT\ , \tag{13}$$

where a and b are substance dependent constants and $\phi$ is a characteristic exponent.

This equation fits the fluidity accurately and involves the exponent $\phi$ = 0.30 (the characteristic exponent enriched in the correlation applies universally to all ILs).[132]

The second one is a correlation of viscosity with surface tension involving the exponent $\phi$, and can fit ILs quite accurately.[133] These correlations have been used as an explanation about the mechanism which a viscous flow is influenced by the nature of the inter-molecular and inter-ionic interactions as well as by the particular structural packing characteristics of ILs.

The temperature dependence of viscosity is a phenomenon where the viscosity ($\eta$) of a liquid decreases or equivalently its fluidity ($\eta-1$) increases with the temperature. Normally, the viscosity of a liquid is a non-linear function of temperature. (At low temperature values increases sharply, and at high temperatures approaches to a small value asymptotically).

Ribeiro et al[134] reported the use of molecular dynamics simulations (MDS) in order to evaluate the influence of alkoxy chain units on the viscosity of a Quaternary Ammonium Ionic Liquid. The MD simulations revealed differences on cation correlation between ILs N-ethyl-N,N,-dimethyl-N-(2-methoxyethyl) ammonium bis(trifluoromethanesulfonyl)imide ($[N_{2,1,1,2\text{-}OR}][NTf_2]$) and N-ethyl-N,N,-dimethyl-N-butyl ammonium bis(trifluoromethanesulfonyl)imide ($[N_{2,1,1,4}][NTf_2]$) beyond the more evident charge ordering effect, which determines the main features of the equilibrium structure of ILs. The key structural difference between these two systems is related with the ether function which for larger conformational freedom of the long chain, in spite of closer approach between the alkoxy chain proper to its higher polarity in comparison to the alkyl chain counterpart. Due to many van der Waals interactions between the long chains of neighbouring cations, there is significant aggregation between the chains within a rather apolar environment. The MD simulations also indicated that the decreases of viscosity, and increase of ionic conductivity, are not due to any change on ionic pairing in the case of ether functionalized ionic liquid. The relevant ether effect on the equilibrium structure is related with short-range cation-cation correlations; i.e., interactions between long alkyl chains in close contact are more effective than between the more flexible alkoxy chains. This explanation can justify the less viscosity values of IL $[N_{2,1,1,2\text{-}OR}][NTf_2]$ than $[N_{2,1,1,4}][NTf_2]$.

Anion conformation of a low viscous RTIL 1-ethyl-3-methylimidazolium bis(trifluorosulfonyl)imide ([EMIM][$NTf_2$]) has been studied by Raman spectra and theoretical DFT calculations by Ishiguro and co-workers.[135] Theoretical calculations involved the evaluation of the torsion potential energy surface (PES) with respect to the F-S-N-S dihedral angle and full geometry optimization followed by normal frequency analyses for the single $NTf_2$ anions were carried out on the basis of Hartree-Fock (HF) theory, as well as density functional theory. They concluded that two possible conformers of the $NTf_2^-$ anion coexist in equilibrium when in the liquid state. A stronger dipole-dipole interaction is thus expected for one of the conformers with EMIM cations, which might lead to the favourable formation of the conformer in the IL [EMIM][$NTf_2$] at 298 K.

A few theoretical and computational studies have already addressed in some detail the problem of viscosity in ILs.[136] However, a complete microscopic theory of viscosity is currently not available. It is a challenging task to accurately compute the viscosity of a complex system by means of simulation methods. For a system with high viscosity, it is extremely difficult to reach the hydrodynamic limit (zero wave number) where the experimental data is observed. This is because, in order to reach this limit, a very large simulation box is required. Traditional simulation methods normally used for shear viscosity of fluids fall into two categories: (a) the evaluation of the transverse-current autocorrelation function (TCAC) through equilibrium molecular dynamics (EMD) trajectories and (b) non-equilibrium molecular dynamics (NEMD) simulations that impose a periodic perturbation.[137] In recent work, Hess[138] compared most of the above methods by performing simulations of Lennard-Jones and water system. They concluded that the NEMD method using a periodic shear perturbation can be the best option.

Margulis and Hu[139] presented a detailed study about the response of IL 1-hexyl-3-methylimidazolium chloride ([$C_6$MIM][Cl]) to external perturbations and the calculation of shear viscosity. It seems after analysis of all the techniques used for the authors that only the periodic perturbation method is feasible. Other methods have been described as useful in order to validate these systems of linear response theory. The very large simulations are still far from the hydrodynamic limit, the transport coefficients of shear viscosity extracted from them using the periodic perturbation method qualitatively agree with experimental data. Accurate knowledge of the long time behaviour of TCACs is important in order to calculate the coefficient of viscosity on the basis of equilibrium simulations. Because of the complex nature of the ILs, this requires very long runs on extremely large simulation boxes to reach the limit of zero k and infinite time. In contrast, these limits are easily reached for systems such as water on normal simulation boxes and standard run times.

Magin et al[140] described atomistic simulations studies about the dependence of the shear viscosity of [EMIM][$NTf_2$] at specific temperature and water percentage. Atomistic simulations have proven helpful in order to understand the correlation between the physical properties of a fluid and its structure and composition. Yan et al[141] described for the first time the use of simulations to determine the viscosity of an ionic liquid. They computed the viscosity of 1-ethyl-3-methylimidazolium nitrate ([EMIM][$NO_3$]) at 400 K from the momentum fluctuations in an equilibrium molecular dynamics (MD) simulation.[138] Using a fixed charge model, they found that the simulations yielded a viscosity that was about of 50% higher than the experimental value. The addition of electronic polarization parameters to the model, allowed a drop in the viscosity value of 7% comparing with experimental value. Looking for this observation the authors suggested that polarization parameters should be introduced properly in order to capture the charge screening that takes place in these liquids with a large effect on viscosity values.

Bhargava and Balasubramanian[142] carried out equilibrium MD simulations with a fixed charge model of 1,3-dimethylimidazolium chloride ([mmim][Cl]) at 425 K. Using a Green-Kubo expression (that is, the long-time integral of the stress-stress time correlation function) they obtained a viscosity for [mmim][Cl] that was about four times higher than the experimental value for [emim][Cl]. Apparently, there were no experimental data at this temperature for [mmim][Cl], but the authors assumed that the values would be similar to [emim][Cl].

Micaelo and co-workers[143] conducted MD simulations of [bmim][$PF_6$] and [bmim][$NO_3$] at temperatures ranging from 298 to 363 K.

Unlike the previous studies in which the viscosity was computed from integrating correlation functions obtained from equilibrium MD trajectories, a non-equilibrium periodic perturbation method[144] was used. In this method, the system is driven away from equilibrium by a spatially varying force and the velocity response is used to obtain the viscosity values.[145]
The shear viscosity $\eta(\gamma)$ is defined according to the following constitutive equation

$$J_y = -\eta(\gamma)\delta v/\delta y \quad (14)$$

where $J_y$ is the momentum flux along the (arbitrarily selected) Cartesian y direction and $\gamma = \delta v/\delta y$ is the velocity gradient or shear rate ($\gamma$).
Note that the dependence of the shear viscosity on shear rate has been explicitly noted. Alternatively, a non-equilibrium MD simulation can be conducted in which the response of the system to an external perturbation have been considered. The most widely used non-equilibrium approach for viscosity calculations is called "SLLOD" algorithm[146] in which a shear rate is imposed on the system and the resulting stress is computed. The shear viscosity is found at a given shear rate from where $P_{ij}$ is an off-diagonal component of the stress tensor, i is the direction of flow caused by the imposed shear rate, and j is the direction normal to the flow. For the SLLOD algorithm, special "*sliding brick*" boundary conditions are also typically used, which require modification of the Ewald sum if charged systems are simulated.[147]
A non-equilibrium molecular dynamics procedure is used along with an established fixed charge force field. It is found that the simulations quantitatively capture the temperature dependence of the viscosity as well as the drop in viscosity that occurs with increasing water content. Using mixture viscosity models, the authors showed that the relative drop in viscosity with water content is actually less than the predicted values for an ideal system. This means that dissolved water is actually less effective at lowering the viscosity of these mixtures when compared to a solute obeying ideal mixing behaviour.

## 5. Toxicity

Several studies have been reported on the literature as an attempt to predict the effect of the ILs on aquatic and terrestrial environments as well as in humans. Different models have been used including aquatic organisms, aquatic and terrestrial plants, rat and human cell lines and enzymatic systems, for instance. All models allowed establishing some relations between the structure of the ions and cytotoxicity. Experimental data of several authors are in agreement with the increasing toxicity with the increasing of the alkyl chain length of the substituents in the case of methylimidazolium ([MIM]) cations[148] (Table 1). Methylimidazolium based ILs have been one of the most studied cations, but more recently some new classes have emerged, such as Pyrrolidinium ([Pyr]), Pyridinium ([Py]), Tetra-alkylammonium ([$N_{x,y,w,z}$] and Tetra-alkylphosphonium ([$P_{x,y,w,z}$]). Toxicity of ammonium and phosphonium based ILs have also been demonstrated to increase significantly with the length of the substituent chains and in particular the case of ILs tri-n-octylmethylammonium ([Aliquat]) and tri-n-hexyl-tetradecylphosphonium ([$P_{6,6,6,14}$]) are in general very toxic as demonstrated by Frade, R.F.M *et al.*[149] Same authors have also reported toxicity studies for the new ILs based on tetramethylguanidinium ([TMG]) and dimethylguanidinium ([DMG]) cations. For example the tetrabutyl-dimethylguanidinium tetrafluoroborate [$(di\text{-}b)_2$dmg] [$BF_4$] was classified as toxic for CaCo-2 cells while diethyl-dimethylguanidinium tetrafluoroborate [$(eb)_2$dmg] [$BF_4$] was not toxic.[151] This might be

due to the fact that these cations have a higher number of alkyl chains and therefore a slight increase in the number of carbons leads to a significant effect in the lipophilicity of the cation and as already reported this parameter and toxicity behaviour are closely related.[150] Besides [MIM] cations of short alkyl chains as well as other cations including [Pyr], [Py], [dmg] and tetrabutylammonium [$N_{4,4,4,4}$] have allowed the preparation of safe ILs to the CaCo-2 toxicity model.[151] Furthermore, the addition of functional groups on the cation such as ether or carboxylic groups have been incorporated in order to reduce significantly the toxicity (Table 2).[151] The first toxicological studies with ILs were not able to demonstrate an evident effect of the anion in toxicity behaviour, however the most common anions were based on inorganic structures such as halogens (e.g. bromide, [Br] or chloride, [Cl]), tetrafluoroborate ([$BF_4$]) and hexafluorophosphate ([$PF_6$]). Later a wider range of anions including organic structures were also tested such as dicyanamide ([DCA]), bis-(trifluoromethylsulfonyl)imide ([$NTf_2$]), hexafluoroantimonate ([$SbF_6$]), acesulfame ([ACS]) and saccharin ([SAC]) among others, which became clear that the type of anion can affect the overall toxicity of the ionic liquid (Table 2).[151] Cytotoxicity data of some representative ILs including different classes of cations and anions are shown in Table 2. Estimated values produced from modelling studies were also introduced for comparison. Experimental and estimated $Log_{10}EC_{50}$ values were taken from several reported studies and were converted to $EC_{50}$ (concentration that reduces viability in about 50%).

| **CATION ALKYLIC CHAINS** | ***Vibrio fischeri* (experimental) ppm, μM, mg/L** | ***Vibrio fischeri* (estimated) μM, mg/L** | **IPC-81 (experimental) μM** | **IPC-81 (estimated) μM** |
|---|---|---|---|---|
| ***IMIDAZOLIUM IONIC LIQUIDS*** | | | | |
| [MMIM]$^+$ | [$MeSO_4$]- 57544 | [$MeSO_4$] - **57544** | | |
| [EMIM]$^+$ | [Cl] - 35481<br>[$EtSO_4$] - **10471** | [Cl]- **36509**<br>[$EtSO_4$]- **10447** | [$CF_3SO_3$]- 12303<br>[$BF_4$]- 2754<br>[$MeSO_4$]- 8511<br>[$PF_6$]- 8318<br>[BBDB]-* 10<br>[BOB]-* 860 | [$CF_3SO_3$]- 12023<br>[$BF_4$]- 3090<br>[$MeSO_4$]- 8128<br>[$PF_6$]- 7244<br>[BBDB]- 13<br>[BOB]- 890 |
| [$C_2$OHMIM]$^+$ | | | [$NTf_2$]- 5800 | |
| [BMIM]$^+$ | [Cl]- 2500/5.12/891<br>[Br]- 1175/10.23<br>[$BF_4$]- 3500/3548<br>[DCA]- 977/4.68<br>[$NTf_2$]- 300/2.45<br>[$PF_6$]- 1175 | [Cl]- 2.95/**855**<br>[Br]- **1203**/2.95<br>[$BF_4$]- **3753**<br>[DCA]- **959**/2.95<br>[$NTf_2$]- 0.56<br>[$PF_6$]- **1203** | [$MeSO_3$]- 3236<br>[$NTf_2$]- 500<br>[Cl]- 3548<br>[Br]- 2692<br>[$BF_4$]- 1318<br>[$PF_6$]- 1259<br>[DCA]- 1400<br>[$SbF_6$]- 180<br>[$HSO_4$]- 1700 | [$MeSO_3$]- 3631<br>[Cl]- 3388/1489<br>[Br]- 3311/1489<br>[$BF_4$]- 1489<br>[$PF_6$]- 1489<br>($k_0$=4.67)<br>[DCA]-2900<br>[$SbF_6$]- 190<br>[$HSO_4$]- 1600 |
| [$C_3$OMIM]$^+$ | | | [I]- 4000<br>[$NTf_2$]- 1600 | |

| | | | | |
|---|---|---|---|---|
| $[C_6MIM]^+$ | [Br]- 6.46/0.03<br>[Cl]- 87<br>$[PF_6]$- 148<br>$[BF_4]$- 1514 | [Br]- **6.43**/0.35<br>[Cl]- **88**<br>$[PF_6]$- **155**<br>$[BF_4]$- **1511** | [Cl]- 708<br>$[BF_4]$- 955<br>$[PF_6]$- 813 | [Cl]- 352<br>$[BF_4]$- 352<br>$[PF_6]$- 352<br>($k_0$=17.38) |
| $[C_8MIM]^+$ | [Br]- 1.17/0.004<br>[Cl]- 15<br>$[PF_6]$- 9<br>$[BF_4]$- 26 | [Br]- **1,17**/0.089<br>[Cl]- **16**<br>$[PF_6]$- **9.04**<br>$[BF_4]$- **25** | [Cl]- 102 | |
| $[C_{10}MIM]^+$ | [Cl]- 3,16<br>$[BF_4]$- 0,66 | [Cl]- **3,25**<br>$[BF_4]$- **0,66** | [Cl]- 22<br>[Br]- 3.39<br>$[BF_4]$- 5.89<br>$[PF_6]$- 32 | [Cl]- 20<br>$[BF_4]$- 20<br>$[PF_6]$- 20<br>($k_0$=234.42) |
| **PYRIDINIUM IONIC LIQUIDS** | | | | |
| $[C_4Py]^+$ | [Br]- 538<br>[Cl]- 437/2.57<br>[DCA]- 407/2.04 | [Cl]- **432**/1.35<br>[DCA]- **432**/1.35 | [Br]-8000/7043<br>$[BF_4]$- 1445 | [Br]- 1871<br>$[BF_4]$- 1871<br>($k_0$=3,80) |
| $[C_3Opy]^+$ | | | [Cl]- 2100<br>$[NTf_2]$- 1300 | |
| $[C_4MPy]^+$ | [DCA]- 98/0.46<br>[Br]- 130/0.56 | [DCA]- 0.37<br>[Br]- 0.37 | $[BF_4]$- 1995 | $[BF_4]$- 1279<br>($k_0$=5.37) |
| $[C_4MMPy]^+$ | [DCA]- 56/0.24<br>[Br]- 119/0.49 | [DCA]- 0.76<br>[Br]- 0.76 | $[BF_4]$- 1778 | $[BF_4]$- 771<br>($k_0$=8.51) |
| $[C_6MPy]^+$ | [Br]- 0.11 | [Br]- 0.15 | | |
| $[C_6MPy]^+$ | [Br]- 1.77/0.006 | [Br]- 0.003 | | |
| **PYRROLIDINIUM IONIC LIQUIDS** | | | | |
| $[C_4Pyr]^+$ | | | [Br]- 5888 | [Br]- 4266 |
| $[C_2OHMPyr]^+$ | | | $[NTf_2]$- 5200 | |
| $[C_4MPyr]^+$ | | | [Cl]- >20000<br>[Br]- 5888<br>$[BF_4]$- 794<br>[DCA]-16982<br>$[NTf_2]$- 1000 | [Br]- 1919<br>$[BF_4]$- 1919<br>($k_0$=3,72) |
| $[C_6MPyr]^+$ | [Cl]- 977 | [Cl]- **959** | [Cl]- 1479 | $[BF_4]$- 420<br>($k_0$=14,79) |
| $[C_3OMPyr]^+$ | | | [Cl]- 850<br>$[NTf_2]$- 1800 | |
| **QUATERNARY AMMONIUM IONIC LIQUIDS** | | | | |
| $[N_{1,1,1,1}]^+$ | [Br]- >100 | [Br]- 234 | | |
| $[N_{4,4,4,4}]^+$ | [Br]- 1.86 | [Br]- 0.83 | [Br]- 178 | |
| $[N_{2,1,1,4}]^+$ | | | [Cl]- > 20000 | |
| $[N_{2,1,1,2\text{-}OH}]^+$ | | | $[NTf_2]$- 6300<br>[I]- > 20000 | |
| $[N_{2,1,1,2\text{-}OMe}]^+$ | | | [Cl]- 3900<br>$[NTf_2]$- 6300 | |

| QUATERNARY PHOSPHONIUM IONIC LIQUIDS | | | | |
|---|---|---|---|---|
| $[P_{4,4,4,4}]^+$ | $[Br]^-$ 0.51 | $[Br]^-$ 5.75 | $[Br]^-$ 45.71 | $[BF_4]^-$ 13.40 ($k_0$=338.84) |
| *QUINOLIDINIUM IONIC LIQUIDS* | | | | |
| $[C_4Qui]^+$ | | | $[Br]^-$ 209<br>$[BF_4]^-$ 145 | $[Br]^-$ 555<br>$[BF_4]^-$ 555<br>($k_0$=11.48) |
| $[C_8Qui]^+$ | | | $[BF_4]^-$ 1.38 | $[BF_4]^-$ 29.38<br>($k_0$=165.96) |

* [BBDB]- bis-[1,2-benzenodiolato(2-)] borate; [BOB]- bis-[oxalato(2-)]-borate

Table 2. Concentration of the ionic liquid that causes 50% decrease of viability ($EC_{50}$) of two of the most currently applied models: the aquatic microorganism *Vibrio fischeri* and the leukemia rat cell line IPC-81. Some values are calculated experimentally whereas others are determined from quantitative structure-activity relationship models (estimated).

### 5.1 Prediction of ILs toxicity by quantitative structure-activity relationship (QSAR) modelling

Owing to the possibility of generating many thousands of new ILs, the prediction of their toxicity will be facilitated by the existence of quantitative structure-activity relationship (QSAR) methods. Therefore, several studies have already been performed by some groups with the attempt of establishing equations that correlate ionic liquid structure with their experimentally determined toxicity. Correlations are evaluated by statistical parameters and validated by comparison of predict and experimental values ILs that did not participate in the modelling. If the calculated data well-fits the experimental data, the equation will be successful; otherwise it will have to be optimized. For modelling several methods exist of different complexity, which are based on different mathematical functions and different computational algorithms. The first QSAR study correlating ILs structure and toxicity was published in 2004 by Ranke J. *et al.*[152] and they used a logistic model, which correlates the cell viability to the logarithm of the tested concentrations, and linear regression analysis performed with the R language and development for statistical computing. For these studies were selected ILs based on methyl and ethyl ($R_1$) alkyl ($R_2$) imidazolium (IMI) cations combined with [Cl], [Br], [$BF_4$], [$PF_6$] and para-toluenosulfonate ([pTsO]) anions and the regression analysis leaded to the following equations according of used toxicity model:

$$Log_{10}(EC_{50}) = (-0.69 x nR_1) - (0.31 x nR_2) + 5.24 \quad (r^2 = 0.9137) \text{ (IPC-81 leukemia cells)}$$

$$Log_{10}(EC_{50}) = (-0.54 x nR_2) + 6.92 \quad (r^2 = 0.988) \text{ (C6 glioma cells)}$$

$$Log_{10}(EC_{50}) = (-0.66 x nR_1) - (0.57 x nR_2) + 6.65 \quad (r^2 = 0.93) \text{ (*Vibrio fischeri*)} \qquad (15)$$

where $nR_1$ and $nR_2$ are the number of carbons of the substituent chains $R_1$ and $R_2$, respectively, and $EC_{50}$, the concentration which induces 50% viability decrease.

The correlation coefficients ($R^2$) demonstrated that the structural parameters and the $EC_{50}$ values were well-correlated. The models showed that toxicity clearly increases with the length of the substituent chains, as seen in previous studies. In this case, the toxicity of the anion is not taking into account in the estimative of the ionic liquid toxicity.[1] Later, a similar equation (to equation 16) was obtained in an independent study with [MIM]-based

ILs, proofing the linearity of the variable $Log_{10}EC_{50}$ and the alkyl chain length, for this type of cation combined with small anions such as [Cl], [$PF_6$], [$BF_4$] and [Br].[153]
More recent, Couling D. J. *et al.*[154] published a QSAR study including other organic cations besides imidazolium such as pyridinium [Py], tetra-alkylammonium [$N_{x,y,w,z}$] and tetra-alkylphosphonium [$P_{x,y,w,z}$]. The study involved four different parameters (descriptors); each of them were calculated with other parameters that can reflect the electrostatic and steric influences of individual atoms in the molecule, the partial positive (or negative) charges of cation (or anion), the solvent-accessible surface and the molecular structure. These descriptors were considered for both cation and anion separately and were used in order to generate correlations of the genetic function approximation (GFA) statistical method (which is an algorithm that provides multiple models rather than a single model as an attempt to generate the best fitting). Likewise, a different correlation was obtained for each toxicity model:

$$Log_{10}EC_{50}/mmolL^{-1}=0.885055 + 1.90609\,[RNCG] - 3.81771\,[Shadow\text{-}v] - 1.13277\,[RPCG^*]$$

$$(R^2=0.782)\ (\textit{Vibrio fischeri}) \qquad (16)$$

where [RNCG] is the partial charge of the most negative atom divided by the total negative charge of the cation; [RPCG*] is the partial charge of the most positive atom divided by the total positive charge of the anion; and [Shadow-v] is the ratio of the longest to the shortest side of the rectangle that envelops the molecular structure.

$$Log_{10}LC_{50}/mmolL^{-1} = 1.37806 - 3.62486[DPSA_3] - 1.50205[S_{aasN}] -$$

$$- 1.54858[S_{aaCH}]\ (R^2=0.862)\ (\textit{Daphnia magna}) \qquad (17)$$

where [$DPSA_3$] is the difference between the atomic charge weighted positive and negative solvent-acessible surface area; [$S_{aasN}$] is the sum of the E-state indices for all carbon atoms with 2 aromatic bonds and one hydrogen bond; and [$S_{aaCH}$] is the sum of the E-state indices for all carbon atoms with 2 aromatic bonds and one single bond.
These models suggest that ILs toxicity decreases with the increase of localized negative (or positive) charge in the anion (or cation), which means that anions with a single negative atom are likely less toxic or do not affect significantly toxicity which agrees with the study performed by Ranke et al.[154] From Table 2, it´s possible to observe that the predicted data (values calculated with equation 16 and indicated in italic and underlined) do not vary significantly with the anion. These models also demonstrated the significantly toxicity increase with the number of alkyl chain unit of the aromatic carbons and the slightly increase with the number of nitrogen atoms having two aromatic bonds and one single bond. As result of these studies a toxicity trend was reported based on [$N_{x,y,w,z}$] (less toxic) < [Py] < [IMI] (more toxic).[156]
In 2004, Stolte S. *et al.*[155] build a different toxicity model using cytotoxicity data gather from studies including several anions and 1-alkyl-3-methylimidazolium cations (with ethyl, butyl and hexyl chains) and perfomed in the IPC-81 rat leukemia cell line. Firstly, intrinsic toxicity of the anions and cations were assessed assuming that sodium chloride and lithium chloride and, the chloride as anion, respectively, had no impact on toxicity behaviour. These studies revealed that only 10 anions from a total of 27 demonstrated considerable toxicity

having an anion effect ratio (AR) > 5 (AR is the ratio of the $EC_{50}$ value of the chloride containing reference ionic liquid and the $EC_{50}$ value measured for the same cation with a different anion). The model was build having in consideration the combinations with AR > 5 and assumed that toxicity of the ionic liquid was a sum of the intrinsic toxicities of the cation and the anion as separated entities (model of concentration addition). Non-linear least-squares method was fitted to the experimental data using the logistic model. In a presence of a sub-toxic stimulus, the linear logistic model parameterised by Van Ewijk and Hoekstra was used, instead. Calculations were done with the software library drift for the R language and environment for statistical computing. Model demonstrates that toxicity increases with the ions lipophilicty and susceptibility to hydrolytic cleavage, and that the model of concentration addition may be useful to predict the $EC_{50}$ values of not studied ILs.[157] As seen in Table 2, this model reflects the toxicity of the different anions (values double underlined) showing that toxicity may depend on the anion structure. Putting the data together, we may assume that the non evidence of anion toxicity in the earlier studies was due of the lower size and lipophilicty of selected anions.

Luis, P. *et al.*[156] have proposed a new QSAR model based on a novel group contribution method considering that the properties of a molecule is a result of the contributions of its atoms and/or fragments[9]. As a consequence, anions were grouped into three main descriptors ($A_1$ - [$BF_4$], $A_2$ – [$PF_6$], [Cl], [$CH_3SO_4$] and $A_3$ – [Br], [$N(CN)_2$], [$C_2H_3SO_4$]) while cations were classified in to three classes (imidazolium, [IM], [Py] and [Pyr]) giving origin to more three descriptors ($C_1$, $C_2$ and $C_3$) and the number of carbon atoms in the three alkyl chain substituents were also considered contributing to more new three descriptors (R, $R_1$ and $R_2$). A dimensionless toxicity (Y*) was calculated by the sum of each group of descriptors contributions, where $A_{1/2/3}$ and $C_{1/2/3}$ were counted as 0 or 1 if absent or present, respectively, and R, $R_{1/2}$ were counted as a number within the interval [0-10] for R, 1 or 2 for $R_1$ and 0, 1 or 2 for $R_2$ representing the number of carbon atoms in the alkyl chains. This dimensionless parameter was used to build the following equation, using multi-linear regression analysis and Polymath 5.0 software:

$$Log_{10}EC_{50}(\mu M) = 4.76 - (4.76+0.18)xY^* \text{ (}\textit{Vibrio fischeri}\text{)} \ (r^2=0.925) \quad (18)$$

The model shows that the lowest toxicity is confined to the [Pyr] cation following by [IM] and [Py] cations and reflects the effect of the anion. Predicted results fit well the experimental data (Table 2, values in bold).

Furthermore, an interesting model correlating lipophilicity ($K_0$), determined by high performance liquid chromatography (HPLC), and toxicity was demonstrated to result in a linear model ($Log_{10}EC_{50}(\mu M)$ versus $Log_{10}(K_0)$) of a great convenience.[150] The study was confined to the classes of cations [IM], [Py], [Pyr], [$N_{x,y,w,z}$], [$P_{x,y,w,z}$] and Quinolidinium [Qui] and produced the following equation:

$$Log_{10}(EC_{50}) = 3,91 - 1,1 \times Log_{10}(k_0) \ (r^2=0,78) \quad (19)$$

where $k_0$ is the liphophilicity parameter calculated by HPLC.

The model does not take into account the anion effect and the differences between experimental and predicted data are still significant, especially for high $k_0$ and then this model should be applied only for $k_0$ <5.[150] Garcia-Lorenzo *et al.* (2008) has developed a

new a QSAR model using the Topological Sub-structural Molecular Design (TOPS-MODE) approach, which calculates the spectral moments of the fragments constituting each molecule.[157] The software used was the MODESLAB 1.5 software. Following this approach, the spectral moment is determined by the construction of a matrix where non-diagonal entries are ones or zeros if the corresponding bonds share one atom or not and diagonal entries describe several bond weights such as bond dipole moments, bond distance, partition coefficient, polar surface area, polarizability, Gasteiger-Marsilli atomic charges, van der Waals atomic radii and molar refractivity. Genetic algorithm was used to select the variables and its number and regression-based approach was used for the modelling. QSAR model determinates the total contribution to the toxicity of the different fragments of the molecule (P) by summing the different bond contributions ($\mu_k$), being $\mu_k$ defined as follows:

$$\mu_k^T(i) = b_{ii}(T)^k \quad (20)$$

corresponding $\mu_k^T(i)$ to the bond i and $b_{ii}(T)^k$ to the diagonal entries of the weighted E matrix being T the type of bond weight.

A large number of ILs based on the imidazolium cation and their $Log_{10}EC_{50}$ in CaCo-2 model were used for this QSAR study. From the group of selected ILs, [MIM] cations with alkyl chains of 4 or 6 carbons or fluorobenzyl-3-methylimidazolium, 1-p-chlorobenzyl-3-methylimidazolium and 1-benzyl-3-methylimidazolium cations produced a similar impact on toxicity and were seen to influence negatively toxicity behaviour (increased $Log_{10}EC_{50}$) compared with [MIM] with alkyl chains of 8 and 10 carbons that contributed positively to the toxicity (decreased $Log_{10}EC_{50}$).[159] A positive contribution was seen for the anion chloride whereas methyl sulphate ([$MeSO_4$]) and ethyl sulphate ([$EtSO_4$]) contributed negatively for the toxicity.[159]

For the methods mentioned before, the computer is set to follow a number of instructions in order to solve the problem however it exists more complicated algorithms that can solve the problem by itself using several functions and at the same time adjusting certain parameters until solving the problem. Some more recent works have followed this approach named Neural Network. The network contains rows of processing elements (neurons) inter-connected to each other. Independent variables are sent to the input neurons and the parameters, used to count the relative importance of each variable, are determined (weights) and then multiplied by the different variables, using an activation function, in the hidden neurons. This process can generate several components or descriptors but reduces the number of variables. The values determined for the different descriptors are transformed by a transfer function in the output neuron(s) and the output (calculated $Log_{10}EC_{50}$) is generated. The weights have to be optimized (learning or training process) in order to generate the best fitting between experimental and calculated data (validation process). Information can travel only one way (from input to output) (feed-forward networks) or in both directions (feedback networks). Multilayer perception (MLP) functions, radial-basis (RB) functions and linear functions can be also used in the learning process. Torrecilla J. S. *et al.*[158] reported MLP functions as a better model than either linear models or RB models. They used a database of $Log_{10}EC_{50}$ in IPC-81 cells and Acetyl cholinesterase enzyme (AChE) systems obtained from the literature and MATLAB version 7.01.24704 (R14). From 46

independent variables related with elemental composition and molecular weight of the ILs, 12 components were determined and multiplied by the weights using the function TrainBR (Bayesian regularization algorithm) as activation function and afterwards the sigmoid function for calculation of the output value. For the MLP model, the mean predictor error (MPE) and $R^2$ were 3.9% (2.8%) and 0.982 (0.973) for the IPC-81 (AChE) system, respectively. Recently, a quantum-chemical-based guide was also established by Torrecilla J.S. *et al.* in order to predict cytotoxicity of ILs.[160] Molecular structures and surface charges under a conductor environment were determined independently for the cation and anion using the B3LYP/6-31++G** computational level (Gaussian03 package) and the continuum salvation COSMO model using the BVP86/TZVP/DGA1 level of theory, respectively. The aim was to build a 3D distribution of polarization charges (σ) of each molecule and to convert this data in to a surface composition function (σ-profile) by the COSMO term program, which was necessary to determine the molecular descriptor $S_{\sigma\text{-profile}}$ (which measures the distribution of the polar electronic charge of a molecular structure on the polarity σ scale). $S_{\sigma\text{-profile}}$ of a pure ionic liquid was defined as the sum of those $S_{\sigma\text{-profile}}$ values of their independent ions (4 descriptors for cations and 6 descriptors for anions). Multi-linear regression relationships (MATLAB version 7.01.24704) were used to calculate and optimized the $Log_{10}EC_{50}$ using toxicity data of a wide group of ILs in IPC-81 cells (86 ILs plus 15 ILs as validated sample). The sigmoid function was used as a transfer function and the activation function was based on the back-propagation (BP) algorithm. In order to design the best MLP model, the regression model selection (RMS) analysis was tested (SPSS software version 15.0.1). The MLP model presented an acceptable goodness of fit, with $R^2 > 0.96$ and MPE < 5.7%. The $S_{\sigma\text{-profile}}$ of the cation located at the non-polar region was found to correlate with the lipophilicity parameter ($LogK_0$) determined by HPLC by Ranke et al. and co-workers.[157] This neural network is able to demonstrate the lower toxicity of the imidazolium cations with oxygenated side chains as a result of the charge shift of the structure toward more polarized regions. Some of the estimated values can be seen in Table 2 and they are very close to the experimental values.

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