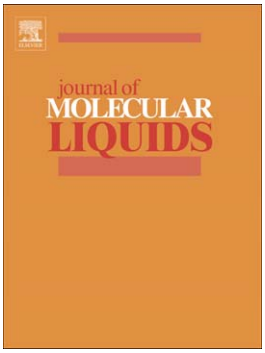

Structural feature based computational approach of toxicity prediction of ionic liquids: Cationic and anionic effects on ionic liquids toxicity

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Structural feature based computational Approach of Toxicity Prediction of Ionic liquids: Cationic and Anionic Effects on Ionic Liquids Toxicity

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ABSTRACT

The density functional theory (DFT) based a unique model has been developed to predict the toxicity of ionic liquids using structural-feature based quantum chemical reactivity descriptors. Electrophilic indices (ω), the energy of highest occupied (E_{HOMO}) and lowest unoccupied molecular orbital, (E_{LUMO}) and energy gap (ΔE) were selected as the best toxicity descriptors of IL's via Pearson correlation and multiple linear regression analyses. The principle components analysis (PCA) demonstrated the distribution and inter-relation of descriptors of the model. A multiple linear regression (MLR) analysis on selected descriptors derived the model equation for toxicity prediction of ionic liquids. The model predicted toxicity values and mechanism are very consistent with observed toxicity. Cationic and side chains length effect are pronounced to the toxicity of IL's. The model will provide an economic screening method to predict the toxicity of a wide range of ionic liquids and their toxicity mechanism.

Keywords: Ionic liquid, DFT, Toxicity, Electrophilicity Index, E_{HOMO}, E_{LUMO}, Cations, Anions

Introduction

Ionic liquids made up a fascinating family of material for many industrial applications. Some unique physical properties of IL's have made them highly important. A numerous number of combinations of anions and cations provide expected properties for the different industrial application. Currently, IL's are used as industrial solvents, lubricants, additives, catalyst, biomass conversion agent, corrosion inhibitor and much more where they enhance the sustainability and efficiency [1, 2, 3]. Liquid crystals properties are intermediate that between crystalline solid state and liquid state. BMIM (1-butyl-3-methylimidazolium) crystals are a liquid-crystalline compound that consisted with anions and cations. Ionic liquids show nematic columnar phase due to the interaction between both ions (anions and cations) that stabilize the structure. It is one of the designer solvents that properties can be tuned by incorporating different anion and cations. Different imidazolium ionic liquid crystals [4] can be formed by quantization methods. According to literature, it is demonstrated different properties due to the chain length of imidazolium-based IL's. Eco-toxicity investigations on IL's have demonstrated that some ionic liquids exhibit greater toxicity than traditional solvents. So, ionic liquids cannot be regarded as 'green'. It showed toxic effects on plants, invertebrate, fish and human [5, 6, 7, 8]. Toxic IL's could be released easily into the environment through aqueous waste streams [9]. A large number of organisms can be affected by cytotoxicity of IL's. Toxicity prediction of different IL's under a wide range of experimental conditions is time-consuming, wasting resources, impractical and costly.

According to the literature, toxicity of ionic liquids can be predicted using quantitative structure activity relationship (QSAR), acute toxicity and partial least square discriminant method [10, 11, 13, 16,17]. Quantitative structure-activity relationships (QSAR) are quantitative method [10, 11] where correlation makes between activity/toxicity of the chemicals/IL and the chemical structure of the IL's using regression analysis. The significant limiting factor of the method is the inability to delineate biological responses [12]. Moreover, the method is limited is because of encoding chemical structure and quantifying biological responses for analysis. Acute toxicity method is basically experimenting the exposure to the substance on laboratory animals. They would expose the chemical to the animals and later record their observation and symptoms on the animal. It is time-consuming as they would have to wait sometimes for 90 days before the symptoms can take effect. For example, in the research of acute and chronic toxicity of

imidazolium-based ionic liquids on *Daphnia Magna* stated that the IL-exposure bioassay was conducted as a 48 h static acute test according to standard procedures. Hence, it can be concluded that the tests are run at extremely long hours and it would need to sacrifice a lot of animals. Therefore, it is much more expensive and time-consuming to conduct. Furthermore, the partial least square discriminant analysis (PLS-DA) developed by Manuel Alvarez-Guerra and Angel Irabien can be used to predict the toxicity of ionic liquids. Partial least square discriminant analysis [13] is a classification method that encompasses the properties of partial least squares regression with the discrimination power of discriminant analysis. However, the reliability of the data are not finalized before the model can fulfill its potential, it needs to be tested against other data sets such as toxicity data for cells of other species and higher organism. So the PLS-DA is also time-consuming and needs an update for better toxicity prediction. An efficient and sustainable toxicity prediction method of IL is very important to cover the inadequacies of the database within the limited time frame and without killing animals or organism. Therefore, quantitative structure-toxicity relationship (QSTR) method will definitely reduce the use of laboratory animals in predicting the toxicity of ionic liquids as well as minimize the cost of experiments and time [14, 15]. The quantitative structure-toxicity relationship (QSTR) method [16, 17] predicts toxicity is based on the pysico-chemical and quantum-chemical descriptors those are directly related to the structural properties of ionic liquids. Fatemi and Izadiyan established QSTR model using multidimensional structural descriptors of 227 ionic liquids such as molecular weight, H-bond acceptor, topological polar surface area, heavy atom count and formal charge. A couple of different quantum chemical descriptors are considered below to predict the toxicity of ionic liquids. A prediction method that directly correlate between chemical structure and the chemical properties via quantum chemical descriptors is the density functional theory (DFT) based QSTR method. The study uses the reactivity descriptors and physiochemical descriptors.

Most of the studies have highlighted the effect of the cations ignoring the effect of the anions. It is generally well known that the head group of the cations has a significant role in toxicity [5,6]. The longer side chains of head groups showed the more significant impact of toxicity on living cells [7,8]. The anions also demonstrate their role to the physicochemical properties of ionic liquids that impact to the overall toxicity of the ionic liquids. Though the impact of anions is less compared to cations of ionic liquids [9]. A correlation has been made between the toxicity and

lipophilicity of the cations or anions of the IL's. Moreover, branching or elongation of anions reduces the lipophilicity that causes the reduction of toxicity [23, 24]. To have a clear interpretation of those effects, an extensive experimentations, and molecular level explanations [25] is required. Quantum molecular descriptors might explore the details clarification of toxicity for the effect of the cations and side chain and elongation of alkyl chains.

Many studies have been reported on the toxicity prediction methods of IL's and their limitations. Basically, most of the QSAR(quantum structure activity relationship)/QSPR (quantum structure property relationship) studies predicted the toxicity and correlated with the physio-chemical properties such as melting point, viscosity, conductivity, molar volume, density, molecular weight, H-bond acceptor, topological polar surface area, heavy atom count and formal charge. A convenient and economical toxicity prediction method is very important now a day to design an ionic liquid for its practical application. The present study extensively computed a couple of quantum chemical descriptors using Dmol^3 computation code and interpreted. The descriptors are ionization potential ($-E_{HOMO}$), energy gap (ΔE), electrophilicity index (ω) [26], electron affinity ($-E_{LUMO}$), dipole moment (μ), polarization (α), hardness(η) and softness(σ), electronegativity (χ), heat capacity (C_v) enthalpy (H), entropy (S_E), Gibbs energy(G) of the ionic liquids (IL's). The toxicity prediction model based on the structure featured based quantum chemical descriptors of IL's is rarely studied. The model not only depends on descriptors but also on the algorithm used for the selection of training and test sets. The aim of the investigation is to find the best quantum chemical toxicity descriptors and to develop a quantitative structure-featured based toxicity relationship model for ionic liquids. Moreover, the model is validated for different head groups of cations and their chain length to observe the cationic and anionic effect of IL's toxicity using DFT methods.

2. Materials and methods

2.1. Dataset /Materials

Seventeen IL's have been selected with a different head group of cations (Imidazolium, Pyrrolidinium, and Pyridinium) , anions and chain lengths for the further study. Based on cytotoxicity data, the toxicity of selected seventeen (17) toxic ionic liquids was obtained and tabulated in Table 1. The molecular structures of 1-butyl-3-methylimidazolium (BMIM[X]) with different anions (X = PF_6^-, BF_4^-, Br^-, I^-, Cl^-, SCN^-, NO_3^-, ClO_4^-), 1-ethyl-3-methylimidazolium chloride (EMIM[Cl]), 1-Hexyl-3-methylimidazolium chloride (HMIM[Cl]), 1-decyl-3-methylimidazolium chloride (DMIM[Cl]), 1-butyl-3-methylpyrrolidinium chloride (BMPYR[Cl]), 1-hexyl-3-methylpyrrolidinium chloride (HMPYR[Cl]), 1-methyl-3-methylpyridinium chloride (BMPY[Cl]), 1-hexyl-3-methylpyridinium chloride (HMPY[Cl]), 1-octyl-3-methyl Pyrrolidinium chloride (OMPYRI[Cl]) and their corresponding cytotoxicity to *Leukemia Rat Cell Line* IPC-81 were obtained from 'UFT/Merck Ionic Liquids Biological Effects Database'-centre for environmental research and sustainable technology [27]. All cytotoxicity values (EC_{50} in μM) were converted to molar lethal concentration (EC) of ionic liquids. The strength of the toxicity is expressed as $\log_{10}[EC_{50}]$ for the development of the model.

2.2. Computational methods of molecular descriptors:

The plane-wave DFT code of Dmol^3 [28] is used to calculate all descriptors under spin-unrestricted method. The computation of molecular descriptors have been made for 16 (sixteen) geometrically optimized IL's crystals. The most stable crystallographic surface (0 0 1) was used for further calculation. The geometry optimization of crystals was performed using PW91/GGA level of theory and the double numerical plus polarization (dnp) basis set. It was applied to account the electron exchange and correlation that provide précised descriptors values and describe toxicity keeping consistent with observed toxicity. All geometries of IL's were optimized until convergence criteria satisfy to total energy (10^{-5} Ha), the largest gradient (2×10^{-3} Ha/Å) and largest atomic position change (10^{-3}Å). Total electronic energy (E_T), ionization potential ($-E_{HOMO}$), energy gap (ΔE), electron affinity ($-E_{LUMO}$), dipole moment (μ), polarization (α), heat capacity (C_v) enthalpy (H), entropy (S), Gibbs energy (G) have been obtained in atomic unit (a.u) for one mole of corresponding IL's directly from DFT computed results at the PW91/GGA level of theory. Thermodynamics quantities measured using frequency calculation

of optimized ionic liquids. Moreover, electrophilicity index (ω), electro-negativity (χ), hardness (η) and softness (σ) were calculated by using the equations/theory [29] given below;

The well established DFT based quantum chemical equation for electrophilicity index (ω) can be expressed in terms of chemical potential and hardness [29, 30] as below;

Electrophilicity index, $\omega = \frac{\mu^2}{2\eta}$ (1)

μ and η are the chemical potential and hardness respectively. Again, μ and η can be written in terms of highest occupied (E_{HOMO} = -IP) and lowest occupied (E_{LUMO} = -EA) molecular orbital energies based on Mullikan definition [21, 22] as given below;

$\mu = \left(\frac{\partial E}{\partial N}\right)_{v(r)} = -\chi$ and, $\eta = \frac{1}{2}\left(\frac{\partial^2 \mu}{\partial N^2}\right)_{v(r)}$ (2)

Where N is the number of atoms in IL molecules. The softness of IL's can be obtained from the inverse value of hardness as defined in equation (2).

2.3. Statistical Analysis

The Pearson (n) correlation between observed/experimental toxicity ($\log_{10}[EC_{50}]$) and computed 14 descriptors have been made using Microsoft Excel, version 2010 to select the highly correlated descriptors with observed toxicity. Further studies such as principal components analysis (PCA) and multiple linear regressions (MLR) were conducted on selected descriptors to develop a model for IL's.

To understand the descriptors distribution and correlation between descriptors of eight (8) IL's (1-butyl-3-methylimidazolium derived IL's), PCA analysis was performed using the software; XLSTAT version, 2014. The analyses present the distribution in graphic form and summarize useful informations. The principle components are linear combinations of the main variables. It is a technique to uncover the unknown trends in the data.

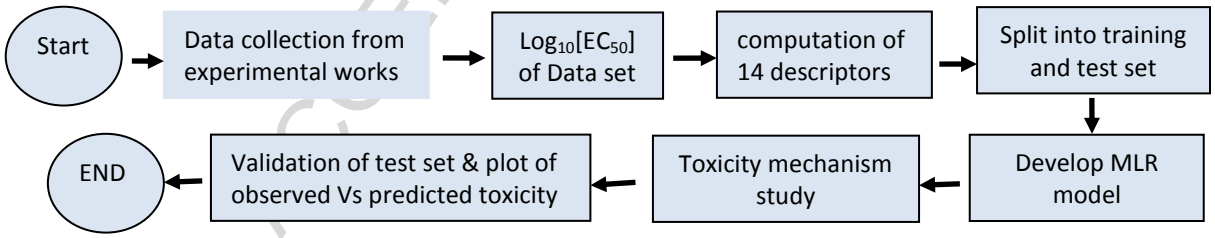
Finally, multiple linear regressions (MLR) have been performed to get the exact relation between one dependent ($\log_{10}$ $[EC_{50}]$) quantity (toxicity) and 5 selected descriptors as variables. The multiple linear regressions (MLR) were conducted using the software XLSTAT version, 2014

and calculated $\log_{10}[EC_{50}]$ using model equation and relevant statistical parameters. Based on the statistical information, structural-featured based toxicity prediction model was developed.

2.4. Training and test sets

For developing a précised model, all descriptors for selected ionic liquids (IL's) were split out into the training set and test set. In the present study, fourteen (14) descriptors of anions and cations were used as input variables to develop a structured featured based toxicity relationship of IL's. A Pearson correlation analysis was conducted on 14 descriptors and five best-correlated descriptors with the observed toxicity of IL's were selected. 50% of the IL's (8 IL's with different anions; X = PF_6^-, BF_4^-, Br^-, I^-, Cl^-, SCN^-, NO_3^-, ClO_4^-) were considered to develop the MLR model and remaining IL's (9 IL's with different cations) were used for the validation of the model. For the correlation between descriptors and toxicity, three head groups with different alkyl side chains (-ethyl, -butyl, -hexyl, -octyl, -decyl) were added. The test set comprises with three aromatic head groups of Imidazolium, Pyrrolidinium, and Pyridinium.

The details of model development flow chart is provided below;



3. Results and discussion

The crystal structure of the different BMIM (1-butyl-3-methylimidazolium) exhibits discreteness of the anions and cations. Imidazolium rings and cations are segregated by inter-digitized dodecyl rings. Both parts form a "spoon shaped" structure due to the disrupture of the dodecyl chain. The interlayer spacing of the crystal depends on the anions and increment order of the space are; $[PF_6^-] < [BF_4^-] < [ClO_4^-] < [Br^-] < [NO_3^-] < [Cl^-] < [I^-]$. Anions are contacted with

imidazolium cations via the H-bonds. The H-bonded interactions are weak and Columbic in nature. One of the crystal structures; BMIM is shown in Fig. 1. The studied descriptors are total electronic energy (E_T in au), Highest occupied molecular energy (E_{HOMO} in au), energy gap (ΔE in au), Electrophilicity index (ω in au), lowest unoccupied molecular energy (E_{LUMO} in au), dipole moment (μ in au), polarization (α in au), hardness(η in au) and softness(σ in au), electro-negativity (χin au), heat capacity (C_v in cal/mol.K), enthalpy (H in kcal/mol), entropy (S_E in cal/mol.K), Gibbs energy(G in kcal/mol) and tabulated in atomic unit. All descriptors were calculated using the optimized crystals structure of sixteen (17) IL's and values of descriptors is shown in Table 2 and Table 3(a,b&c). A Pearson correlation analysis was conducted on 14 descriptors of anions and seven best-correlated descriptors with the observed toxicity of IL's were selected and highlighted in Table 4. The selected descriptors are highest occupied molecular energy (**E_{HOMO}**), energy gap (Δ**E**), electrophilicity index (**ω**), electro-negativity (χ), lowest unoccupied molecular energy (**E_{LUMO}**) softness and hardness (η). The further discussion has been made on toxicity mechanism of imidazolium-based IL's. The mechanism study was focused to the descriptors of **E_{HOMO}, E_{LUMO},** Δ**E,** χ and **ω** since MLR predicted these four descriptors are well enough for toxicity prediction. Moreover, the model has been validated using different head groups of cations and chain lengths. The toxicity variation for different cations and chain lengths is discussed details based on quantum chemical descriptors.

3.1. Statistical Analysis:

3.1.1. Principle Component analysis (PCA):

The descriptors set was subjected to PCA to get the training set from eight (8) ionic liquids. According to the Pearson data matrix, 3 principle axes are enough to explain the information. The variances are 57.87%, 22.43% and 9.02% for the axes of F1, F2 and F3, respectively. The sum of information is approximately 89.32%. The PCA demonstrate the interrelation between the different variables. Highlighted descriptors are different from 0 with a significant level of 0.05. Summarized Pearson correlation matrix indicates the positive and negative correlation between descriptors and represented in correlation circle (Fig. 2). It can be observed that descriptors EHOMO, ELUMO, χ and $\log_{10}[EC_{50}]$ are far from the center and close to each other which is corresponding to the significant positive interrelation (r close 1) between them. Similar

trends are also observed for (η, S & ΔE) and a set of descriptors. Again, η, S and ω are placed opposite side of $Log_{10}[EC_{50}]$ of the correlation circle. Therefore, they are significantly negatively correlated (r close to -1). According to the squared cosine of the descriptors E_{HOMO} (0.880), ΔE (0. 854) and ω (0.553) are well linked with F2 axis and E_{LUMO} (0.755) linked with F3 axis.

3.1.2. Multiple linear regressions:

To develop a QSTR relationship between toxicity $Log_{10}[EC_{50}]$ and selected 7 toxicity descriptors; E_{HOMO}, E_{LUMO}, ΔE, η, S, ϰ and ω, as the data set were subjected to multiple linear regression (MLR). The best relationship between the indicator variable $Log_{10}[EC_{50}]$ and dependent variables are E_{HOMO}, E_{LUMO}, ΔE, and ω has been made. The correlation is a linear combination of dependent variables/descriptors. According to the statistical values, the QSTR correlation model equation is quite significant.

Equation of the model (Log_{10} $[EC_{50}]$):

$$\mathbf{Log_{10}[EC_{50}] = 4.122 - 46.699 \times E_{HOMO} + 42.138 \times E_{LUMO} - 51.882 \times \Delta E - 5.301 \times \omega} \quad (3)$$

N= 8, R^2 = 0.999, Adjusted R^2 = 1, RMSE = 0.000

RMSE value 0.000 indicates the better precision of model prediction and performed the best goodness-of-fit. Though the four descriptors are required to modeling the $Log_{10}[EC_{50}]$ of IL's, remaining ten descriptors are correlated better with each other. Therefore, remaining ten (10) descriptors are less correlated with $Log_{10}[EC_{50}]$ and significant. Fig. 3 shows the regular distribution of predicted toxicity values considering with experimental toxicity values.

3.2. Toxicity mechanism and ionics effect based on Quantum Chemical descriptors:

Generally, toxicants are electrophiles. They do a reaction with biological nucleophiles or bio-molecules. Reactivity descriptors study able to find toxic behavior precisely. To observe the

anionic effect of IL's, imidazolium derived IL's containing Hexafluorophosphate (PF_6^-), tetrafluoroborate (BF_4^-), Bromide (Br^-), Iodide (I^-) Chloride (Cl^-), Thiocyanate (SCN^-), Nitrite (NO_3^-), Per chloride (ClO_4^-) anions were investigated extensively via quantum mechanical descriptors and a real mechanism of toxicity of IL's has been explained, compared and discussed in details below;

Toxicity Mechanism:

HOMO and LUMO energy of IL's on the van der Waals surface are shown in Table 2 and Table 3. According to an observation (Table 2), IL's with higher HOMO and LUMO energies shows more toxic than IL's with lower energies of HOMO and LUMO. HOMO and LUMO energies of Bmim[PF_6^-] are -0.1726 and -0.0788; $\log_{10}[EC_{50}]$ = 3.07; whereas, HOMO and LUMO energies of Bmim[SCN] are -0.0765 and -0.0335; $\log_{10}[EC_{50}]$= 3.77. E_{HOMO} and E_{LUMO} energy level attribute the trend of reactivity or electrons sharing tendency of ILs with the organism. The valance electron of HOMO donates or accepts electrons to/from the organisms. Therefore, the energy gap of (E_{HOMO}-E_{LUMO}) can be significant descriptors of reactivity of toxicant (IL's). IL with extended π systems or polarizable atoms show small HOMO-LUMO energy gap. The small energy gap is observed for toxic IL's but other descriptors confirm their level of toxicity. According to HSAB (hard-soft-acid-base) theory and DFT based equations (equation 1 & 2), soft electrophiles (with low η; hardness) attributes low electrophilic indices (ω) and vice versa. According to the electrophilicity indices (ω) values of electrophiles in Table 2, Bmim[PF_6^-], Bmim[BF_4^-] and Bmim[Br^-] are softer electrophiles and those are more toxic; whereas, soft electrophiles; Bmim[I^-], Bmim[Cl^-] and Bmim[SCN^-], are less soft and shows less toxic. A similar trend also can be observed for the electrophilicity indices (ω). Electrophilicity indices measure the ability of IL's to accept electrons. The nominal discrepancy is because of the similar alkyl chain of IL's shown in Fig. 4. Moreover, nucleophilic indexes (ω-) predict reaction possibility to given electrophiles. To find nucleophilic indexes (ω-) precisely, hardness and chemical potential of both the nucleophilic and electrophilic should be accounted as below;

$$\omega^- = \eta_A(\mu_A - \mu_B)^2/2(\eta_A + \eta_B)^2$$

HOMO and LUMO energy value are key parameters to calculate others important descriptors such as hardness, softness, electronegativity, chemical potential , energy gap and electrophilicity indices. The polarizability of IL's can be predicted via hardness of IL's. The higher energy gaps indicate that high energy is required to transfer charge from toxicant to organism and vice versa. Therefore, IL's are highly polarizable in nature and with low energy gap, ΔE. Thus, it can be termed as "soft molecules" and "highly reactive". BMIM[ClO_4^-] and BMIM[NO_3^-] shows highest and lowest energy gap, respectively indicate that BMIM[ClO_4^-] less polarizable than BMIM[NO_3^-]. The electronegativity characterizes the tendency of IL molecules to attract electrons from organism. Upon interaction with a reaction partner electron charge, it will be transferred from lower EN (the donor molecules) to higher EN (the acceptor molecules). Therefore, highly toxic IL shows higher value of electronegativity.

Effects of Anions:

The variations of selected descriptors for different anions are consistent with observed toxicity. Though, the observed toxicity variation of BMIM based IL's for different cations are nominal and not significant but the molecular level clarification can be made based on variation of toxicity descriptors. The presence of positively charged atoms in the anions leads to higher toxicity than anions with negatively charged atoms. Selected descriptors of this model determine the level of toxicity of IL's and impact of the variation to organism cell can be clarified based on E_{HOMO}, E_{LUMO}, ΔE, and ω as discussed above. An electropositive atom intend to lose electron/electrons and form positive charged ion. Therefore, higher number of electrons influence to the organism by sharing the charged ions that intensify the toxicity. It can be summarized that the strength of toxicity (the range of strength of $\log_{10}[EC_{50}]$ = 3.07 to 3.77) observed for the training set is because of the 1-butyl 3-methyl imidazolium (BMIM) IL and the decimal scale variation in μM is due to the effects of anions.

Effect of Cations:

To observe the cationic effects of IL's toxicity, three types of head group (Imidazolium, Pyrrolidinium, and Pyridinium) of cations is considered in the test set (Table 3) and chloride as counter anions for all. The computation has been made for one mole of IL that was cleaved

(Adjusted thickness) from a corresponding crystal of IL to observe the standard descriptors variation. Three head groups of cations in IL's demonstrate similar toxicity mechanism as detailed above and few uncommon scenarios are observed for descriptors variation for different head groups. The model (Equation 3) can be applied to predict the toxicity of IL's for different head groups. A small discrepancy of predicted toxicity as shown in Fig 4 is because of different head groups and side chains length. In general, the order of toxicity for the three head groups is; Imidazolium < Pyrrolidinium < Pyridinium. Incorporation of carbon to the head group ring lead to the higher toxicity of IL's and incorporation of nitrogen into the aromatic ring reduces the toxicity. Electrophilicity indices of BMPy[Cl], BMIM[Cl], and BMPyr[Cl] are 0.07532 0.071745, and 0.025701. The inconsistent relation between electrophilicity indices and observed toxicity for Pyrrolidinium head group is because of multiple alkyl branching with the common nitrogen of the head group ring that makes the cation more reactive to the system. A similar trend also observed for the descriptors of the energy gap, E_{HOMO} and E_{LUMO}. Electronegativity of (BMIM[Cl] < BMPyr[Cl] < BMPy[Cl] = -0.0545< -0.0530, < -0.0494) and dipole moment (BMIM[Cl] > BMPyr[Cl] > BMPy[Cl] = 4.156 > 4.041 > 2.111) (refer to Table 3) of all head groups maintain a nice order of variation that consistent with observed toxicity of IL's. Dipole moment shows an inverse correlation with observed toxicity.

Side Chains length effect:

In order to get the alkyl chains length effect on toxicity towards the leukemia rat cell, a test kit comprising with 1 alkyl-3 methyl Imidazolium / Pyrrolidinium /Pyridinium chloride, with alkyl varying from ethyl to decyl was used. The significant variation of toxicity is due to the different chain length of the head group of cations. The values of different descriptors (E_{HOMO}, E_{LUMO}, ΔE, and ω) for EMIM, BMIM, HMIM and DMIM increase consecutively according to the alkyl chains length (Table 3(b) & Table 3(c)). predicted the toxicity of IL's is consistent with observed toxicity using the descriptors data. The descriptors correspond that there is a distinct relationship between toxicity and alkyl chains lengths that is true for Imidazolium, Pyrrolidinium, and pyridinium based IL's (Figure 4). The impact of the chain length effect is higher for Pyridinium than Imidazolium-based IL's. It increases the electronegativity and electrophilicity index of Pyridinium based IL's and makes more toxic.

Conclusion:

The nontesting toxicity prediction technique based on quantum chemical structural properties of the ionic liquids help to find hazards of IL's to human and the environment. Molecular attributes related to chemical reactivity directly correlate the toxicity of the ionic liquids. In conclusion, cations and side chains length show the greater impact to the toxicity of the ionic liquids (IL's) though the nominal impact showed by anions of the IL's. The first time DFT based effort of structure- feature based toxicity prediction of ionic liquids is one of the milestones that can be used to design IL's for different applications (industrial reagent, solvents, catalysts etc. that harmful as toxic for human and environment) without killing animals and using assumption. E_{HOMO}, E_{LUMO}, ΔE, and ω are the key descriptors to describes the toxicity mechanism and to categorize the toxic IL's considering head group of cations, side chains length and anions. The model will be a unique tool for a toxicologist to bridge and to enrich the database of toxic IL's and to design non-toxic solvent or catalyst for industry application.

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Figure Captions

Fig. 1: Crystal of Bmim[NO_3^-]

Fig. 2: Correlation circle (Generated by PCA analysis)

Fig. 3: Graphical representation of observed vs model predicted toxicity of anions.

Fig. 4: Graphical representation of observed vs model predicted toxicity of Cations

Table Captions

Table 1: Molecular Structures of investigated IL's and their observed toxicity ($Log_{10}[EC_{50}]$) values.

Table 2: Quantum molecular reactivity and chemical descriptors of Imidazolium based IL's with different anions.

Table 3 : Quantum molecular reactivity and chemical descriptors of Imidazolium (Table 3(a)), Pyrrolidinium (Table 3(b)) & Pyridinium (Table 3(c)) based IL's with common Cl anions.

Table 4: Correlation matrix (Pearson Matrix) of computed toxicity descriptors.

Table 5: Predictions and residuals of $[Log_{10}[EC_{50}]$

Figures

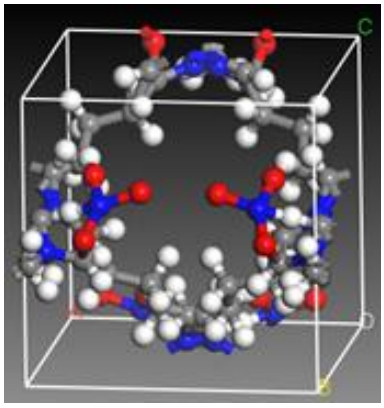


Fig. 1: Crystal of Bmim[NO_3^-]

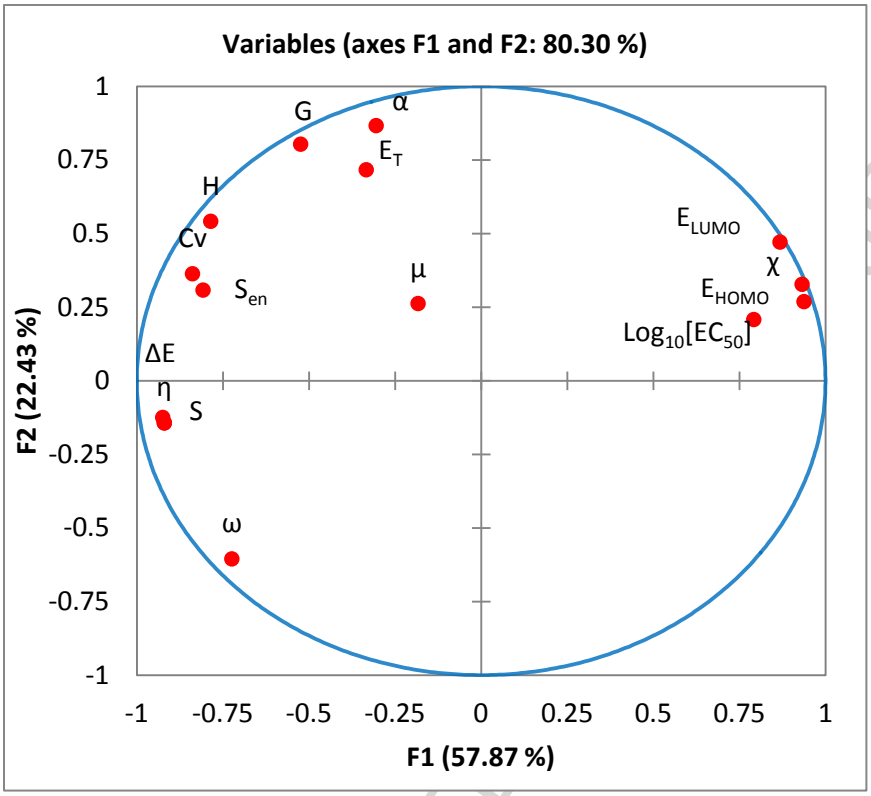


Fig. 2: Correlation circle (Generated by PCA analysis)

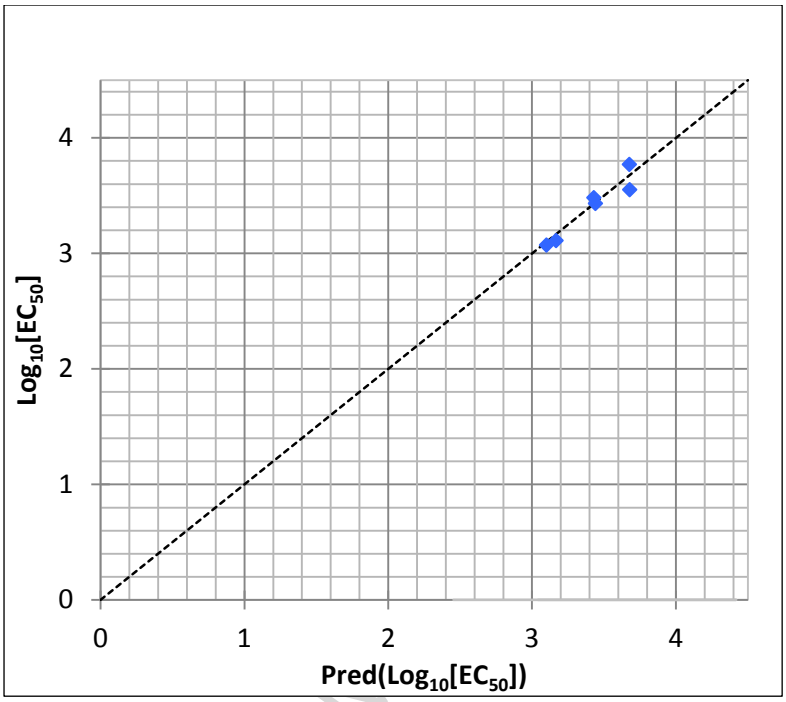


Fig. 3: Graphical representation of observed vs model predicted toxicity of anions.

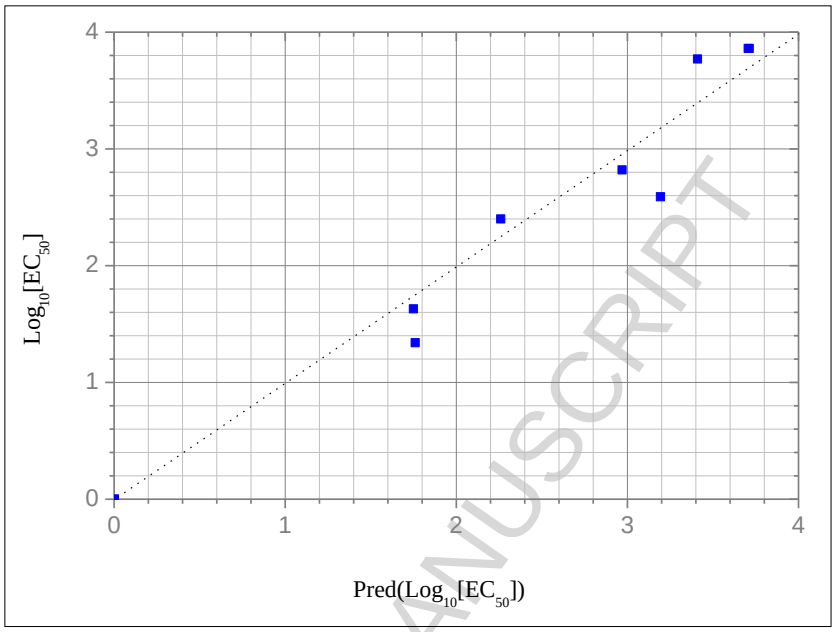
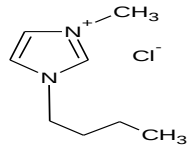
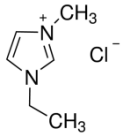
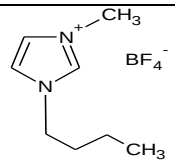
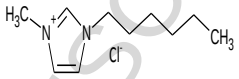
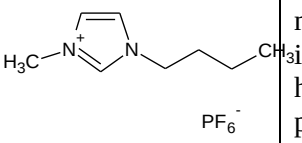
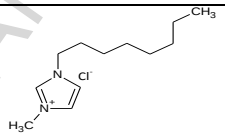
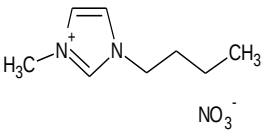
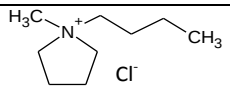
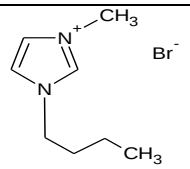
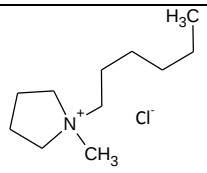
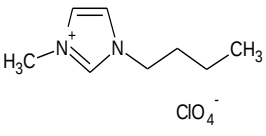
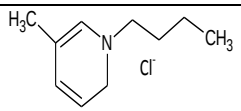
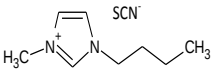
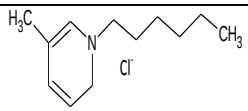


Fig. 4: Graphical representation of observed vs model predicted toxicity of cations.

Table 1: Molecular Structures of investigated IL's and their observed toxicity ($Log_{10}[EC_{50}]$) values.

Symbol of IL's	Name of IL's	**$Log_{10}[EC_{50}]$**	Symbol of IL's	Name of IL's	**$Log_{10}[EC_{50}]$**
	1-butyl-3-methylimidazolium chloride ($C_8H_{15}ClN_2$)	3.55		1-etyl-3-methylimidazolium chloride ($C_7H_{13}ClN_2$)	3.86
	1-butyl-3-methylimidazolium tetrafluoroborate $C_8H_{15}BF_4N_2$	3.11		1-Hexyl-3-methylimidazolium chloride ($C_{10}H_{19}ClN_2$)	2.82
	1-butyl-3-methylimidazolium hexafluorophosphate $C_8H_{15}F_6PN_2$	3.07		1-Octyl-3-methylimidazolium chloride ($C_{12}H_{23}ClN_2$)	1.34
	1-butyl-3-methylimidazolium nitrate $C_8H_{15}N_3O_3$			1-butyl-3-methylPyrrolidinium chloride ($C_9H_{15}ClN_2$)	3.77
	1-butyl-3-methylimidazolium bromide $C_8H_{15}BrN_2$	3.43		1-Hexyl-3-methylPyrrolidinium chloride ($C_{11}H_{20}ClN_2$)	
	1-butyl-3-methylimidazolium perchlorate $C_8H15ClN_2O_4$			1-butyl-3-methylPyridiniu m chloride ($C_{10}H_{17}ClN_2$)	3.86
	1-butyl-3-methylimidazolium thyocyanade $C_8H_{15}N_3S$	3.77		1-hexyl-3-methylPyridiniu m chloride ($C_{12}H_{21}ClN_2$)	2.4

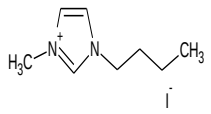
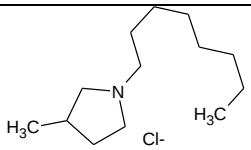
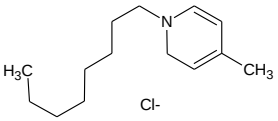
	1-butyl-3-methylimidazolium iodide $C_8H_{15}IN_2$	3.48		4-methyl-1-octyl Pyrrolidinium chloride	2.59
	4-methyl-1-octyl Pyridinium chloride	1.63			

Table 2: Quantum molecular reactivity and chemical descriptors of Imidazolium based IL's with different anions.

IL's	$Log_{10}[EC_{50}]$	ET(au)	E_{HOMO} (au)	E_{LUMO} (au)	ΔE(au)	μ(au)	α(au))	η(au)	S(au)	ω(au)	X(au)	Cv (Cal/mol.K)	S_{en} (Cal/mol.K)	H (Kcal/mol)	G (Kcal/mol)
Bmim[PF6]	3.07	-1363.966	-0.1726	-0.0788	0.0938	5.3554	1.4768	0.0469	0.0235	0.1684	-0.1257	69.8770	93.561	163.349	134.858
Bmim[BF4]	3.11	-847.911	-0.1658	-0.0712	0.0946	5.5703	1.4489	0.0473	0.0237	0.1484	-0.1185	61.1390	85.642	158.644	133.110
Bmim[Br]	3.43	-2997.723	-0.1380	-0.0668	0.0680	4.4710	1.3157	0.0356	0.0178	0.1473	-0.1024	42.4280	50.169	144.862	129.904
Bmim[I]	3.48	-7344.401	-0.0866	-0.0525	0.0341	4.8406	1.2948	0.0171	0.0085	0.1419	-0.0696	44.5630	59.277	146.426	128.753
Bmim[Cl]	3.55	-883.583	-0.0752	-0.0338	0.0414	4.1560	1.3775	0.0207	0.0104	0.0717	-0.0545	44.2870	51.559	145.546	130.173
Bmim[SCN]	3.77	-914.429	-0.0765	-0.0335	0.0430	7.2240	1.5299	0.0215	0.0108	0.0703	-0.0550	49.7070	63.831	153.183	134.748
Bmim[NO3]	-	-703.732	-0.0712	-0.0386	0.0326	3.8180	1.6875	0.0163	0.0082	0.0925	-0.0549	54.9280	70.473	157.476	136.465
Bmim[ClO4]	-	-1184.282	-0.1916	-0.0693	0.1223	5.1888	1.6127	0.0612	0.0306	0.1391	-0.1305	56.2190	70.341	157.522	136.550

Table 3 : Quantum molecular reactivity and chemical descriptors of Imidazolium, Pyrrolidinium & Pyridinium based IL's with common Cl anions.

IL's	$Log_{10}[EC_{50}]$	ET(au)	E_{HOMO} (au)	E_{LUMO} (au)	ΔE(au)	μ(au)	α(au)	η(au)	S(au)	ω(au)	X(au)	Cv (Cal/mol.K)	S_{en} (Cal/mol.K)	H (Kcal/mol)	G (Kcal/mol)
Table 3(a): Imidazolium based IL's with different chain length															
EMIM [Cl]	3.86	-804.9580	0.07 02	-0.03 13	0.0389	5.4320	1.0877	0.0195	0.0097	0.0662	-0.05 08	34.804	43.083	109.118	96.272
HMIM [Cl]	2.82	-962.1940	0.07 61	-0.03 51	0.0410	5.5040	1.6673	0.0205	0.0103	0.0754	-0.05 56	55.966	66.802	182.844	162.927
DMIM [Cl]	1.34	-1040.8090	0.13 14	-0.07 83	0.0531	5.4350	1.9571	0.0266	0.0133	0.0070	-0.10 49	66.321	84.264	219.277	194.154
Table 3 (b): Pyrrolidinium based IL's with different chain length															
BMPyl [Cl]	3.77	-869.8180	0.10 78	-0.00 17	0.1095	4.0410	1.5346	0.0548	0.0274	0.0257	-0.05 31	46.385	55.286	179.601	163.117
HMPyl[Cl]	--	-948.4490	0.10 07	-0.00 34	0.0973	3.9290	1.8244	0.0487	0.0243	0.0278	-0.05 21	55.585	54.246	218.360	202.187
OMPyl[Cl]	2.59	-1027.120	0.15 20	-0.01 14	0.1406	12.103	2.114	0.0703	0.0351	0.0474	-0.08 17	64.494	68.100	254.979	234.524
Table 3(c): Pyridinium based IL's with different chain length															
BMpyr[Cl]	3.86	-905.5960	0.06 56	-0.03 32	0.0324	2.1110	1.4124	0.0162	0.0081	0.0753	-0.04 94	47.351	57.575	156.718	139.552
HMPyr[Cl]	2.40	-984.2890	0.18 80	-0.08 35	0.1045	2.0090	1.7022	0.0523	0.0261	0.0763	-0.13 58	58.649	69.630	198.155	177.379
OMPyr[Cl]	1.63	-1062.838	0.26 95	-0.08 83	0.1812	35.088	1.9920	0.0906	0.0453	0.0766	-0.17 89	68.398	89.972	226.177	199.352

Table 4: Correlation matrix (Pearson Matrix) of computed toxicity descriptors.

Descriptors	*$Log_{10}[EC_{50}]$*	*ET*	*E_{HOMO}*	*E_{LUMO}*	*ΔE*	*μ*	*α*	*η*	*S*	*ω*	*χ*	*Cv*	*S_{en}*	*H*	*G*
$Log_{10}[EC_{50}]$	1														
ET	-0.1247	1.0000													
E_{HOMO}	**0.9176**	-0.1819	1.0000												
E_{LUMO}	**0.9057**	0.0723	0.9280	1.0000											
ΔE	**-0.8839**	0.3148	-0.9765	-0.8265	1.0000										
μ	0.2607	0.1417	-0.1388	-0.0270	0.1990	1.0000									
α	-0.0468	0.6487	-0.0746	0.1350	0.1987	0.0803	1.0000								
η	**-0.8762**	0.3086	-0.9795	-0.8338	0.9994	0.1910	0.1836	1.0000							
S	**-0.8762**	0.3086	-0.9795	-0.8338	0.9994	0.1910	0.1836	1.0000	1.0000						
ω	**-0.8300**	-0.3417	-0.7880	-0.9534	0.6437	-0.0691	-0.2701	0.6517	0.6517	1.0000					
χ	**0.9228**	-0.1155	0.9949	0.9609	-0.9499	-0.1104	-0.0188	-0.9540	-0.9540	-0.8443	1.0000				
Cv	-0.7691	0.4465	-0.6042	-0.5725	0.6010	0.2274	0.4906	0.5855	0.5855	0.4591	-0.6043	1.0000			
Sen	-0.7726	0.3405	-0.5701	-0.5748	0.5501	0.2816	0.4165	0.5336	0.5336	0.4945	-0.5796	0.9811	1.0000		
H	-0.6628	0.5195	-0.5280	-0.4466	0.5577	0.2759	0.6886	0.5406	0.5406	0.3213	-0.5136	0.9638	0.9406	1.0000	
G	-0.2373	0.6778	-0.2978	-0.0909	0.4064	0.2561	0.9538	0.3920	0.3920	-0.0766	-0.2460	0.6700	0.5945	0.8307	1.0000

Table 5: Predictions and residuals of [$Log_{10}[EC_{50}]$] for anions

Observation	E_{HOMO}	E_{LUMO}	ΔE	ω	$Log_{10}[EC_{50}]$	Pred.($Log_{10}[EC_{50}]$)	Residual
Bmim[PF6]	-0.173	-0.079	0.094	0.168	3.070	3.102	-0.032
Bmim[BF4]	-0.166	-0.071	0.095	0.148	3.110	3.170	-0.060
Bmim[Br]	-0.138	-0.067	0.068	0.147	3.430	3.443	-0.013
Bmim[I]	-0.087	-0.053	0.034	0.142	3.480	3.433	0.047
Bmim[Cl]	-0.075	-0.034	0.041	0.072	3.550	3.681	-0.131
Bmim[SCN]	-0.077	-0.034	0.043	0.070	3.770	3.679	0.091
Bmim[NO3]	-0.071	-0.039	0.033	0.092	-	3.639	-
Bmim[ClO4]	-0.192	-0.069	0.122	0.139	-	3.067	-

Highlight

● Predictive structure feature based model have been developed using DFT methods.

● Reactivity descriptors and MLR based model showed appreciable predictivity and reproducibility.

● Quantum chemical reactivity descriptors of E_{HOMO}, E_{LUMO}, ΔE, ω predicted toxicity of ionic liquids precisely.

● Head group of cations and side chains length showed significant impact to ionic liquids toxicity.