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Toxicity prediction of ionic liquids based on Daphnia magna by using density functional theory

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Abstract. By using a model called density functional theory, the toxicity of ionic liquids can be predicted and forecast. It is a theory that allowing the researcher to have a substantial tool for computation of the quantum state of atoms, molecules and solids, and molecular dynamics which also known as computer simulation method. It can be done by using structural feature based quantum chemical reactivity descriptor. The identification of ionic liquids and its Log[EC50] data are from literature data that available in Ismail Hossain thesis entitled "Synthesis, Characterization and Quantitative Structure Toxicity Relationship of Imidazolium, Pyridinium and Ammonium Based Ionic Liquids". Each cation and anion of the ionic liquids were optimized and calculated. The geometry optimization and calculation from the software, produce the value of highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO). From the value of HOMO and LUMO, the value for other toxicity descriptors were obtained according to their formulas. The toxicity descriptor that involves are electrophilicity index, HOMO, LUMO, energy gap, chemical potential, hardness and electronegativity. The interrelation between the descriptors are being determined by using a multiple linear regression (MLR). From this MLR, all descriptors being analyzed and the descriptors that are significant were chosen. In order to develop the finest model equation for toxicity prediction of ionic liquids, the selected descriptors that are significant were used. The validation of model equation was performed with the Log[EC50] data from the literature and the final model equation was developed. A bigger range of ionic liquids which nearly 10^8 of ionic liquids can be predicted from this model equation.

1. Introduction

Salts which have a melting point temperature below the boiling point of water is also known as ionic liquids(ILs) which is now nearly 10^8 [1, 2]. Usually, ILs consist of an organic cation and combine with some inorganic anion such as Cl^-, BF_4^-, PF_6^- which will be matching to the organic cation. Since the ionic liquids have high capability to be used in many applications in the world such as fuel cells [3, 4], batteries [5-7], sensors [8-10], extractants [11, 12], capacitors [13, 14], ionogels and solvents [11, 15-19] in analysis, synthesis [15, 20, 21], catalysis and separation [22], they have been one of the interest in the industry. Most of the ionic liquids can be considered as a "green", but nowadays the development of these compounds also may cause some accidental discharge and immoral pollution [16, 23].

The definition of toxicity is the measure of its harmful effects on living organisms and it can be classified into three categories which are chemical toxicity, biological toxicity and physical toxicity. Recently, the toxicity of ILs has been given more consideration. Studies have shown that ILs do give harmful effect to human [16, 23], fish [20, 24], bacteria [25, 26] and many more. Therefore, ionic liquids are not so being considered as a naturally "green" [2, 16, 18, 24, 26]. Since the interest on ILs has raised, it's only feasible to come up with a solution to measure its toxicity without the sacrifice of animals as lab tests. This could be done by a computational approach towards the properties of the ionic liquids and developing a model to analyze the toxicity levels of the liquid. The most important theory that needs to be implemented in this research paper will be the Density Functional Theory [27-29]. The density functional theory is used to compute the descriptors such as chemical potential, ionization potential, electrophilicity index, as well as electron affinity of those ionic liquids [30-32]. All these properties are later compared with the different experimental data done on laboratory animals. From these validation, the toxicity with just the information needed from the density functional theory can be determined.

In this project, the main apprehension will be to develop the theoretical model based toxicity descriptors such as HOMO, LUMO, electrophilicity index, electronegativity, refractive index, enthalpy, entropy, Gibbs free energy, polarization and dipole moment so that observation can be done on the characteristics of these descriptors and compare the results obtained with toxicity through experimentation. The objective of this research is to develop a theoretical model equation to predict the toxicity ILs based on Daphnia Magna. The scope of this project is to identify the theoretical model using density functional theory in Material Studio software specifically using a Dmol3 modules calculation for ILs based on Daphnia Magna.

2. Materials and methods

2.1. Dataset

Ionic liquids based on Daphnia Magna with different head group of cations such as (Imidazolium, Pyridinium, Ammonium, Sulfonium), there were 31 ionic liquids have been chosen. The log[EC_{50}] is considered as the direction for the toxicity which also being used for the model equation to develop.

2.2. Computational Methods

Determination of interaction between the cation and anion in term of geometric optimizations and electronic structure calculations were made through a density functional theory computations using $DMol^3$ module of Materials Studio software [33]. First, full structural optimization for cations and anions for each ILs were carried out; the generalized gradient approximation (GGA) and Perdew and Wang functional 91 (PW91) exchange-correlation functional in Dmol3 module calculation [34]. The basis set in Dmol3 module is set to the Double numerical plus polarization function (DNP) [35]. A real-space orbital global cut off of 3.7 Å was used for the geometry optimization and the self-consistent field (SCF) convergence was set to 10^6. The convergence calculation conditions were compute as follows: energy = $1x10^{-5}$ Ha; Force = $2x10^{-3}$ Ha/ Å; displacement = 0.005 Å. The calculation process includes both geometry optimizations and energy calculation.

At the PW91/GGA level of theory in Dmol3 module, the HOMO and LUMO were calculated from density functional theory results. The other molecular descriptor which are Electrophilicity Index (ω), Energy Gap (ΔE), Chemical Potential (μ), Electronegativity (χ), and Hardness (η), were obtained basically from the formulas that involve HOMO and LUMO value as shown in Table 1.

Table 1. Descriptors Calculation

Descriptors	Formula
Energy Gap (ΔE)	$\Delta E = E_{LUMO} - E_{HOMO}$
Chemical Potential (μ)	$\mu = (E_{HOMO} + E_{LUMO}) / 2$
Hardness (η)	$\eta = (E_{LUMO} - E_{HOMO}) / 2$ $\eta = (\Delta E) / 2$
Electrophilicity Index (ω)	$\omega = (\mu^2) / (2\eta)$
Electronegativity (χ)	$\chi = (- E_{HOMO} - E_{LUMO}) / 2$

2.3. Statistical Analysis

To develop a model equation for ILs, a data analysis known as multiple linear regressions (MLR) were conducted on selected descriptors that are significant to the $Log_{10}[EC_{50}]$ from literature data. The reason in doing this MLR is because to obtain the best correlation between one dependent $Log_{10}[EC_{50}]$ quantity (toxicity) with selected significant descriptors as variables. The multiple linear regressions (MLR) were conducted using the Data Analysis in Microsoft Excel 2016. Toxicity prediction model was developed based on the statistical information from the data analysis.

2.4. Data Training and Test Sets

To develop a precise and accurate model equation, all the molecular descriptors were performed by MLR and from the results of MLR, the best correlated descriptors were selected. 80% of the ILs from based on Daphnia Magna were randomly picked to develop the MLR model and another 20% of ILs were used for the validation of the model. Flow chart below in Figure 1 shows the details of the model development.

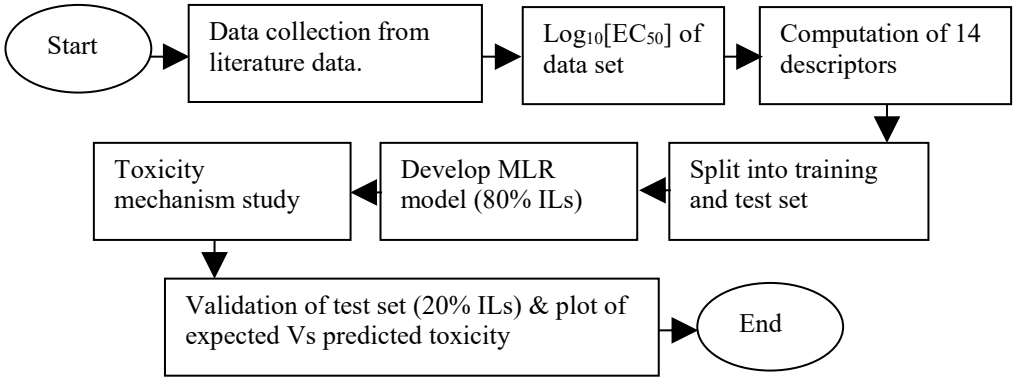

Figure 1 : Flow chart of methodology

3. Results and discussion

The studied descriptors were lowest unoccupied molecular orbital energy (E_{LUMO} in kJ/mol), highest occupied molecular orbital energy (E_{HOMO} in kJ/mol), hardness (η in kJ/mol), chemical potential (μ in kJ/mole), electrophilicity index (ω in kJ/mol), energy gap (ΔE in kJ/mol), and electronegativity (χ in kJ/mol). After the optimization of crystals structure of 31 ILs based on Daphnia Magna in Material Studio software, all the descriptors have been calculated after the HOMO and LUMO value was obtained from the computation of Dmol3 module in Material Studio software.

3.1. Statistical Analysis

3.1.1 Multiple Linear Regressions (MLR)

All the data sets consist of 14 descriptors were subjected to multiple linear regressions (MLR) to develop the model equation and the best relationship between one dependent variable log[EC_{50}] and significant variables (descriptor) has been made for ILs based on Daphnia Magna. The significant descriptors were HOMO and LUMO for both cation and anion, and the electrophilicity index (ω in kJ/mol) of cation. The correlation is a linear equation is shown in Table 2.

Table 2. Model Equation

Category of ILs	Equation of the model
Daphnia Magna	$\log[EC_{50}] = -1.1263 - 0.00991(E_{HOMO,\,cation}) + 0.0039995(E_{LUMO,\,cation}) + 0.00005(\omega_{,\,cation}) + 0.00535(E_{HOMO,\,anion}) - 0.004511(E_{LUMO,\,anion})$

The computation of 14 descriptors were done after division of the descriptors for cations and anions. Therefore, there were 7 descriptors for cations and 7 descriptors for anions. The subject that being focused on is the log[EC_{50}]. From MLR, Anova results produced and from it, the descriptors that significant to the log[EC_{50}] from literature data can be determined. As can be seen in Table 2, the model equation, there are some descriptors that are correlated with log[EC_{50}] and significant. The descriptors that significant to the log[EC_{50}] of Daphnia Magna are 5 descriptors which are HOMO and LUMO of cation and anion, and electrophilicity index of cation. Only these 5 descriptors are significant to the log[EC_{50}] of literature data, while the other 9 descriptors are not significant and correlated.

For the organism, the HOMO and LUMO energy level feature to the pattern of reactivity and to the liability of electrons sharing in the ionic liquids. The lower the toxicity if the HOMO and LUMO value are lower. While for the electrophilicity index, it indicates the ability of ILs to accept electrons which means the lower the value of electrophilicity index, the lower the toxicity. The ILs which can be categorized as hard ILs also have a lower value of electrophilicity index.

After the result of MLR, the final equation for toxicity prediction of ILs based on Daphnia Magna was produced. By using this equation, the validation of the value of log[EC_{50}] for the ILs were done. As shown in Figure 2, the predicted log[EC_{50}] are the value of log[EC_{50}] by using the model equation and the experimental log[EC_{50}] are the value of log[EC_{50}] from the literature data.

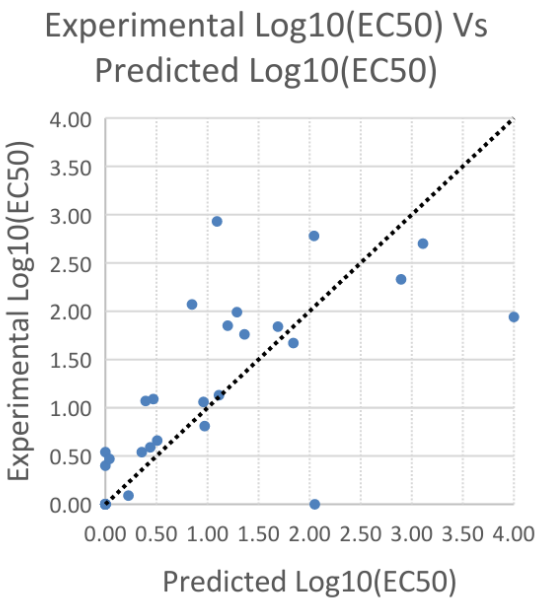

Figure 2 : Graphical representation of experimental vs predicted toxicity of ILs (Daphnia Magna)

Figure 2 shows graphical representation of experimental $Log_{10}[EC_{50}]$ data from literature against predicted $log_{10}[EC_{50}]$ from the model equation developed of Daphnia Magna. This graph plotted to show the consistency of the predicted data with the experimental data from literature. If the experimental data and predicted data lies on y=x line, it means that the predicted data are align and accurate with the experimental data from the literature. As can be seen in the graphs that, there are some inconsistency of predicted data against experimental data. This is because of there are some literature data that have different value of $log[EC_{50}]$ because it is from lot of reference. These outliers may be due to variability in the measurement or it may indicate as an experimental error.

4. Conclusion

The toxicity prediction technique without experimental work based on density functional theory on ionic liquids based on Daphnia Magna help to find risk of ionic liquids that have high toxicity to environment and human. The discovery of this density functional theory based determination on toxicity prediction of ionic liquids based on Daphnia Magna can be used to design ILs for wide applications such as (solvents, catalyst etc. that harmful as toxic for environment and human) without sacrificing animals, plant, fish and some sort of experimental organism. A lot of sets of data can also be featured and computed in the future works.

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References

[1] F. Dommert, J. Schmidt, C. Krekeler, Y. Y. Zhao, R. Berger, L. Delle Site, *et al.*, "Towards multiscale modeling of ionic liquids: From electronic structure to bulk properties," *Journal of Molecular Liquids,* vol. 152, pp. 2-8, 2010.

[2] M. H. Fatemi and P. Izadiyan, "Cytotoxicity estimation of ionic liquids based on their effective structural features," *Chemosphere,* vol. 84, pp. 553-563, 2011.

[3] R. F. De Souza, J. C. Padilha, R. S. Gonçalves, and J. Dupont, "Room temperature dialkylimidazolium ionic liquid-based fuel cells," *Electrochemistry Communications,* vol. 5, pp. 728-731, 2003.
[4] B. Lin, L. Qiu, J. Lu, and F. Yan, "Cross-linked alkaline ionic liquid-based polymer electrolytes for alkaline fuel cell applications," *Chemistry of materials,* vol. 22, pp. 6718-6725, 2010.
[5] L. J. Hardwick, M. Holzapfel, A. Wokaun, and P. Novák, "Raman study of lithium coordination in EMI-TFSI additive systems as lithium-ion battery ionic liquid electrolytes," *Journal of Raman Spectroscopy,* vol. 38, pp. 110-112, 2007.
[6] C. Sirisopanaporn, A. Fernicola, and B. Scrosati, "New, ionic liquid-based membranes for lithium battery application," *Journal of Power Sources,* vol. 186, pp. 490-495, 2009.
[7] C. Y. Wang, V. Mottaghitalab, C. O. Too, G. M. Spinks, and G. G. Wallace, "Polyaniline and polyaniline–carbon nanotube composite fibres as battery materials in ionic liquid electrolyte," *Journal of Power Sources,* vol. 163, pp. 1105-1109, 2007.
[8] M. Elyasi, M. A. Khalilzadeh, and H. Karimi-Maleh, "High sensitive voltammetric sensor based on Pt/CNTs nanocomposite modified ionic liquid carbon paste electrode for determination of Sudan I in food samples," *Food chemistry,* vol. 141, pp. 4311-4317, 2013.
[9] H. Khani, M. K. Rofouei, P. Arab, V. K. Gupta, and Z. Vafaei, "Multi-walled carbon nanotubes-ionic liquid-carbon paste electrode as a super selectivity sensor: application to potentiometric monitoring of mercury ion (II)," *Journal of hazardous materials,* vol. 183, pp. 402-409, 2010.
[10] D. Wei and A. Ivaska, "Applications of ionic liquids in electrochemical sensors," *Analytica Chimica Acta,* vol. 607, pp. 126-135, 2008.
[11] S. Dai, Y. Ju, and C. Barnes, "Solvent extraction of strontium nitrate by a crown ether using room-temperature ionic liquids," *Journal of the Chemical Society, Dalton Transactions,* pp. 1201-1202, 1999.
[12] G.-T. Wei, Z. Yang, and C.-J. Chen, "Room temperature ionic liquid as a novel medium for liquid/liquid extraction of metal ions," *Analytica Chimica Acta,* vol. 488, pp. 183-192, 2003.
[13] A. Lewandowski and M. Galiński, "Carbon–ionic liquid double-layer capacitors," *Journal of Physics and Chemistry of Solids,* vol. 65, pp. 281-286, 2004.
[14] T. Sato, G. Masuda, and K. Takagi, "Electrochemical properties of novel ionic liquids for electric double layer capacitor applications," *Electrochimica Acta,* vol. 49, pp. 3603-3611, 2004.
[15] E. R. Cooper, C. D. Andrews, P. S. Wheatley, and P. B. Webb, "Ionic liquids and eutectic mixtures as solvent and template in synthesis of zeolite analogues," *Nature,* vol. 430, p. 1012, 2004.
[16] M. J. Earle and K. R. Seddon, "Ionic liquids. Green solvents for the future," *Pure and applied chemistry,* vol. 72, pp. 1391-1398, 2000.
[17] R. D. Rogers and K. R. Seddon, "Ionic liquids--solvents of the future?," *Science,* vol. 302, pp. 792-793, 2003.
[18] V. Tsarpali, A. Belavgeni, and S. Dailianis, "Investigation of toxic effects of imidazolium ionic liquids,[bmim][BF 4] and [omim][BF 4], on marine mussel Mytilus galloprovincialis with or without the presence of conventional solvents, such as acetone," *Aquatic Toxicology,* vol. 164, pp. 72-80, 2015.
[19] A. Zakari, S. Waziri, B. Aderemi, and S. Mustapha, "Computational study of environmental fate of ionic liquids using conductor-like screening model for real solvents (COSMO-RS) method," *Journal of Environmental Chemistry and Ecotoxicology,* vol. 5, pp. 90-95, 2013.
[20] M. I. Hossain, "Synthesis, characterization and quantitative structure toxicity relationship of imidazolium, pyridinium and ammonium based ionic liquids," Chemical Engineering Department, Universiti Teknologi PETRONAS, IRC, UTP, 2013.
[21] J. Sun, S.-i. Fujita, and M. Arai, "Development in the green synthesis of cyclic carbonate from carbon dioxide using ionic liquids," *Journal of Organometallic Chemistry,* vol. 690, pp. 3490-3497, 2005.
[22] H. Olivier-Bourbigou, L. Magna, and D. Morvan, "Ionic liquids and catalysis: Recent progress from knowledge to applications," *Applied Catalysis A: General,* vol. 373, pp. 1-56, 2010.
[23] T. P. T. Pham, C.-W. Cho, and Y.-S. Yun, "Environmental fate and toxicity of ionic liquids: a review," *Water research,* vol. 44, pp. 352-372, 2010.
[24] M. I. Hossain, B. B. Samir, M. El-Harbawi, A. N. Masri, M. A. Mutalib, G. Hefter, *et al.*, "Development of a novel mathematical model using a group contribution method for prediction of ionic liquid toxicities," *Chemosphere,* vol. 85, pp. 990-994, 2011.
[25] R. J. Bernot, M. A. Brueseke, M. A. Evans-White, and G. A. Lamberti, "Acute and chronic toxicity of imidazolium-based ionic liquids on Daphnia magna," *Environmental Toxicology and Chemistry,* vol. 24, pp. 87-92, 2005.

[26] Y. Zhao, J. Zhao, Y. Huang, Q. Zhou, X. Zhang, and S. Zhang, "Toxicity of ionic liquids: Database and prediction via quantitative structure–activity relationship method," *Journal of hazardous materials,* vol. 278, pp. 320-329, 2014.
[27] H. Eschrig, *The fundamentals of density functional theory* vol. 32: Springer, 1996.
[28] S. R. Pilli, T. Banerjee, and K. Mohanty, "HOMO–LUMO energy interactions between endocrine disrupting chemicals and ionic liquids using the density functional theory: Evaluation and comparison," *Journal of Molecular Liquids,* vol. 207, pp. 112-124, 7// 2015.
[29] M. Appell and W. B. Bosma, "Assessment of the electronic structure and properties of trichothecene toxins using density functional theory," *Journal of Hazardous Materials,* vol. 288, pp. 113-123, 5/15/ 2015.
[30] B. Elidrissi, A. Ousaa, M. Ghamalia, S. Chtitaa, M. Ajanaa, M. Bouachrineb, *et al.*, "Toxicity in vivo of nitro-aromatic compounds: DFT and QSAR results," *J Comput Aided Mol Des,* vol. 4, pp. 28-37, 2014.
[31] M. Ghamali, S. Chtita, A. Adad, R. Hmamouchi, M. Bouachrine, and T. Lakhlifi, "Combining DFT and QSAR results for predicting the cytotoxicity of a series of orthoalkyl substituted 4-X-phenols."
[32] M. Zhu, F. Ge, R. Zhu, X. Wang, and X. Zheng, "A DFT-based QSAR study of the toxicity of quaternary ammonium compounds on Chlorella vulgaris," *Chemosphere,* vol. 80, pp. 46-52, 2010.
[33] K. Z. Sumon, A. Henni, and A. L. East, "Predicting p K a of Amines for CO2 Capture: Computer versus Pencil-and-Paper," *Industrial & Engineering Chemistry Research,* vol. 51, pp. 11924-11930, 2012.
[34] J. P. Perdew, J. Chevary, S. Vosko, K. A. Jackson, M. R. Pederson, D. Singh, *et al.*, "Atoms, molecules, solids, and surfaces: Applications of the generalized gradient approximation for exchange and correlation," *Physical Review B,* vol. 46, p. 6671, 1992.
[35] B. Delley, "From molecules to solids with the DMol3 approach," *The Journal of chemical physics,* vol. 113, pp. 7756-7764, 2000.