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TOXICITY PREDICTION OF IMIDAZOLIUM AND PYRIDINIUM IONIC LIQUIDS: A DFT-BASED APPROACH

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ABSTRACT

Ionic liquids (ILs) are defined as salts that melt below 100^0C and are typically made up of bulky organic cations paired with inorganic/organic anions. Even though ILs are green solvents due to their unique properties like low volatility, high thermal stability, and recyclability, they will have a certain level of toxicity. This study investigates the structural properties of imidazolium and pyridinium-based ionic liquids and predicts their toxicity using density functional theory (DFT) calculations. The study examines the influence of size, symmetry, and electronegativity of anion and cation on the structural properties and toxicity of ILs. A methodical investigation of ILs is conducted by considering various combinations of cations and anions. Structural features, including the highest occupied molecular orbital, lowest unoccupied molecular orbital, and electronic descriptive parameters, are examined using DFT calculations by Gaussian16. The analysis provides insights into the electronic structure, stability, and reactivity of the ILs, with a particular emphasis on understanding the impact of anion and cation properties. Computational methods are employed to predict toxicity, with a notable observation that toxicity effects are more pronounced when altering the anion component compared to the cation component.

KEYWORDS: Toxicity, Ionic Liquid, Daphnia Magna, Gaussian, DFT, Imidazolium, Pyridinium

INTRODUCTION

Ionic liquids (ILs) are materials composed of large organic or inorganic cations (e.g., imidazolium, pyridinium) and small anions (e.g., nitrate, tetrafluoroborate, dicyanamide), which are liquid at or below 100°C. They possess unique properties such as negligible vapor pressure, low flammability, high ionic conductivity, and excellent thermal and chemical stability, making them suitable for various applications, including fuel cells, batteries, sensors, and pharmaceutical drug discovery [1][2]. A critical application of ILs in pharmaceuticals is improving the solubility of poorly soluble drugs, which is essential for their efficacy at target sites [3].

While many ionic liquids are considered environmentally benign, their production and use can inadvertently lead to environmental pollution. Toxicity is the measure of the harmful effects on living organisms. Some studies have shown that ILs do have harmful effects on fish, bacteria, humans, and many more [13]. The purpose of toxicity measurement of ILs is to provide data that ensure safety, assess potential risks to human health and the environment, and help to develop greener and more sustainable ionic liquids with reduced environmental and health risks. The toxicity of ionic liquids can be measured in experiments with living organisms like animals, fungi, bacteria, etc., and the level of toxicity is represented by EC50 values. Even though there are other methods to find toxicity, computational methods dominate since it is cost-effective, timesaving, easier to handle, etc.

Imidazolium and pyridinium-based ionic liquids have a wide range of applications. For different types of applications, the unique combination of various alkyl substituents allows adjustment of properties. Imidazolium ionic liquids have drawn attention for a variety of reasons, particularly because of their thermal stability, relatively high ionic conductivity, tunable nature, wide electrochemical window, and amphoteric nature behavior in solution. Disubstituted imidazolium ionic liquid containing chloride, acetate, phosphate, and dicyanamide can be used as solvents. The absorption of 1-butyl-3-methyl imidazolium into the polymer film affects the ionic conductivity, thermal properties, and mechanical properties of the polymer film. eg:1-butyl-3-methyl imidazolium dicyanamide,1-ethyl-3-methyl imidazolium dicyanamide etc. Trialkyl-substituted imidazolium-based ionic liquids are being considered as potential electrolytes in electroplating and other electrochemical applications e.g. 1-butyl-2,3-dimethylimidazolium tetrafluoroborate (BMMImBF4) [5][11]. The pyridinium base ionic liquids, which contain pyridinium cation are readily available due to their reactivity, stability,

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and catalytic performance in organic synthesis. In the synthesis of some pharmaceutical products such as 1,4-dihydropyridine, dihydropyridines, and 3,5- bis(dicyloxycarbonyl)-1,4-dihydropyridine derivatives, the catalytic activity of pyridinium based ILs has a remarkable contribution. In the n-butyl pyridinium tetrafluoroborate ionic liquid, the aldehyde, ammonium acetate, and acetoacetate can be used to synthesize the 1,4-dihydropyridine derivatives [21]. Due to the potential biological applications of imidazolium and pyridinium, we are reporting the toxicity of imidazolium and pyridinium-based ionic liquid via the computational method by using density functional theory.

Theoretical Details

Toxicity Representation

The EC50 value provides important information about the potency or effectiveness of a substance in producing a desired effect and is used in various fields, including toxicology, pharmacology, environmental science, and risk assessment. It serves as a valuable tool for comparing the activities of different substances, assessing dose-response relationships, and informing regulatory decisions regarding exposure limits and safety thresholds. EC50 is a metric employed in toxicology and pharmacology to determine the concentration of a substance that elicits a specified response in half of a test population or experimental system. In toxicology, EC50 typically refers to the concentration of a toxicant (e.g., a pesticide, industrial chemical, or pollutant) that induces a specific toxic effect in 50% of the exposed organisms or cells. The specific toxic effect may vary depending on the study design and the organism or cell type under investigation. Common endpoints include mortality, growth inhibition, reproductive impairment, or biochemical changes. In pharmacology, EC50 is used to quantify the concentration of a drug or pharmacological agent that produces a specific therapeutic effect in 50% of the treated individuals or experimental samples. The therapeutic effect may include pain relief, inhibition of cell proliferation, relaxation of smooth muscle, or enhancement of neurotransmitter activity, among others [19]. The EC50 value is determined through dose-response experiments, where a range of concentrations of the substance of interest is tested on the target organism, cells, or tissues, and the resulting response is measured. Typically, the response is plotted against the logarithm of the concentration, and the concentration corresponding to 50% of the maximum response is determined, representing the EC50 value. The EC50 values can vary over a wide range of concentrations, spanning several orders of magnitude. In some cases, the EC50 values may be very small, especially when dealing with potent substances or highly sensitive test systems. The mathematical transformation of common logarithms is commonly used to compress a wide range of concentration values into a more manageable scale for analysis and interpretation. The log [EC50] value, which is the logarithm of the effective concentration (EC50) of an ionic liquid serves as a crucial indicator of its toxicity to aquatic organisms, specifically Daphnia Magna in this case. This logarithmic representation signifies the concentration at which 50% of the test organisms, in this instance, Daphnia Magna, experience adverse effects, such as mortality or immobilization, over a defined period of exposure. This value provides valuable insight into the toxicity of the substance to Daphnia magna. A lower log [EC50] value indicates higher toxicity, as it signifies that a lower concentration of the substance is required to cause adverse effects on the test organisms. The negative logarithm of the EC50 value (log [EC50]) quantifies the acute toxicity of an ionic liquid toward Daphnia magna. The log [EC50] value of ILs is determined through dose-response experiments, where different concentrations of the IL are tested on a target organism or cell culture, and the resulting response is measured. The concentration corresponding to 50% of the maximum response is then calculated, and its logarithm is taken to obtain the log [EC50 value. This information is essential for evaluating the risks associated with the use, production, and disposal of the ionic liquid, thereby facilitating informed decision-making in regulatory and environmental management contexts. By comparing this value to other substances with known toxicities and regulatory standards, can assess the relative hazard posed by the ionic liquid. The log [EC50] is also being used for the model equation to develop.

Modeling of Equation

In this work, we used a model equation developed by Nu'Aim et.al to determine the toxicity of selected ionic liquids (ILs). This model, based on multiple linear regression (MLR) analysis, predicts toxicity (log [EC50]) by correlating it with significant molecular descriptors. Molecular descriptors encompassing highest occupied molecular orbital energy (E_{HOMO}), lowest unoccupied molecular orbital energy (E_{LUMO}), hardness (η), chemical potential (μ), electrophilicity index (ω), energy gap (ΔE), and electronegativity (χ) were examined. The analysis identified E_{HOMO} and E_{LUMO} for both cation and anion and the cation's electrophilicity index (ω) as significant descriptors. This approach helps in predicting the toxicity of ILs to Daphnia magna based on these molecular properties. The correlation is a linear equation in the form [4],

$$\log[EC50] = -1.1263 - 0.00991(E_{-HOMO}, cation) + 0.0039995\,(E_{-LUMO}, cation) + 0.00005(\omega, cation) + 0.00535(E_{-HOMO}, anion) - 0.004511(E_{-LUMO}, anion)$$

Computational Details

In the model equation for predicting the toxicity (log [EC50]) of ionic liquids to Daphnia Magna, five significant descriptors were identified: the electrophilicity index of the cation, and the HOMO and LUMO energies of both the cation and anion. These descriptors are estimated using density functional theory (DFT) in Gaussian16. The structures of the chosen ionic liquids are optimized using Becke's three-parameter practical hybrid methods with the Lee, Yang Parr (LYP) functional [24] at DFT/B3LYP/6-311++G (d,p) level of the theory [25]. The EHOMO and ELUMO values for both cations and anions are obtained from their optimized structures. Additionally, other descriptors such as the energy gap, chemical potential, electronegativity, and hardness are calculated using formulas involving the HOMO and LUMO values [8][23].

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

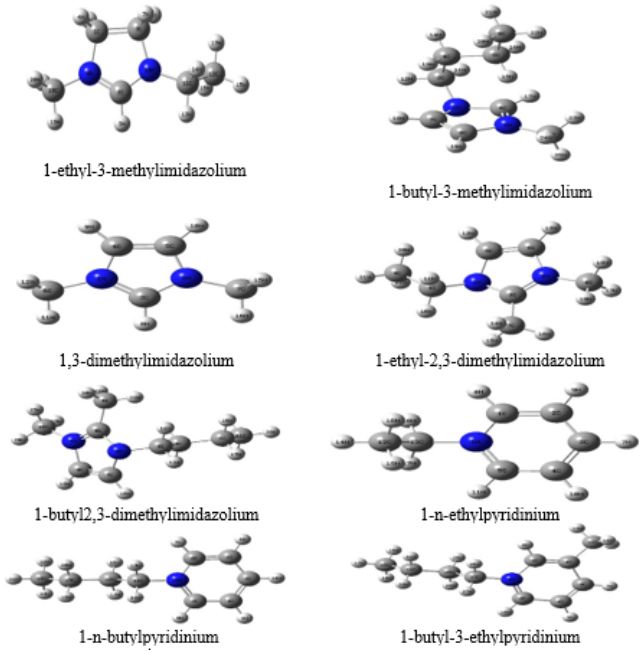
MATERIALS AND METHODS

Due to the potential applications of imidazolium and pyridinium-based ionic liquids, five different imidazolium cations, and pyridinium cations each are taken for investigation. Thiocyanate, dicyanamide, hexafluorophosphate, tetrafluoroborate, diethyl phosphate, and borate are the six different anions used for the study and which constitute a total of 60 ionic liquids, whose toxicity is calculated. Five imidazolium cations (1-ethyl-3-methylimidazolium, 1-butyl-3-methylimidazolium, 1,3-dimethyl imidazolium, 1-ethyl-2,3-dimethylimidazolium, and 1-butyl-2,3-dimethylimidazolium) and one pyridinium cation (1-n-ethyl pyridinium), 5 different pyridinium cations (namely 1-n-ethyl pyridinium, 1-n-butyl pyridinium, 1-butyl-3-ethylpyridinium, 1-butyl-4-methylpyridinium and 1(carboxymethyl)pyridinium) and 6 anions are drawn using gauss view software package and are optimized using gaussian16 software package using DFT.

RESULT AND DISCUSSION

Molecular Geometry

The optimized molecular geometries of all the investigated cation and anion parts separately are shown below in Figure 1.



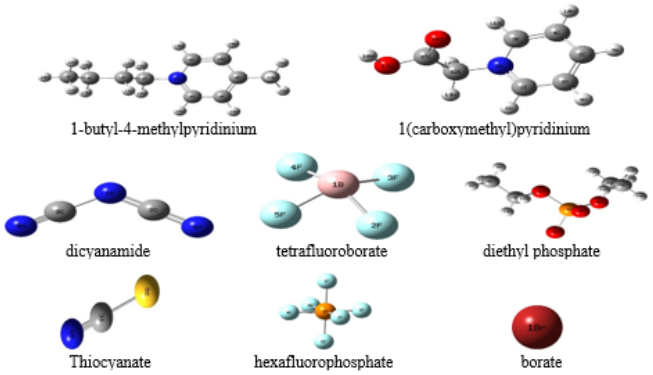


Figure1: Optimized geometries of cations and anions

Molecular Descriptors

Molecular descriptors of the above ten different cations are listed in Table 1. From the values of HOMO and LUMO energies Chemical Potential, Hardness, Electrophilicity index, and Electronegativity are calculated. Based on hardness and electrophilicity index values, the reactivity trend among the imidazolium cations was determined as follows: 1-ethyl-2,3-dimethyl imidazolium > 1,3-dimethyl imidazolium > 1-butyl-3-methyl imidazolium > 1-butyl- 2,3-dimethyl imidazolium > 1-ethyl-3-methyl imidazolium and that of pyridinium are in the order 1(carboxymethyl) pyridinium > 1-n-ethyl pyridinium > 1-n-butyl pyridinium > 1-butyl-3-methyl pyridinium > 1-butyl-4-methyl pyridinium

Cation	E_{HOMO} (eV)	E_{LUMO} (eV)	Chemical potential (eV)	Hardness (eV)	Electrophilicity index (eV)	Electronegativity (eV)
1-ethyl-3-methylimidazolium	-0.413	-0.104	0.258	0.155	0.216	-0.258
1-butyl-3-methylimidazolium	-0.434	-0.189	0.311	0.123	0.396	-0.311
1,3-dimethylimidazolium	-0.443	-0.197	0.319	0.123	0.415	-0.319
1-ethyl-2,3-dimethylimidazolium	-0.428	-0.214	0.321	0.107	0.480	-0.321
1-butyl2,3-dimethylimidazolium	-0.416	-0.176	0.296	0.120	0.364	-0.296
1-n-ethylpyridinium	-0.469	-0.249	0.359	0.109	0.589	-0.359
1-n-butylpyridinium	-0.455	-0.246	0.350	0.105	0.586	-0.350
1-butyl-3-methyl pyridinium	-0.444	-0.238	0.341	0.103	0.566	-0.341

1-butyl-4-methylpyridinium	-0.450	-0.233	0.342	0.109	0.538	-0.342
1(carboxymethyl) pyridinium	-0.451	-0.254	0.352	0.099	0.629	-0.352

Table 1: Electronic descriptors of imidazolium and pyridinium cations

Toxicity calculations of ionic liquids

Ionic Liquids with pyridinium	Log [EC_{50}]	Ionic Liquids with imidazolium	Log [EC_{50}]
1-ethyl pyridinium dicyanamide	-1.1236	1-ethyl-3-methyl imidazolium dicyanamide	-1.1236
1-ethyl pyridinium tetrafluoroborate	-1.1239	1-ethyl-3-methyl imidazolium tetrafluoroborate	-1.1239
1-ethyl pyridinium Diethyl phosphate	-1.1235	1-ethyl-3-methyl imidazolium Diethyl phosphate	-1.1234
1-ethyl pyridinium thiocyanate	-1.1235	1-ethyl-3-methyl imidazolium thiocyanate	-1.1235
1-ethyl pyridinium bromide	-1.1236	1-ethyl-3-methyl imidazolium bromide	-1.1216
1-ethyl pyridinium hexafluorophosphate	-1.1244	1-ethyl-3-methyl imidazolium hexafluorophosphate	-1.1244
1-butyl pyridinium dicyanamide	-1.1237	1-butyl-3-methyl imidazolium dicyanamide	-1.1237
1-butyl pyridinium tetrafluoroborate	-1.1240	1-butyl-3-methyl imidazolium tetrafluoroborate	-1.1240
1-butyl pyridinium Diethyl phosphate	-1.1236	1-butyl-3-methyl imidazolium Diethyl phosphate	-1.1236
1-butyl pyridinium thiocyanate	-1.1236	1-butyl-3-methyl imidazolium thiocyanate	-1.1236
1-butyl pyridinium bromide	-1.1237	1-butyl-3-methyl imidazolium bromide	-1.1237
1-butyl pyridinium hexafluorophosphate	-1.1245	1-butyl-3-methyl imidazolium hexafluorophosphate	-1.1245
1-butyl-3-methyl pyridinium dicyanamide	-1.1238	1,3-dimethyl imidazolium dicyanamide	-1.1237
1-butyl-3-methyl pyridinium tetrafluoroborate	-1.1241	1,3-dimethyl imidazolium tetrafluoroborate	-1.1239
1-butyl-3-methyl pyridinium Diethyl phosphate	-1.1236	1,3-dimethyl imidazolium Diethyl phosphate	-1.1235
1-butyl-3-methyl pyridinium thiocyanate	-1.1237	1,3-dimethyl imidazolium thiocyanate	-1.1236
1-butyl-3-methyl pyridinium bromide	-1.1238	1,3-dimethyl imidazolium bromide	-1.1237
1-butyl-3-methyl pyridinium hexafluorophosphate	-1.1246	1,3-dimethyl imidazolium hexafluorophosphate	-1.1244
1-butyl-4-methyl pyridinium dicyanamide	-1.1237	1-ethyl-2,3-dimethyl imidazolium dicyanamide	-1.1239
1-butyl-4-methyl pyridinium tetrafluoroborate	-1.1240	1-ethyl-2,3-dimethyl imidazolium tetrafluoroborate	-1.1242
1-butyl-4-methyl pyridinium Diethyl phosphate	-1.1235	1-ethyl-2,3-dimethyl imidazolium Diethyl phosphate	-1.1237
1-butyl-4-methyl pyridinium thiocyanate	-1.1236	1-ethyl-2,3-dimethyl imidazolium thiocyanate	-1.1238
1-butyl-4-methyl pyridinium bromide	-1.1237	1-ethyl-2,3-dimethyl imidazolium bromide	-1.1239
1-butyl-4-methyl pyridinium hexafluorophosphate	-1.1245	1-ethyl-2,3-dimethyl imidazolium hexafluorophosphate	-1.1247
1-(carboxymethyl) pyridinium dicyanamide	-1.1238	1-butyl-2,3-dimethyl imidazolium dicyanamide	-1.1238
1-(carboxymethyl) l pyridinium tetrafluoroborate	-1.1241	1-butyl-2,3-methyl imidazolium tetrafluoroborate	-1.1242
1-(carboxymethyl) pyridinium Diethyl phosphate	-1.1236	1-butyl-2,3-methyl imidazolium Diethyl phosphate	-1.1237
1-(carboxymethyl) pyridinium thiocyanate	-1.1236	1-butyl-2,3-methyl imidazolium thiocyanate	-1.1237
1-(carboxymethyl) pyridinium bromide	-1.1237	1-butyl-2,3-methyl imidazolium bromide	-1.1238
1-(carboxymethyl) pyridinium hexafluorophosphate	-1.1240	1-butyl-2,3-methyl imidazolium hexafluorophosphate	-1.1246

Table 2. Toxicity values of the ionic liquids.

One imidazolium IL was selected (1-ethyl-3-methyl imidazolium Dicyanamide) as the baseline, while four additional imidazolium ILs were chosen (1-ethyl-3-methyl imidazolium tetrafluoroborate, 1-ethyl-3-methyl imidazolium diethyl phosphate, 1-ethyl-3-methyl imidazolium thiocyanate, 1-ethyl-3-methyl imidazolium hexafluorophosphate, 1-ethyl-3-methyl imidazolium Bromide), each featuring a different anion while maintaining a consistent imidazolium cation. By calculating the difference in Log [EC50] values between each imidazolium IL and the baseline, the relative toxicity variation attributed to different anion substitutions was quantified. This process was repeated across five imidazolium cations (1-ethyl-3-methyl imidazolium, 1-butyl-3-methyl imidazolium,1,3-dimethyl imidazolium,1-ethyl- 2,3-dimethyl imidazolium,1-butyl-2,3-dimethyl imidazolium) each paired with six distinct anions (dicyanamide, diethyl phosphate, thiocyanate, tetrafluoroborate, hexafluorophosphate, Bromide). Finally, averages of the toxicity differences were computed which is 0.000441(4.41 times ten to minus four), providing an overall measure of the impact of anion variation on IL toxicity. Subsequently, the reverse calculation is done by maintaining the anion part constant and changing the cation part. Four additional imidazolium ILs were selected, each featuring a different cation while maintaining a consistent anion. The same procedure, of calculating toxicity differences was applied to assess the impact of cation variation on IL toxicity while keeping the anion part constant. This process was repeated across six different anions, each paired with five distinct imidazolium cations, and an average toxicity difference was calculated, which is 0.00015 (1.5 times ten to minus four),

providing cation impact on IL toxicity. Similarly, the same procedure was followed for the analysis of pyridinium cations. When substituting anions (dicyanamide, diethyl phosphate, thiocyanate, tetrafluoroborate, hexafluorophosphate) while keeping the cation constant (1-butyl-3- methyl pyridinium), the average toxicity difference was 0.000564. Conversely, when varying the cation (substituting 1-ethyl pyridinium, 1-butyl pyridinium, 1- butyl-4-methyl pyridinium, 1-carboxymethyl pyridinium) while keeping the anion constant (bromide), the average toxicity difference was 0.000094. This indicates that changes in the anion component have a greater impact on IL toxicity compared to changes in the cation component.

CONCLUSION

This exploration undertook a comprehensive investigation into the structural properties and toxicity prediction of certain ionic liquids using density functional theory (DFT) calculations. Through a methodical analysis of various factors such as cation and anion properties, toxicity representations, and reactivity orders, several key findings emerged. The DFT calculations revealed valuable insights into the electronic structure and reactivity of the studied ionic liquids, shedding light on their potential toxicity and implications for environmental and health hazards. Our study has revealed an important insight into the toxicity effects of ionic liquids (ILs). The identification of the reactivity order of pyridinium and imidazolium cations provides crucial insights into the toxicity of ionic liquids (ILs) in pharmaceutical applications. This knowledge enables the selection of safer cations for drug formulations, minimizing the risk of adverse effects while optimizing functionality. Through a systematic investigation of various IL compositions, we have found compelling evidence that the toxicity effect is more pronounced when altering the anion component compared to the cation component. The implications of this finding extend beyond the scope of our study, offering valuable insights for researchers and practitioners working in fields such as environmental science, toxicology, and materials chemistry. By understanding the relative contributions of cation and anion components to IL toxicity, we can better mitigate potential risks and design safer ILs for industrial and commercial use. Moving forward, it will be important to further investigate the mechanisms underlying the observed differences in toxicity between cation and anion variations. Additionally, future research efforts should explore the relationship between IL structure, toxicity, and environmental fate to develop predictive models and guidelines for the rational design of environmentally benign ILs.

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