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# COMPUTATIONAL INVESTIGATION OF IMIDAZOLIUM IONIC LIQUIDS AND THEIR INTERACTIONS WITH CERTAIN BIO-SPECIES USING DENSITY FUNCTIONAL THEORY

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## ABSTRACT

Ionic liquids, particularly imidazolium-based variants, have gained significant attention due to their unique properties, such as tunable polarity, high thermal stability, and potential applications in electrochemical devices and biosensing. A detailed computational analysis of imidazolium-based ionic liquids (ILs) and their interactions with biologically significant molecules—dopamine, ascorbic acid, and uric acid—was conducted. Using Density Functional Theory (DFT) with the 6-311++G(d,p) basis set, the electronic properties, molecular structures, and interaction energies of three ILs—EMI-SCN, EMI-DCA, and BMI-PF6—were explored. Structural optimization, HOMO-LUMO gap analysis, and molecular electrostatic potential mapping were employed to uncover binding characteristics and reactivity of the ILs toward the biomolecules. Among the tested ILs, EMI-SCN exhibited the highest interaction energies with all analytes, particularly showing strong affinity for ascorbic acid, indicating its potential in electrochemical sensors. The calculated global reactivity descriptors support the stability and reactivity trends, with EMI-SCN demonstrating superior electronic and electrostatic interactions compared to EMI-DCA and BMI-PF6. EMI-SCN's unique interaction profiles suggest its suitability for selective detection of dopamine, ascorbic acid, and uric acid in biological environments. These findings pave the way for the rational design of ionic liquids aimed at enhancing the performance of biosensors and electrochemical devices, offering improved sensitivity and selectivity for biological molecule detection.

**KEYWORDS:** Imidazolium, Ionic Liquids, Dopamine, Ascorbic Acid, Uric Acid, Density Functional Theory (DFT), Interaction Energy, Global Reactivity Descriptors, Bioanalyte Detection

## INTRODUCTION

Ionic liquids (ILs) are a class of salts that remain in the liquid state at temperatures below 100°C, distinguishing them from conventional salts with higher melting points. They are typically composed of a bulky organic cation, such as imidazolium, phosphonium, tetraalkyl-ammonium, or pyrrolidinium,paired with an inorganic or organic anion like tetrafluoroborate ($BF_4^-$), hexafluorophosphate ($PF_6^-$), or bis(trifluoromethyl-sulfonyl) imide ($[Tf_2N]^-$). The ionic and molecular structures of these components allow ILs to exhibit unique physicochemical properties, such as a wide liquid range, low melting point, negligible vapor pressure, high ionic conductivity, and extensive electrochemical and thermal stability. These properties make ILs promising candidates for various applications in materials science, electrochemistry, and beyond.

ILs have garnered significant attention due to their potential for diverse technological applications, including their use in catalysis, battery electrolytes, separations, and advanced sensing technologies. The tunability of ILs, achieved by modifying the cation, anion, or both, offers researchers the flexibility to design systems with tailored properties for specific applications. Imidazolium-based ionic liquids have been extensively studied for their superior electrochemical properties. These include a broad electrochemical window, high ionic conductivity, and excellent solvation abilities for a variety of substances, positioning them as ideal candidates for applications in electrochemical sensing and energy storage devices.

In electrochemical sensing, ILs are utilized either as autonomous sensing films or as binders that facilitate the interaction between the transducer and the bioreceptor layer. The electrochemical stability of ILs, along with their low volatility, ensures that they can withstand harsh conditions and prolonged use, making them suitable for the development of long-lasting sensors. The ability of ILs to mediate electron transfer and their wide electrochemical windows are particularly advantageous in enhancing sensor performance, sensitivity, and selectivity.

To gain a deeper understanding of the electrochemical behaviour of ILs, particularly those based on imidazolium cations, computational approaches such as Density Functional Theory (DFT) are employed. DFT offers insights into the molecular and electronic structure of ILs, allowing for the prediction of properties like molecular electrostatic potential (MESP) surfaces, dipole moments, and HOMO-LUMO (Highest Occupied Molecular Orbital - Lowest Unoccupied Molecular Orbital) energies. This approach is instrumental in elucidating the structure-activity relationships and fundamental interactions that govern the performance of ILs in electrochemical applications.

The present study focuses on imidazolium-based ILs, specifically 1-ethyl-3-methylimidazolium thiocyanate (EMI-SCN), 1-ethyl-3-methyl-imidazolium dicyanamide (EMI-

DCA), and 1-butyl-3-methylimidazolium hexafluorophosphate (BMI-$PF_6$). These ILs were selected for their structural diversity and electrochemical potential, making them suitable candidates for use in sensing applications. Computational analysis using DFT was carried out at the B3LYP/6-311G++(d,p) level of theory with the Gaussian software suite to explore the total energy, dipole moment, MESP surfaces, HOMO-LUMO gaps, and other global descriptive parameters. These calculations provide a comprehensive picture of the electronic properties of these ILs, which are crucial for understanding their role in electrochemical systems.

The interactions between ILs and analytes are of particular importance in the context of electrochemical sensing. In this study, we investigate the interaction energies between imidazolium-based ILs and three biologically relevant molecules: dopamine, ascorbic acid, and uric acid. Dopamine, a neurotransmitter, is critical for regulating various physiological functions, including mood, motor control, and the reward system. It is often used as a biomarker in diagnosing neurological diseases such as Parkinson's disease and depression. Ascorbic acid (vitamin C) acts as a potent antioxidant that supports the immune system, collagen synthesis, and iron absorption, while also being a cofactor for several enzymatic reactions. Uric acid, the final metabolite of purine breakdown, plays a role in maintaining cellular homeostasis, but elevated levels are associated with medical conditions like gout and cardiovascular diseases.

The interaction of these biomolecules with ILs is central to the design of selective and sensitive electrochemical sensors. Understanding these interactions at the molecular level allows for the rational design of sensor interfaces that can selectively bind or interact with specific analytes, enhancing the performance of the sensing device. For instance, in sensors aimed at detecting neurotransmitters like dopamine, the affinity between the sensing surface modified with ILs and the analyte can significantly influence the sensitivity and limit of detection. Similarly, for ascorbic acid and uric acid, the ability of ILs to form stable interactions with these molecules could improve the selectivity of sensors designed to detect these compounds in complex biological matrices.

This study leverages DFT to calculate the interaction energies between imidazolium-based ILs and these analytes. By exploring the interaction energies, this research aims to provide insights into the fundamental mechanisms governing the interactions between ILs and biomolecules. These findings could lead to the development of IL-based sensing systems for real-time monitoring of clinically relevant analytes, potentially enabling advancements in medical diagnostics, environmental monitoring, and food safety.

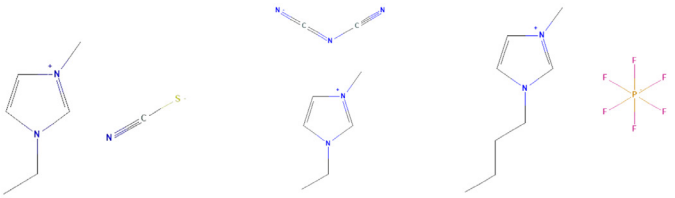
The relevance of ILs in electrochemical sensing extends beyond their role as a medium or binder; they can also actively participate in the sensing mechanism through their interactions with analytes. By modulating the physicochemical properties of ILs, such as polarity, hydrophobicity, and electrostatic potential, it is possible to fine-tune the sensor's performance characteristics. The imidazolium cation, due to its versatile functional groups and high stability, is particularly suitable for such modifications. This adaptability, coupled with the low toxicity and biocompatibility of many imidazolium-based ILs, makes them highly attractive for use in developing biosensors and other analytical devices.

In summary, the present study aims to computationally investigate the structural and electronic properties of imidazolium-based ILs and their interactions with dopamine, ascorbic acid, and uric acid. By combining DFT calculations with insights into molecular interactions, this work contributes to the understanding of how ILs can be optimized for specific electrochemical sensing applications. The results are expected to provide a scientific basis for the development of next-generation IL-based sensing platforms with enhanced sensitivity, selectivity, and stability for a variety of real-world applications.

## MATERIALS AND METHODS

### Materials

The structure of the investigated samples, 1-ethyl-3-methylimidazolium thiocyanate (EMI-SCN) ($C_7H_{11}N_3S$, Molecular Weight 169.25 g/mol), 1-ethyl-3-methylimidazolium dicyanamide (EMI-DCA) (C8H11N5, Molecular Weight: 177.21 g/mol), and 1-butyl-3-methylimidazolium hexafluorophosphate (BMI-$PF_6$) ($C_8H_{15}F_6N_2P$ Molecular Weight: 284.18 g/mol )was taken from the PubChem database [2] with PubChem ID: 16211115, 11159638 and 2734174 respectively. The Open Babel application [3] was used to convert the downloaded SDF (Standard Data File) format to GJF (Gaussian Job File) input files.



(a) (b) (c)

Figure 1: Chemical structures of (a) 1-ethyl-3-methylimidazolium-thiocyanate (EMI-SCN) (b) 1-ethyl-3-methylimidazolium- dicyanamide (EMI-DCA) (c) 1-butyl-3-methylimidazolium- hexafluorophosphate (BMI-PF6)

### Computational Details

All the computational calculations were performed by density functional theory using the Gaussian09 software package [4]. The initial geometry of glipizide was optimized using Becke's three-parameter practical hybrid methods with the Lee, Yang Parr (LYP) functional at DFT/B3LYP/6-311++G (d,p) level of the theory [2]. The total energy, dipole moment, Molecular Electrostatic Potential (MESP) surface, Highest Occupied Molecular Orbital (HOMO), Lowest Unoccupied Molecular Orbital (LUMO) and global descriptive parameters are then evaluated from the optimized geometry. The total energy represents the stability of the molecular configuration. Lower total energy indicates a more stable structure. The dipole moment indicates molecular polarity, influencing analyte interactions with the electrode. An appropriate dipole moment

contributes to favourable electrostatic interactions. Molecular Electrostatic Potential (MESP) surface provides information about charge distribution. A well-distributed ESP can enhance interactions. The HOMO-LUMO gap indicates electronic stability. A small HOMO-LUMO gap can facilitate electron transfer reactions relevant to sensing or catalysis actions.

Global reactivity descriptors give an insight into the reactivity of the molecules. The global reactivity descriptors including softness, hardness, chemical potential, electrophilicity index, and electronegativity was computed with an intention to have a comprehensive insight into the reactive nature of ILs using Koopman's closed-shell theorem as follows[5,6,7],

$$\text{Ionization Potential (IP)} \approx -E_{HOMO}$$

$$\text{Electron Affinity (EA)} \approx -E_{LUMO}$$

$$\text{Hardness } (\eta) \approx \frac{IP - EA}{2}$$

$$\text{Electronegativity } (\chi) \approx \frac{IP + EA}{2}$$

$$\text{Softness (S)} \approx \frac{1}{2\eta}$$

$$\text{Chemical potential } (\mu) \approx -\chi$$

$$\text{Electrophilicity index } (\omega) \approx \frac{\mu^2}{2\eta}$$

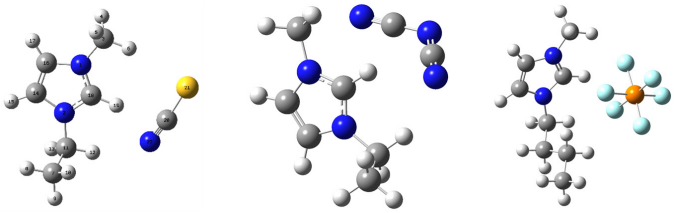
The structures of Dopamine (DA) ($C_8H_{11}NO_2$, Molecular Weight: 153.18g/mol), Ascorbic Acid (AA) ($C_6H_8O_6$, Molecular Weight: 176.12g/mol) and Uric Acid (UA) ($C_5H_4N_4O_3$, Molecular Weight: 168.11g/mol) are taken from the PubChem and optimized using the aforementioned same level of the theory. Then optimized structures of the binaries by combining IL with the bio-species to calculate the interaction energy. Interaction energy provides valuable insight into the strength of the interaction between the analyte and the electrode material. The interaction energy is defined as the difference in the energy of the noncovalent complex and the sum of energies of the monomers constituting it. If AB represents a binary with constituent molecules A and B, then the interaction energy of the binary is calculated using the formula,

$$\Delta E^{int}(AB) = E(AB) - E(A) - E(B)$$

## RESULTS AND DISCUSSION

### Molecular Geometry

The molecular structure of 1-ethyl-3-methylimidazolium-thiocyanate (EMI-SCN) with 22 atoms and 90 electrons, 1-ethyl-3-methylimidazolium-dicyanamide (EMI-DCN) with 24 atoms and 94 electrons and 1-butyl-3-methylimidazolium hexafluorophosphate (BMI-PF6) with 32 atoms and 146 electrons were optimized after examining its distribution and conformational behaviour of it through different possible structures using density functional theory with DFT/B3LYP/6-311++G(d,p). The optimized geometries of the molecules are shown in Figure2. The obtained energies in Hartree and electron volts and dipole moment in Debye are listed in the Table1.



(a) (b) (c)

**Figure 2:** Optimized geometries of (a) 1-ethyl-3-methylimidazolium-thiocyanate (EMI-SCN) (b) 1-ethyl-3-methylimidazolium- dicyanamide (EMI-DCA) (c) 1-butyl-3-methylimidazolium-hexafluorophosphate (BMI-PF6).

| | EMI-SCN | EMI-DCA | BMI-PF6 |
|---|---|---|---|
| **Energy (Hartree)** | -835. 93 | -585.33 | -1364.28 |
| **Energy (keV)** | -19.28 | -15.93 | -37.12 |
| **Dipole Moment (Debye)** | 13.88 | 11.66 | 13.87 |

**Table 1:** Energy and dipole moment of 1-ethyl-3-methylimidazolium-thiocyanate (EMI-SCN), 1-ethyl-3-methylimidazolium- dicyanamide (EMI-DCA), 1-butyl-3 methylimidazolium- hexafluorophosphate (BMI-PF6).

### Frontier molecular orbitals (FMOs) and molecular electrostatic potential (MEP)

To elucidate the reactivity and intermolecular interactions of ILs with analytes, a detailed investigation of the frontier molecular orbitals (FMOs) was conducted. The highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) energies provide insights into the electron-donating and electron-accepting capabilities of the molecules, respectively, and can be considered potential sites for interactions. Figure 3 illustrates the calculated FMO distributions and energies in the gas phase for the studied ionic liquids. Analysis of the frontier molecular orbitals (FMOs) reveals that the LUMO for all studied ionic liquids exhibits characteristic π-like molecular orbitals localized on the imidazolium ring. While the HOMO of EMI-SCN and EMI-DCA also display π-like molecular orbitals distributed over the anion part, the HOMO of BMI-PF6 forms bonding molecular orbitals centered on the imidazolium ring. This suggests a potential difference in reactivity between EMI-SCN and EMI-DCA compared to BMI-PF6.

Molecular electrostatic potential (MESP) mapping is a valuable tool for predicting and understanding molecular reactivity. The regions of the molecule with the lowest electron density, often visualized in blue on MESP maps, are potential sites for interactions with analytes. The MESP maps generated from DFT/B3LYP/6-311++G(d,p) calculations (Figure 4) illustrate the electron density distribution, where blue represents electropositive centers and red represents electronegative centers. As depicted in Figure 4, the MESP analysis reveals that the most electron-rich regions of all three ionic liquids are localized around the anion, while the imidogen (NH) bonds exhibit the most electron-deficient centers. While the analyte interaction is a complex process influenced by multiple factors, the MESP map provides valuable insights into the potential sites for molecular interactions. The global hardness, as defined

by Koopman's closed-shell theorem, reflects the resistance of the electron cloud to deformation under external perturbations. Conversely [8], chemical softness, inversely related to hardness, quantifies the molecule's ability to accept electrons. The chemical potential, a measure of electron escaping tendency, can be calculated as the first derivative of energy with respect to the number of electrons. Electronegativity, representing the tendency to attract electrons in a chemical bond,

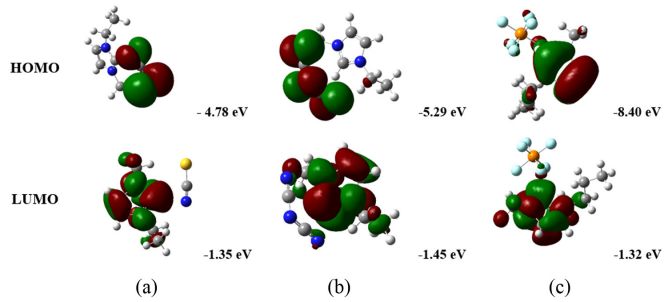



**Figure 3:** HOMO and LUMO structures and energies of (a)1-ethyl-3-methylimidazolium-thiocyanate (EMI-SCN) (b)1-ethyl-3-methylimidazolium- dicyanamide (EMI-DCA) (c)1-butyl-3-methylimidazolium- hexafluorophosphate (BMI-PF6).

is directly related to the negative of chemical potential. The electrophilicity index provides a quantitative measure of the strength of an electrophile. The calculated electronic properties reveal that EMI-SCN and EMI-DCA exhibit higher reactivity than BMI-PF6. Among these two, EMI-SCN demonstrates superior characteristics, likely due to the influence of the thiocyanate anion on the electronic structure and reactivity of the ionic liquid.

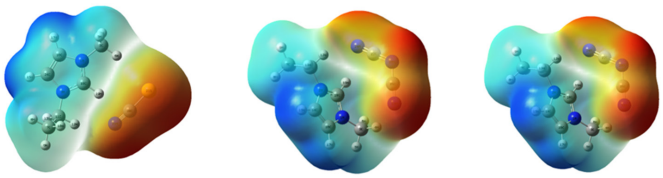



**Figure 4:** MESP surfaces of (a)1-ethyl-3-methylimidazolium-thiocyanate (EMI-SCN) (b)1-ethyl-3-methylimidazolium-dicyanamide (EMI-DCA) (c)1-butyl-3-methylimidazolium-hexafluorophosphate (BMI-PF6)

**Interaction Energy**

The interaction energies calculated using Density Functional Theory (DFT) at the 6-311++G(d,p) level provide critical insights into the molecular interactions between the imidazolium-based ionic liquids (ILs) and the biomolecules dopamine, uric acid, and ascorbic acid. The negative values of the interaction energies indicate favourable binding interactions, with stronger interactions corresponding to more negative energy values. For dopamine, the interaction energies with EMI-SCN, EMI-DCA, and BMI-PF6 were found to be -0.9526, -0.7522, and -0.7160, respectively. These results suggest that EMI-SCN exhibits the strongest interaction with dopamine, followed by EMI-DCA and BMI-PF6. This trend highlights the role of the anionic component in influencing the binding affinity of ILs toward neurotransmitters like dopamine. The relatively weaker interaction of BMI-PF6 with dopamine could be attributed to the larger and more diffuse nature of the $PF6^-$ anion, which reduces its ability to form strong electrostatic interactions with dopamine.

For uric acid, the interaction energies were -1.5591 for EMI-SCN, -1.4109 for EMI-DCA, and -1.2297 for BMI-PF6, indicating that the ILs interact more strongly with uric acid than with dopamine.

| Properties | EMI-SCN | EMI-DCA | BMI-PF6 |
|---|---|---|---|
| Ionisation Energy (IP) | 0.1757 | 0.1945 | 0.3086 |
| Electron Affinity (EA) | 0.0498 | 0.0531 | 0.0485 |
| Hardness ("η" ) | 0.0290 | 0.0707 | 0.1300 |
| Softness (S) | 7.9434 | 7.0726 | 3.8451 |
| Electronegativity (χ ) | 0.1127 | 0.1238 | 0.1786 |
| Chemical Potential ("μ" ) | -0.1127 | -0.1238 | -0.1786 |
| Electrophilicity Index ("ω" ) | 0.1009 | 0.1084 | 0.1226 |

**Table 2:** Global descriptive parameters of 1-ethyl-3-methylimidazolium-thiocyanate (EMI-SCN), 1-ethyl-3-methylimidazolium- dicyanamide (EMI-DCA), 1-butyl-3-methylimidazolium- hexafluorophosphate (BMI-PF6).

The stronger interaction between ILs and uric acid may be due to the molecular structure and functional groups of uric acid, which allow for enhanced hydrogen bonding and electrostatic interactions with the cations and anions of the ILs. Among the ILs, EMI-SCN again displayed the strongest interaction with uric acid, suggesting that the thiocyanate anion ($SCN^-$) is particularly effective in stabilizing this biomolecule through specific non-covalent interactions, likely involving sulphur and nitrogen atoms that participate in hydrogen bonding or dipole interactions.

Ascorbic acid demonstrated the most negative interaction energies, with values of -1.9008 for EMI-SCN, -1.8331 for EMI-DCA, and -1.31602 for BMI-PF6. These results imply that ILs form the strongest interactions with ascorbic acid compared to dopamine and uric acid. The relatively high interaction energies can be attributed to the presence of hydroxyl groups in ascorbic acid, which can engage in strong hydrogen bonding with the ILs. EMI-SCN, with the most negative interaction energy, again proves to be the most effective IL for stabilizing ascorbic acid, while BMI-PF6, with the least negative energy, exhibits the weakest interaction. The trend observed for ascorbic acid is consistent with the overall behaviour of ILs, were smaller, more polarizable anions, such as $SCN^-$ and $DCA^-$, form stronger interactions with polar biomolecules due to better electrostatic and hydrogen bonding capabilities. The optimized binary complexes of ILs and biomolecules further validate these interaction energies, revealing key structural features that influence the binding affinities. The geometry optimizations show that EMI-SCN tends to form more compact and stabilized complexes with all three biomolecules, leading to stronger interactions. This is likely due to the favourable combination of the imidazolium cation's π-system and the $SCN^-$ anion's

ability to form multiple types of non-covalent interactions. In contrast, the bulkier $PF6^-$ anion, with its larger size and lower polarizability, results in less efficient interaction with the biomolecules, as reflected by the less negative interaction energies.

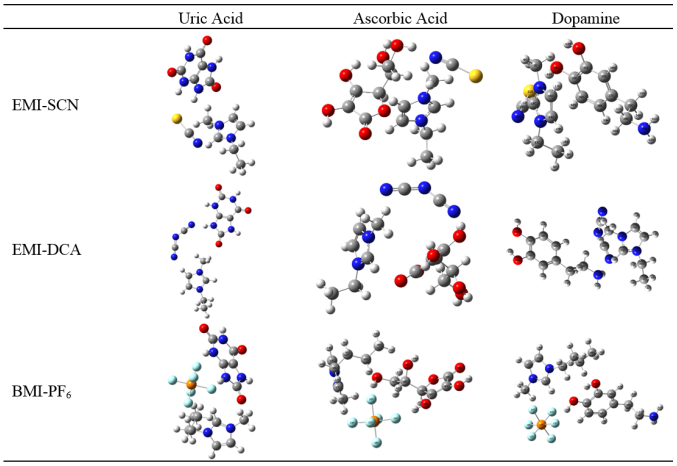



**Figure 5:** Optimized binary structures

The differences in interaction energies among dopamine, uric acid, and ascorbic acid can be explained by the molecular characteristics of each biomolecule. Dopamine, being smaller and having fewer hydrogen bonding sites compared to uric acid and ascorbic acid, shows weaker interactions overall. Uric acid, with its planar structure and multiple hydrogen bonding sites, interacts more strongly with the ILs, while ascorbic acid, with its multiple hydroxyl groups, engages in the strongest interactions due to extensive hydrogen bonding networks. These findings emphasize the importance of the molecular structure of both the IL and the biomolecule in determining the interaction strength.

Overall, the results of this study highlight the versatility of imidazolium-based ILs, particularly EMI-SCN, in interacting with biologically relevant molecules. The strong interactions observed, especially with ascorbic acid and uric acid, suggest that ILs could play a crucial role in the design of electrochemical sensors that target these biomolecules. The differences in interaction strengths also provide insights into how ILs can be tailored for selective sensing applications, where the choice of IL can be optimized based on the target analyte.

## CONCLUSION

Density Functional Theory (DFT) calculations revealed insights into the molecular configurations, HOMO-LUMO gaps, and molecular electrostatic potential (MESP) surfaces of these ILs. EMI-SCN showed the most stable configuration with the lowest energy and highest dipole moment, indicating its strong electrostatic properties. Among the ILs, EMI-SCN consistently exhibited the strongest interactions with all three biomolecules, likely due to the high electron density around its thiocyanate anion. This makes EMI-SCN a promising candidate for electrochemical sensor applications, as its higher interaction energy correlates with enhanced binding affinity for analytes.

The calculated interaction energies suggest that ascorbic acid forms the strongest interactions with all ILs, followed by uric acid and dopamine. This trend indicates that the ILs are particularly well-suited for detecting ascorbic acid in electrochemical sensors. EMI-DCA and BMI-PF6, while also exhibiting favorable interactions, were found to have slightly weaker affinities, especially BMI-PF6, due to the larger and more diffuse nature of its anion. The HOMO-LUMO gap analysis showed that EMI-SCN and EMI-DCA have similar reactivities, while BMI-PF6 demonstrated lower reactivity, making it less suitable for highly selective electrochemical sensing applications.

The global reactivity descriptors, including ionization potential, electron affinity, and hardness, further highlighted EMI-SCN's superior performance in terms of electronic stability and reactivity. The favourable interaction energies for EMI-SCN, particularly with ascorbic acid and uric acid, suggest that this IL could be effectively used in sensors for detecting these biomolecules in real-time. The combination of EMI-SCN's strong electrostatic interactions, favourable electronic properties, and stable molecular configuration positions it as an optimal choice for designing high-performance, selective electrochemical sensors.

In conclusion, EMI-SCN stands out as the most suitable IL for electrochemical sensing applications, particularly for detecting biologically relevant analytes like dopamine, uric acid, and ascorbic acid. This study provides critical insights into the structure-activity relationships of ILs, offering a basis for their rational design in future sensor technologies.

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