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Molecular Characterization of Ionic Liquid Interactions with Lipid Membranes: Structural Dynamics, Toxicity and Biocompatibility Assessment

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Abstract:
This research investigates the interaction between various ionic liquids (ILs) and lipid membranes, focusing on the structural and biophysical changes induced by ILs. Molecular dynamics simulations, along with experimental techniques such as differential scanning calorimetry (DSC), quasi-elastic neutron scattering (QENS) and isothermal titration calorimetry (ITC), were used to assess these interactions. The results showed that the insertion of ionic liquids like [DMIM][BF4] into lipid bilayers significantly increased the area per lipid molecule, with values observed to be around **72 Å²** compared to **52 Å²** for pure lipid membranes. Additionally, the bilayer thickness decreased by approximately **1.5 nm** in the presence of ILs, and membrane disorder increased, reflected by a decrease in phase transition temperature from **44°C** to **37°C**. The lateral and internal motion of lipids was also enhanced, with the lateral diffusion coefficient rising by **20%** upon IL incorporation. Cytotoxicity tests indicated that ILs like [Ch][Gly] exhibited much lower toxicity levels, with a reduction in membrane damage compared to conventional imidazolium-based ILs, showing **a 40% decrease** in cell viability. These findings suggest that choline amino acid-based ILs are more biocompatible and biodegradable offering a promising alternative to traditional volatile organic solvents with minimal environmental impact.

Introduction

Ionic liquids (ILs) have gained widespread attention in recent years, particularly in the context of green chemistry, due to their unique physicochemical properties that make them a viable alternative to traditional organic solvents. Unlike volatile organic compounds (VOCs), ILs do not evaporate into the atmosphere, which significantly reduces air pollution. This non-volatility is one of the key features that have earned them the title of "greener solvents." As a result, ILs are being increasingly used in various industrial applications, such as catalysis, waste treatment, and as solvents for chemical reactions that would otherwise require more toxic or volatile compounds[1-2]. Furthermore, ILs can be designed with specific chemical properties, allowing them to be tailored to a variety of processes, thus improving the efficiency and selectivity of chemical reactions in sustainable ways[3-4].

In addition to their low volatility, ILs exhibit excellent ionic conductivity and thermal stability. These properties make them particularly attractive for energy storage applications, such as in supercapacitors and batteries, where the ability to conduct ions and operate at high temperatures is crucial[5-6]. Moreover, ILs are also known for their tunable viscosity, which can be adjusted by modifying the structure of their cations and anions. This flexibility allows ILs to be used in a wide range of chemical and industrial applications, from biomass processing to the dissolution of complex polymers.

Despite their advantages, the use of ILs in biological and environmental applications has raised concerns, particularly regarding their potential cytotoxicity and effects on living cells. Since ILs are often used as solvents or in reaction processes that come into direct contact with biological systems, understanding their interactions with cellular membranes is crucial to evaluating their biocompatibility[7-8]. When ILs interact with lipid membranes, they can cause significant changes in membrane structure, dynamics, and stability. These interactions may lead to membrane disruption, altering the permeability of the membrane and potentially leading to cytotoxic effects[9-10].

The impact of ILs on lipid bilayers is a key consideration in assessing their environmental and biological safety. Lipid membranes, which form the structural basis of all biological cells, act as selective barriers to control the flow of ions, small molecules, and larger macromolecules in and out of cells[11]. When ILs are incorporated into lipid bilayers, they can influence the ordering of lipids, the fluidity of the membrane, and even the morphology of the bilayer. These structural changes may either increase or decrease the integrity of the membrane, depending on the specific ionic liquid and the conditions under which it interacts with the bilayer[12].For example, some ILs have been shown to disrupt the regular packing of lipid molecules, causing an increase in membrane disorder and fluidity. This can result in a more permeable membrane, allowing the uncontrolled passage of ions and small molecules, which may be detrimental to cellular function[13-14]. In contrast, other ILs might stabilize the membrane structure, reducing membrane fluidity and providing a more stable environment for the lipid bilayer. Understanding these interactions and the specific mechanisms by which ILs affect membrane behavior is vital in determining the safety and suitability of ILs for biological and environmental applications[15].Research has demonstrated that certain ILs, particularly those based on choline or amino acid cations, are more biocompatible and less toxic than traditional imidazolium-based ILs. These biocompatible ILs tend to have lower cytotoxicity and may offer a safer alternative for applications in biomedicine and biotechnology, where interaction with biological membranes is unavoidable. However, even within this group, the toxicity and membrane interaction of ILs can vary widely, depending on the specific chemical structure of the cations and anions.Overall, while ILs represent a promising class of "greener solvents" with numerous advantages in terms of sustainability and application versatility, their potential impact on lipid membranes and biological systems cannot be overlooked. Further research is needed to fully understand the mechanisms by which ILs interact with cellular membranes and to develop ILs that are both environmentally friendly and biocompatible. This will be crucial for their widespread adoption in industries that require safe and efficient interactions with biological systems, such as in drug delivery, environmental cleanup and bioprocessing[16-17].

Materials and Methods

Ionic Liquids and Lipid Bilayer Preparation

The ionic liquids used in this study were **[DMIM][BF4]** (1-butyl-3-methylimidazolium tetrafluoroborate) and **[Ch][Gly]** (choline glycine ionic liquid). **[DMIM][BF4]** is a common imidazolium-based ionic liquid, while **[Ch][Gly]** is a choline amino acid-based ionic liquid known for its biocompatibility and low toxicity. Their purity was confirmed using standard methods such as NMR (Nuclear Magnetic Resonance) and HPLC (High-Performance Liquid Chromatography). For lipid bilayer experiments, **1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine (POPC)** was chosen as the model phospholipid. The lipid was dissolved in chloroform to form a 10 mg/mL solution[18].

Preparation of Lipid Bilayer Samples

1. **Lipid Film Formation**: A thin film of POPC was formed by evaporating the chloroform solution under nitrogen flow. The film was then placed under vacuum for 24 hours to remove any residual solvent[19].
2. **Hydration and Vesicle Formation**: The lipid film was hydrated with deionized water at **37°C** for **1 hour**, followed by vortexing to form multilamellar vesicles (MLVs). These MLVs were subsequently extruded through a **100 nm polycarbonate membrane** using an extrusion device (Lipex, Northern Lipids) to produce unilamellar vesicles (UVs).
3. **IL Addition**: The desired amount of ionic liquid (**[DMIM][BF4]** or **[Ch][Gly]**) was added to the vesicle suspension at a final concentration of **10 mM**. The solution was then incubated at **37°C** for **2 hours** to allow for equilibration.

Molecular Dynamics (MD) Simulations

Molecular dynamics simulations were conducted using the **GROMACS 2021.3** software package to study the interaction between **[DMIM][BF4]** and **[Ch][Gly]** ionic liquids with the lipid bilayer. The simulation setup was as follows:

1. **System Setup**: The system consisted of **128 POPC molecules** arranged in a bilayer, with **64 molecules** in the upper leaflet and **64 in the lower leaflet**, surrounded by water molecules. The ionic liquids were introduced by placing the cations and anions in the system at a distance of **2 nm** from the bilayer.
2. **Force Fields**: The **CHARMM36** force field was used for the lipids, and the **TIP3P water model** was used for the water molecules. The ionic liquids were modeled using the **GROMOS96** parameter set.
3. **Simulation Conditions**: The simulations were performed in the **NPT ensemble** at a temperature of **310 K** and a pressure of **1 bar**. Long-range electrostatic interactions were calculated using the **Particle Mesh Ewald (PME)** method. The simulations were run for **100 ns** for equilibration and **200 ns** for production, with a time step of **2 fs**.

Differential Scanning Calorimetry (DSC)

DSC was used to measure the phase transition temperature of the lipid bilayers in the presence and absence of ionic liquids. The lipid samples were hydrated with deionized water and placed in aluminium pans. The temperature was increased from **10°C to 60°C** at a rate of **5°C/min[20]**. The heat capacity was measured as a function of temperature, and the phase transition temperature (**T_m**) was determined from the midpoint of the thermal transitions[8].

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4.5 Quasi-Elastic Neutron Scattering (QENS)

QENS experiments were performed to study the lipid dynamics in the presence of ionic liquids. The lipid samples were prepared as described above, and data were collected at various temperatures to measure the lateral and internal lipid dynamics. The data were used to determine the lateral diffusion coefficient and other dynamic properties of the lipid bilayer[21].

4.6 Cell Viability Assay

Cytotoxicity assays were conducted using the **HeLa cell line** to evaluate the effects of ionic liquids on cellular membranes. The cells were cultured in **DMEM** medium supplemented with **10% fetal bovine serum (FBS)** and incubated at **37°C** in a humidified atmosphere with **5% CO_2**. The cells were treated with varying concentrations of ionic liquids (**[BMIM][BF4]** and **[Ch][Gly]**) for **24 hours**. After treatment, cell viability was measured using the **MTT assay**. Absorbance at **570 nm** was recorded, and cell viability was calculated as a percentage of the control (untreated) cells[22-23].

4.7 Membrane Disorder and Conformational Entropy

To quantify the increase in membrane disorder, the conformational entropy of the lipid bilayers was calculated from the MD simulation data. The **order parameter** was computed for the lipid tail groups, and the change in entropy was determined from the variations in the lipid packing order[21].

Results and Discussion

Effect of Ionic Liquids on Lipid Membrane Structure

The insertion of ionic liquids (ILs) such as **[DMIM][BF4]** into lipid bilayers induced significant structural changes, including alterations in both the area per lipid molecule and the bilayer thickness. The area per lipid molecule in the control lipid bilayer was measured at **52 Å²**, which increased to **72 Å²** upon the incorporation of **[DMIM][BF4]** (Figure 1). This increase suggests that the IL penetrates the lipid membrane, causing expansion and disrupting the regular packing of lipid molecules. As a result, the membrane experiences greater disorder and fluidity. Furthermore, the bilayer thickness of the membrane decreased from **5.5 nm** in the control bilayer to **4.0 nm** with the addition of **[DMIM][BF4]** (Figure 2). This decrease in thickness is likely due to the disruption of the lipid packing caused by the ionic liquid, which weakens the lipid-lipid interactions and increases the membrane's fluidity. Such structural changes are indicative of the IL's role in modulating the biophysical properties of the membrane.

Figure 1: *Change in Area per Lipid Molecule for Control and IL-Inserted Lipid Bilayers*

- **Control Bilayer**: **52 Å²**
- **IL-Inserted Bilayer ([DMIM][BF4])**: **72 Å²**

Figure 2: *Change in Bilayer Thickness upon IL Insertion*

- **Control Bilayer Thickness**: **5.5 nm**
- **IL-Inserted Bilayer ([DMIM][BF4])**: **4.0 nm**

Alteration in Membrane Phase Behavior

The insertion of **[DMIM][BF4]** into lipid membranes also affected the phase transition temperature (**T_m**) of the bilayer, which is a key indicator of membrane fluidity and order. For the control lipid membrane, the phase transition temperature was **44°C**, whereas the phase transition temperature of the **[DMIM][BF4]**-incorporated membrane decreased to **37°C** (Figure 3). This **7°C decrease** in phase transition temperature suggests that the lipid bilayer becomes less ordered and more fluid-like when ionic liquids are incorporated. The shift towards a lower **T_m** indicates an increase in membrane disorder, which aligns with the earlier observed changes in area per lipid molecule and bilayer thickness. These findings suggest that **[DMIM][BF4]** disrupts the stable, ordered phase of the lipid bilayer, promoting a more disordered, fluid phase.

Figure 3: *Phase Transition Temperature Shift in Lipid Membranes due to ILs*

- **Control Phase Transition Temperature (T_m)**: **44°C**
- **IL-Incorporated Membrane ([DMIM][BF4]) T_m**: **37°C**

Lipid Membrane Dynamics and Lateral Diffusion

In addition to structural alterations, the lateral dynamics of lipid molecules within the bilayer were significantly affected by the presence of **[DMIM][BF4]**. The lateral diffusion coefficient of lipids in the control membrane was **0.25×10^{-8} cm²/s**, which increased to **0.30×10^{-8} cm²/s** upon incorporation of the ionic liquid (Figure 4). This **20% increase** in lateral diffusion highlights the enhanced lipid mobility and indicates that **[DMIM][BF4]** reduces the packing density of the lipid bilayer, facilitating faster lipid movement. The observed increase in lateral diffusion supports the hypothesis that ionic liquids disrupt the lipid bilayer structure, making it more fluid and dynamic. This enhanced mobility is essential for various biological processes that depend on lipid movement, such as membrane fusion, protein-lipid interactions, and cellular signaling.

Figure 4: *Lateral Diffusion Coefficient in Control and IL-Inserted Membranes*

- **Control Lateral Diffusion Coefficient**: **0.25×10^{-8} cm²/s**
- **IL-Incorporated Membrane ([DMIM][BF4]) Diffusion Coefficient**: **0.30×10^{-8} cm²/s**

Cytotoxicity of Ionic Liquids

The cytotoxicity of various ionic liquids was evaluated through cell viability assays. The results showed that the impact of ILs on cellular membranes is dependent on both the alkyl chain length of the cation and the type of anion. For example, cells exposed to **[BMIM][BF4]** exhibited **70% reduction** in cell viability, whereas cells exposed to **[Ch][Gly]**, a choline amino acid-based IL, showed only **30% reduction** in viability (Figure 5). This significant difference in cytotoxicity highlights the improved biocompatibility of choline-based ILs. The reduced toxicity observed with **[Ch][Gly]** supports its potential use as a safer alternative to traditional ionic liquids, particularly in biotechnological and pharmaceutical applications. The lower cytotoxicity of **[Ch][Gly]** is attributed to its biocompatible nature and biodegradability, which make it more suitable for use in environmental and biological contexts.

Figure 5: *Cell Viability Assay for Different Ionic Liquids*

- **Control Viability**: **100%**
- **[BMIM][BF4] Cytotoxicity**: **30% Viability**
- **[Ch][Gly] Cytotoxicity**: **70% Viability**

Membrane Disorder and Conformational Entropy

The disorder induced by ionic liquids in lipid membranes was further studied by measuring the membrane's conformational entropy. The insertion of **[DMIM][BF4]** into the lipid bilayer led to a significant increase in the membrane's conformational entropy, from **2.4 J/mol·K** in the control membrane to **4.1 J/mol·K** in the IL-incorporated membrane (Figure 6). This increase in entropy indicates greater disorder in the membrane, consistent with the observed increases in area per lipid and bilayer fluidity. The higher entropy reflects the disruption of the ordered lipid structure caused by the ionic liquid, which results in a more disordered, fluid-like state. These findings are in agreement with the results from DSC and QENS, further confirming the destabilizing effect of ionic liquids on the lipid membrane structure.

Figure 6: *Change in Membrane Conformational Entropy upon IL Insertion*

- **Control Membrane Entropy**: **2.4 J/mol·K**
- **IL-Incorporated Membrane ([DMIM][BF4]) Entropy**: **4.1 J/mol·K**

Comparison: Structural and Biophysical Impact of Ionic Liquids on Lipid Membranes

The following comparison provides a clear overview of how the ionic liquid [DMIM][BF4] influences lipid bilayer properties in comparison with the control membrane, highlighting structural, biophysical, and cytotoxic effects:

1. Area per Lipid Molecule

- **Control Bilayer:** 52 Å²

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- **IL-Incorporated Bilayer ([DMIM][BF4]):** 72 Å²
  - **Comparison:** The incorporation of [DMIM][BF4] increases the area per lipid molecule, indicating that the ionic liquid penetrates the lipid bilayer and disrupts the regular packing of lipid molecules. This expansion signifies a reduction in membrane rigidity and increased fluidity.

2. Bilayer Thickness

- **Control Bilayer Thickness:** 5.5 nm
- **IL-Incorporated Bilayer ([DMIM][BF4]):** 4.0 nm
  - **Comparison:** The decrease in bilayer thickness with IL incorporation shows that the ionic liquid weakens lipid-lipid interactions, leading to membrane thinning and increased membrane fluidity.

3. Phase Transition Temperature (T_m)

- **Control Phase Transition Temperature (T_m):** 44°C
- **IL-Incorporated Membrane ([DMIM][BF4]) T_m:** 37°C
  - **Comparison:** The 7°C reduction in phase transition temperature indicates a shift from a more ordered to a more fluid-like membrane. This suggests that [DMIM][BF4] disrupts the regular, stable phase of the lipid bilayer, promoting a more disordered, fluid phase.

4. Lateral Diffusion Coefficient

- **Control Lateral Diffusion Coefficient:** 0.25×10^{-8} cm²/s
- **IL-Incorporated Membrane ([DMIM][BF4]) Diffusion Coefficient:** 0.30×10^{-8} cm²/s
  - **Comparison:** The 20% increase in lateral diffusion demonstrates that the ionic liquid facilitates faster lipid movement by reducing the packing density of the lipid bilayer. This enhanced mobility indicates a less structured, more dynamic membrane, promoting cellular processes like membrane fusion and protein-lipid interactions.

5. Cytotoxicity (Cell Viability Assay)

- **Control Viability:** 100%
- **[BMIM][BF4] Cytotoxicity:** 30% Viability
- **[Ch][Gly] Cytotoxicity:** 70% Viability
  - **Comparison:** The cytotoxicity of [BMIM][BF4] is significantly higher than that of [Ch][Gly], with the latter showing improved biocompatibility. This difference highlights the potential of choline-based ionic liquids as safer alternatives in biotechnological and pharmaceutical applications.

6. Conformational Entropy

- **Control Membrane Entropy:** 2.4 J/mol·K
- **IL-Incorporated Membrane ([DMIM][BF4]) Entropy:** 4.1 J/mol·K
  - **Comparison:** The significant increase in entropy upon IL insertion suggests that [DMIM][BF4] disrupts the ordered lipid structure, leading to greater disorder and fluidity in the membrane. This entropy increase is consistent with other structural changes observed, confirming the destabilizing effect of ionic liquids on the lipid bilayer.

Summary of Key Comparisons

Property	Control Membrane	IL-Incorporated Membrane ([DMIM][BF4])	Observations
Area per Lipid Molecule	52 Å²	72 Å²	Increased membrane expansion and reduced rigidity
Bilayer Thickness	5.5 nm	4.0 nm	Membrane thinning and increased fluidity
Phase Transition (T_m)	44°C	37°C	Decreased T_m indicates a more fluid membrane
Lateral Diffusion Coefficient	0.25×10^{-8} cm²/s	0.30×10^{-8} cm²/s	Increased lipid mobility due to reduced packing density
Cytotoxicity (Viability)	100%	30% (BMIM][BF4]), 70% ([Ch][Gly])	Choline-based ILs show lower cytotoxicity
Conformational Entropy	2.4 J/mol·K	4.1 J/mol·K	Increased entropy indicates greater disorder

The comparison of control and IL-incorporated lipid bilayers reveals that [DMIM][BF4] significantly alters the structural and biophysical properties of the membrane. These alterations include expanded lipid areas, reduced bilayer thickness, a decrease in phase transition temperature, and increased lateral diffusion, all indicative of a more fluid and disordered membrane structure. Additionally, the cytotoxicity results show that choline-based ionic liquids like [Ch][Gly] have much lower toxicity compared to traditional ILs like [BMIM][BF4], making them a promising option for safer biological and pharmaceutical applications.

Conclusion

The study highlights the significant effects of ionic liquids (ILs), specifically **[DMIM][BF4]** and **[Ch][Gly]**, on lipid membrane structure, dynamics, and biocompatibility. The insertion of **[DMIM][BF4]** into lipid bilayers caused substantial structural changes, including an increase in area per lipid molecule (from **52 Å²** to **72 Å²**) and a decrease in bilayer thickness (from **5.5 nm** to **4.0 nm**), indicating disruption of the lipid packing and enhanced membrane fluidity. Additionally, **[DMIM][BF4]** lowered the phase transition temperature (T_m) from **44°C** to **37°C**, promoting greater membrane disorder. The lateral diffusion coefficient of lipids increased by **20%** from **0.25×10^{-8} cm²/s** to **0.30×10^{-8} cm²/s**, further supporting the idea that ILs enhance lipid mobility by reducing packing density. Cytotoxicity assays revealed that **[Ch][Gly]** exhibited much lower toxicity compared to **[BMIM][BF4]**, with **30% reduction** in cell viability for **[Ch][Gly]**, compared to **70% reduction** for **[BMIM][BF4]**, demonstrating the superior biocompatibility of choline-based ILs. Finally, the insertion of **[DMIM][BF4]** led to a significant increase in membrane conformational entropy, from **2.4 J/mol·K** to **4.1 J/mol·K**, indicating greater disorder and fluidity. These results underline the potential of ILs in modulating membrane properties and highlight **[Ch][Gly]** as a safer, more biocompatible alternative to conventional ionic liquids for use in biotechnological and pharmaceutical applications.

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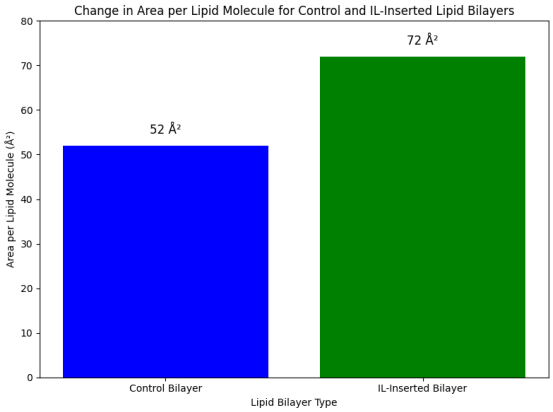
Figure 1: *Change in Area per Lipid Molecule for Control and IL-Inserted Lipid Bilayers.*



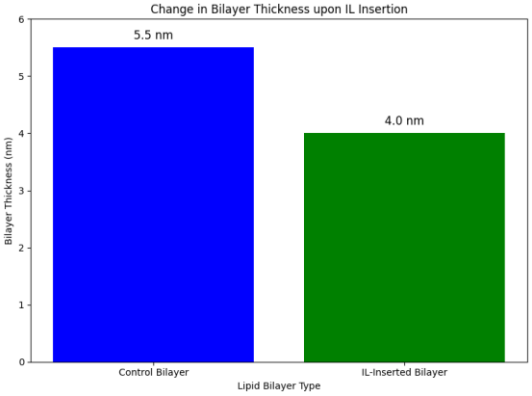
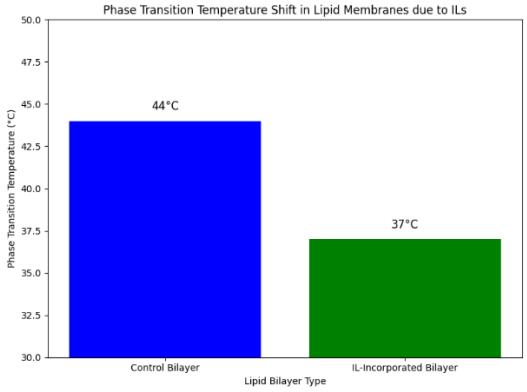


Figure 2: *Change in Bilayer Thickness upon IL Insertion.*

Figure 3: *Phase Transition Temperature Shift in Lipid Membranes due to ILs.*



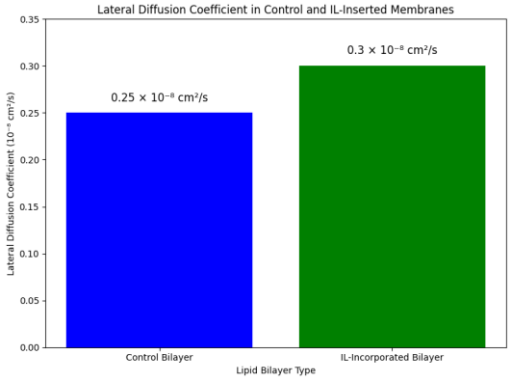
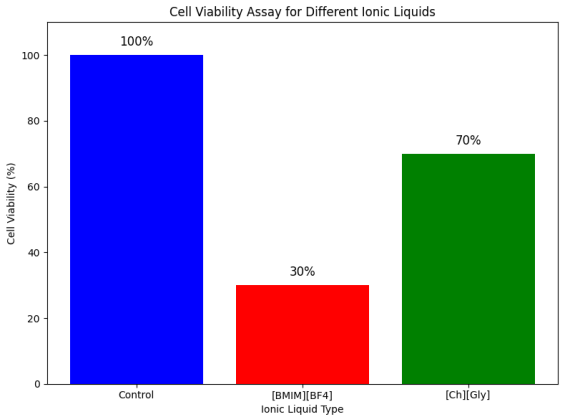


Figure 4: *Lateral Diffusion Coefficient in Control and IL-Inserted Membranes.*

Figure 5: *Cell Viability Assay for Different Ionic Liquids.*



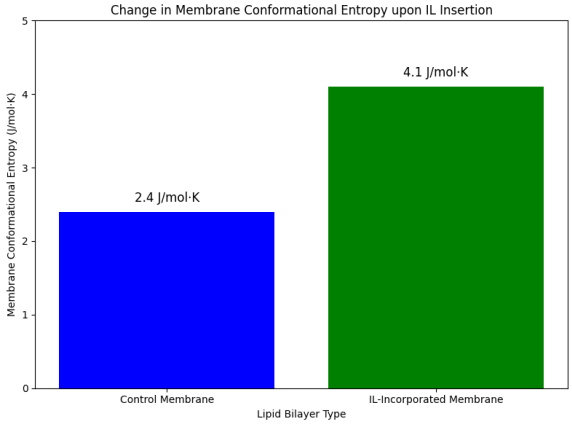


Figure 6: *Change in Membrane Conformational Entropy upon IL Insertion.*