Chemical Methodologies 4(2020) 130-142

Chemical Methodologies

Journal homepage: http://chemmethod.com

Original Research article

The Activity of Alkyl Groups in Morpholinium Cation on Chemical Reactivity, and Biological Properties of Morpholinium Tetrafluroborate Ionic Liquid Using the DFT Method

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ARTICLE INFORMATION

Received: 09 April 2019
Received in revised: 25 April 2019
Accepted: 04 July 2019
Available online: 23 October 2019

DOI: 10.33945/SAMI/CHEMM.2020.2.3

KEYWORDS

QSAR
HOMO
LUMO
Vibrational spectroscopy and UV-visible Spectrum

ABSTRACT

The physical properties are evaluated through the density functional theory (DFT) of molecular mechanics and the chemical and biological properties are also examined. The difference between the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) is starting from -5.91 to 6.15, which means that the chemical reactions change is the same as that of the anion. The biological activity of the predictions given by QSAR calculation is forecasted where the PIC50 of all the designed ionic liquids is near or less than -4.00, as a result, these are considered as the highly bioactive molecules. To identify these molecules, computational data are used to determine the vibrational and electronic spectrum.

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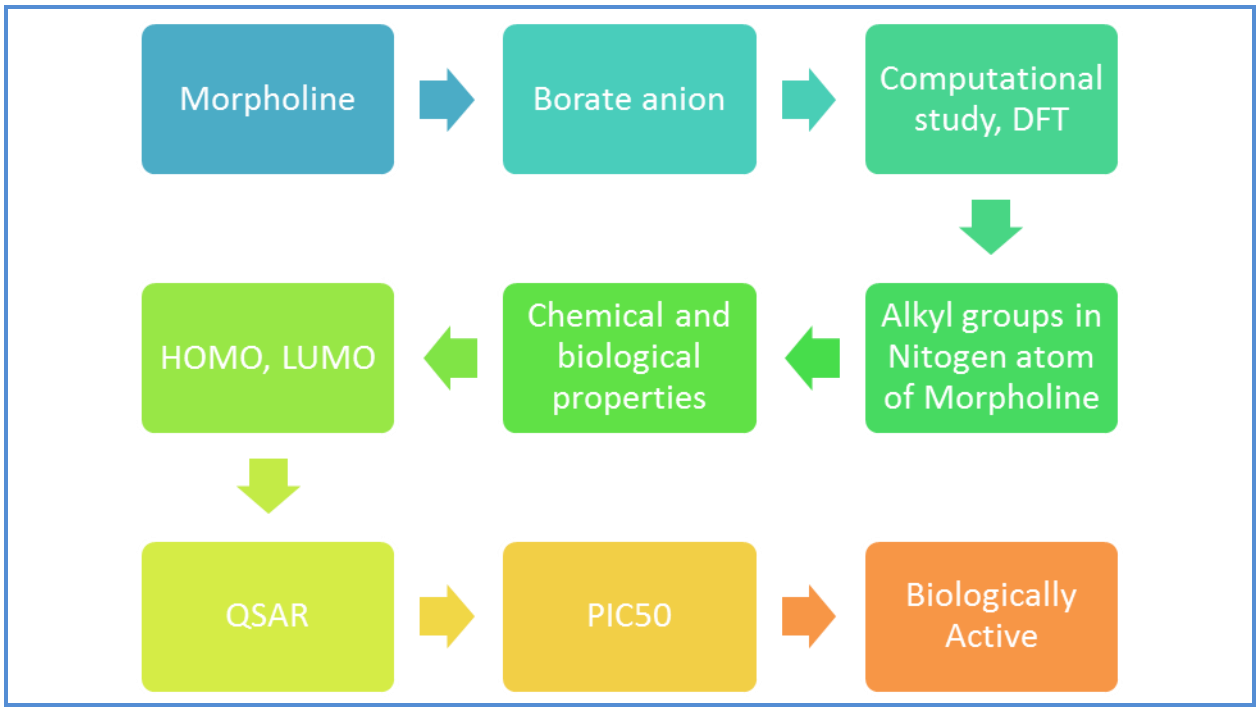
Graphical Abstract



Introduction

The ionic liquid is a molten salt located below 100 °C temperature, which is made in connection to the discrete cation and anion [1]. At present, the ionic liquid is called the engineering solvent due to its physical and chemical properties. Generally, low volatility, high-level thermal stability, biodegradability, low toxicity, higher salvation energy, electromechanical windows and highly conductivity are the interesting properties of ionic liquid [2, 3]. Intimately, the use of ionic liquid started to be an electrochemical battery as the solvent, but due to the interesting physical and chemical properties and the liquidity range, the attraction of scientists continues to increase [4]. Since the year 2007, ionic liquid has been turned into a major field of research in chemistry, resulting in more than 3500 research papers published in this field in one academic year [5]. Their attractive physical properties have been defined as a green solvent *i.e.* ionic liquid in the imidazolium, ammonium, phosphonium, pyronium and morpholinium which include organic cation with a wide variety of organic or inorganic anion for forming third-generation much liquid and are made in accordance to the authorized green chemistry. Our work has been developed to make bioactive molecule by adding some inorganic anion with morpholinium cation ammonium and phosphonium cation which are important for biological activity. By combining carboxylate anion with ammonium cation, a biological ionic liquid whose

toxic is very low can make [6-9]. On the other hand, the morpholin-4-ium, morpholine-4-carbodithioate and aryl (alkyl) halides reactions in the presence of CuCl in an aqueous solvent system was done that is a noble supportive reaction in the area of green chemistry [10].

The morpholine is currently being widely used as additive properties in chemical industries and rubber industries. For these reasons, morpholine has selected, and its biological activity has identified. By changing the morpholinium alkyl chain, the effects of alkyl chain on the biological activity was discussed by comparing molecules through computational chemistry. It has shown that if as alkyl groups were changed with morpholinium cation chain, and then the chemical activity, physical properties, chemical properties, and biological properties would have changed on the chain [11, 12]. Performing the calculation of these properties has done by the density functional theory (DFT) of computational chemistry. In this sense, it provided us with relatively effective and neutral equipment, with the realization of ground state power in real-time models and the real-world models of their surfaces. The reliability of this account depends on the estimated development for exchange-related energy efficiency. In recent years there has been significant progress in the quality of functioning of the exchange relationship as reliance on the local density gradients, semi-localized density and non-interchangeable exchange functions which have been introduced [13, 14].

Experimental

Computing and simulating method

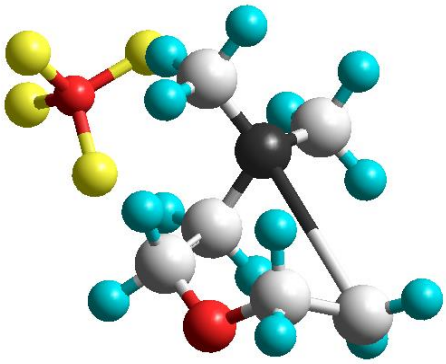
The molecular modeling program permits to build and analyze different molecular structures and determine the molecular, electronic, and biological properties of the material. In order to create the spatial chemical structure of each calculated molecule, the two-dimensional structure of the molecule shall be built step-by-step by drawing the molecules. Then, hydrogen atoms are automatically added from building option and chemical structure is converted into 3D structure. The first step in getting the main characteristic parameters of molecules is to optimize the molecular structure to obtain a configuration characterized by a minimum free energy [15]. After completing the optimization, the theoretical properties of the studied compound such as free energy, entropy, dipole moment, binding energy, nuclear energy, electronics energy, heat of formation, the HOMO and LUMO are studied. The QSAR properties of molecules like charge density, surface area grid, volume, LogP, polarizability, refractivity and molecular mass were calculated.

Results and discussion

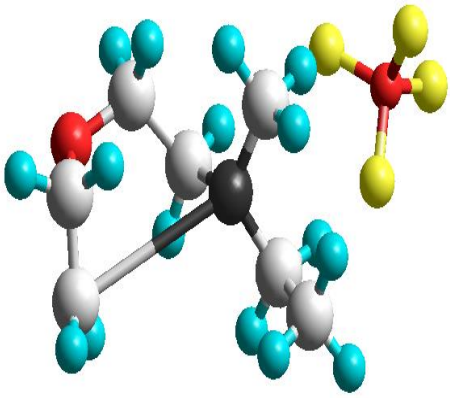
Optimized structure

R=-CH_3, -CH_3, (IL01) -CH_3, CH_3-CH_2- (IL02), CH_3-CH_2-, CH_3-CH_2- (IL03), and -CH_3, CH_3-CH_2-CH_2- (IL04) with morpholinium cations, in the optimized ionic liquids are shown below. The following compounds are designed by adding borate anion shown in Figure 1. in which the indicating red color is oxygen, cyan is hydrogen, brown is carbon, black is nitrogen, boron is red and red is fluorine.

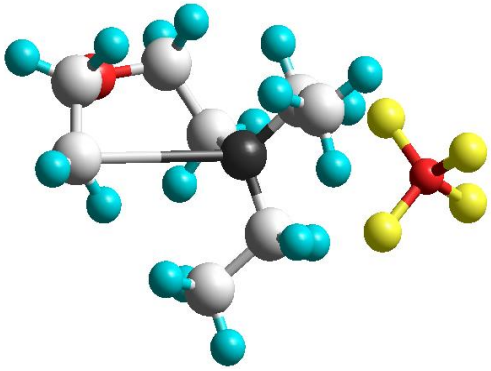
IL01, N,N dimethyl morpholinium borate



IL02, N-ethyl –N-methyl morpholinium borate



IL03, N,N- diethyl morpholinium borate



IL04, N-methyl-N- propyl morpholinium borate

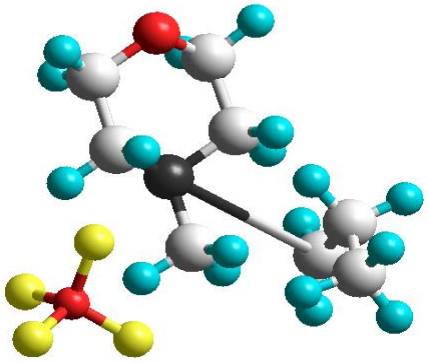


Figure 1. Optimized structure in the cylinder shape

HOMO-LUMO

The energy levels of the molecular orbitals order HOMO and LUMO give information on the possible electronic transition. The HOMO and LUMO indicate the electrophilic and nucleophilic attraction region in the molecule. The LUMO-HOMO gap is the most important parameter for the chemical reactivity. The shorter LUMO- HOMO gap is considered as the high reactivity, which is shown in Figure 2.

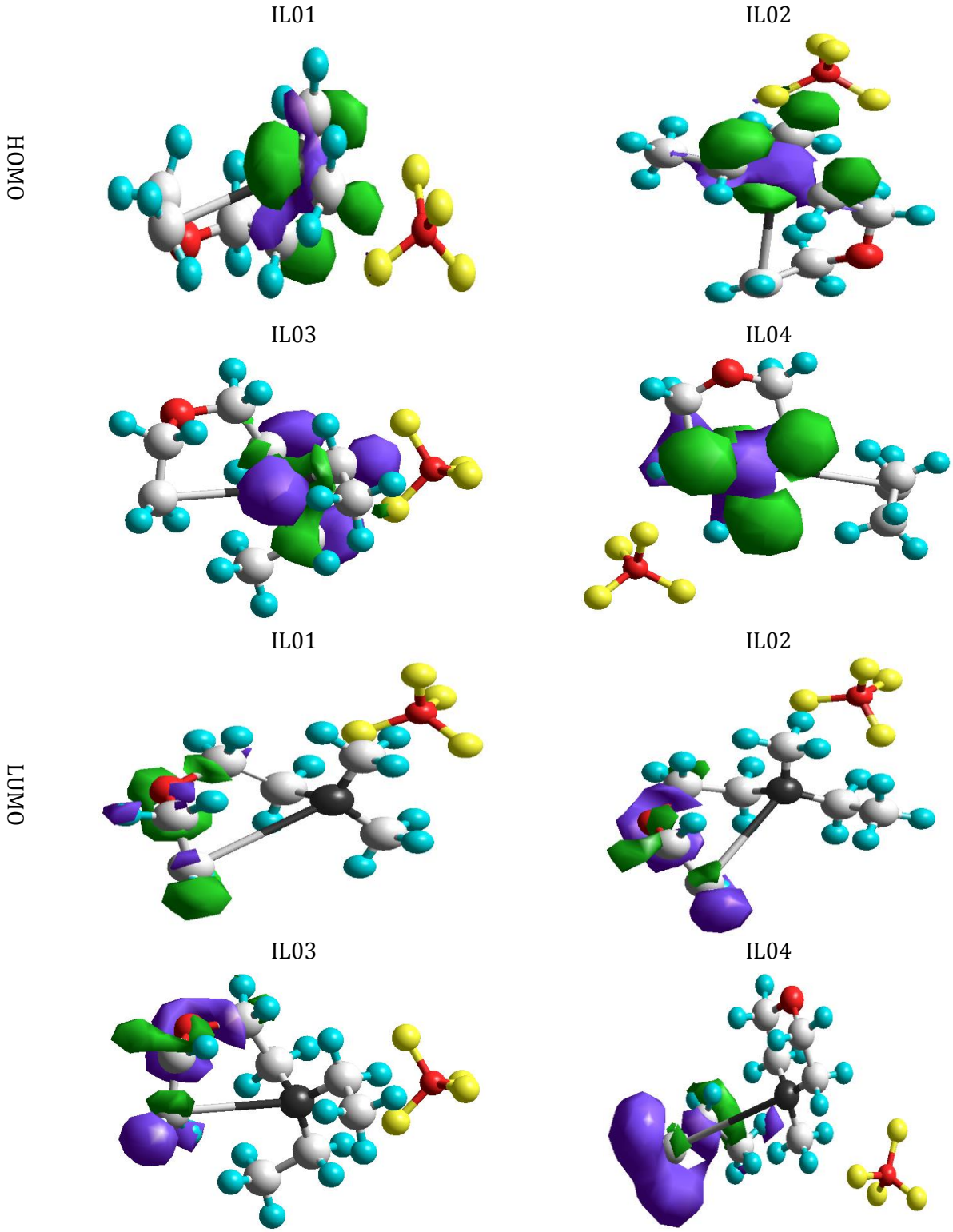


Figure 2. The frontier orbitals: a) HOMO and b) LUMO

Table 1. Data for HOMO, LUMO

	IL01	**IL02**	**IL03**	**IL04**
HOMO (0), eV	-5.9162	-5.9315	-5.88266	-6.2343
HOMO (-1), eV	5.4050	5.2661	5.3347	4.9602
HOMO (-2), eV	5.8265	5.6473	5.6403	5.3805
LUMO (0), eV	5.4050	5.2661	5.3347	4.9602
LUMO (-1), eV	-5.9162	-5.9315	-5.88266	-6.2343
LUMO (-2), eV	-7.0384	-7.1289	-7.0577	-7.5549

The energy of the HOMO and LUMO is directly related to the ionization potential and electron affinity, respectively. Energy difference between HOMO and LUMO orbital is called as the energy gap which is an important parameter determining the stability of the structures. The energy gap is used in determining the molecular-electrical transport properties. In addition, according to Koopmans' theorem, the energy gap (E_{gap}) is defined as the difference between HOMO and LUMO energy [16].

$$E_{gap} = (E_{LUMO} - E_{HOMO}) \approx IP - EA$$

The ionization potential (I) and electron affinity (A) can be estimated from the HOMO and LUMO energy values as illustrated below:

$$I = -E_{HOMO} \quad (1)$$

$$A = -E_{LUMO} \quad (2)$$

Table 2. Data for HOMO, LUMO, IP, EA, and LUMO- HOMO gap (ΔE)

	IL01	**IL02**	**IL03**	**IL04**
HOMO (eV)	-5.9162	-5.9315	-5.88266	-6.2343
LUMO (eV)	5.4050	5.2661	5.3347	4.9602
Δ_{E} (LUMO-HOMO)	11.3212	11.1976	11.1976	11.2173
Ionization potential (I), eV	5.9162	5.9315	5.88266	6.2343
Electron affinity (A), eV	-5.4050	-5.2661	-5.3347	-4.9602

Chemical reactivity and chemical kinetics

The HOMO and LUMO energies are used for the determination of global reactivity descriptors. It is important to note that electrophilicity (ω), chemical potential (μ), electronegativity (χ), hardness (η) and softness (S) are put into a molecular orbital's framework. We focus on the HOMO and LUMO energies in order to determine the interesting molecular/atomic properties and chemical quantities. These are calculated as following equations [17, 18]:

$$(\mu) = -\frac{I+A}{2} \quad (3)$$

$$(\eta) = \frac{I-A}{2} \quad (4)$$

$$(S) = \frac{1}{\eta} \quad (5)$$

$$(\chi) = \frac{I+A}{2} \quad (6)$$

$$(\omega) = \frac{\mu^2}{2\eta} \quad (7)$$

Table 3. Chemical reactivity and chemical kinetics

	IL01	IL02	IL03	IL04
Hardness (η)	5.6606	5.5988	5.6086	5.9725
Softness (S)	0.1766	0.1786	0.1780	0.1674
Electrophilicity (ω)	0.0057	0.0098	0.0066	0.0339
Chemical potential (μ)	-0.2556	-0.3327	-0.2739	-0.6370
Electronegativity (χ)	0.2556	0.3327	0.2739	0.6370

Thermophysical properties

Table 4. shows that with the increase in temperature, all the entropy and heat capacity are changed in a specific way, thus both of the parameters of IL03 are increasing and found to be the highest thermophysical properties. On the other hand, the entropy of IL01, IL02 and IL04 is increasing the two parameters. Thus, it can be said that the ionic liquids enlargement entropy and heat capacity are increasing with the increase in temperature as compared to others. Entropy rules mean that the disturbing of the ordered will increase.

Table 4. Data for entropy and Heat capacity

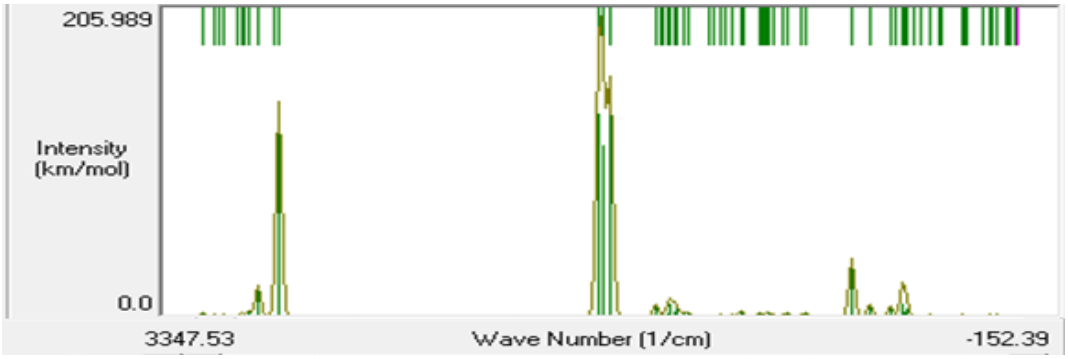
	273 K		298 K		323 K	
	Entropy	Heat capacity, (kcal/mol-deg)	Entropy	Heat capacity, (kcal/mol-deg)	Entropy	Heat capacity, (kcal/mol-deg)
IL01	0.1368	0.0538	0.1419	0.0572	0.1468	0.060
IL02	0.1358	0.0561	0.1411	0.0600	0.1462	0.0639
IL03	0.0771	0.0117	0.0783	0.0125	0.0795	0.0134
IL04	0.1359	0.0572	0.1413	0.0614	0.1466	0.0656

Vibrational spectrum

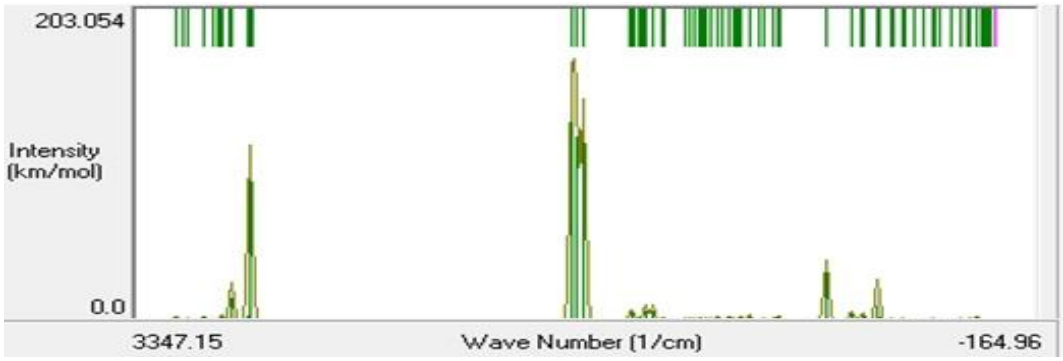
The existence of the functional group in the molecule can be identified through the vibrational spectroscopy. Since morpholinium cation creates ionic liquids in combination with various types of inorganic anion, and then there is a large spectrum between 3000 to 3500 cm^{-1} for NH

levels of morpholinium cation as shown in Figure 3. It is also available for 2500 to 2200 cm^{-1} spectrums for CH of morpholinium cation.

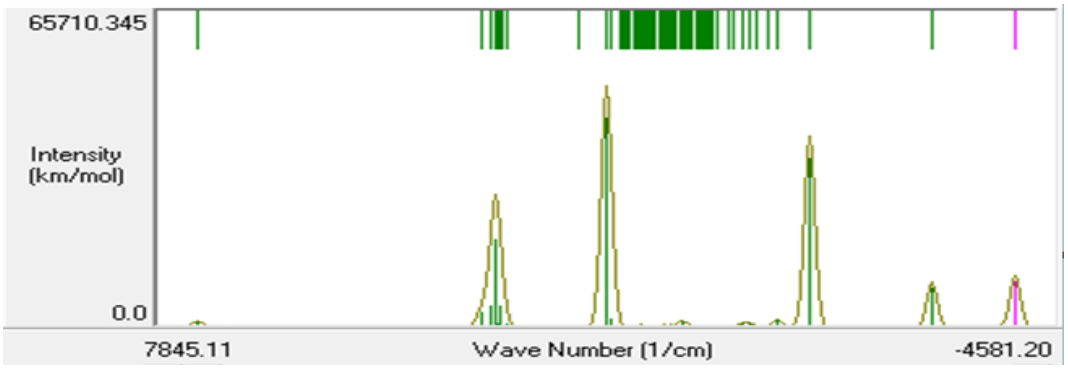
IL01



IL02



IL03



IL04

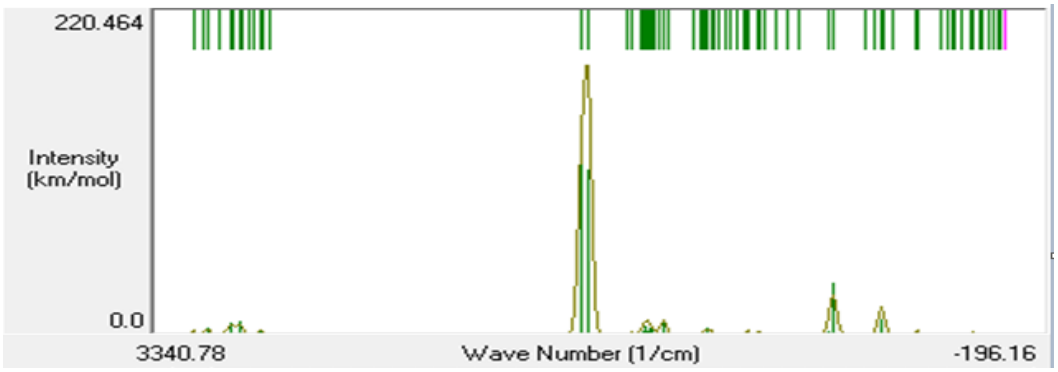


Figure 3. Vibrational spectrum

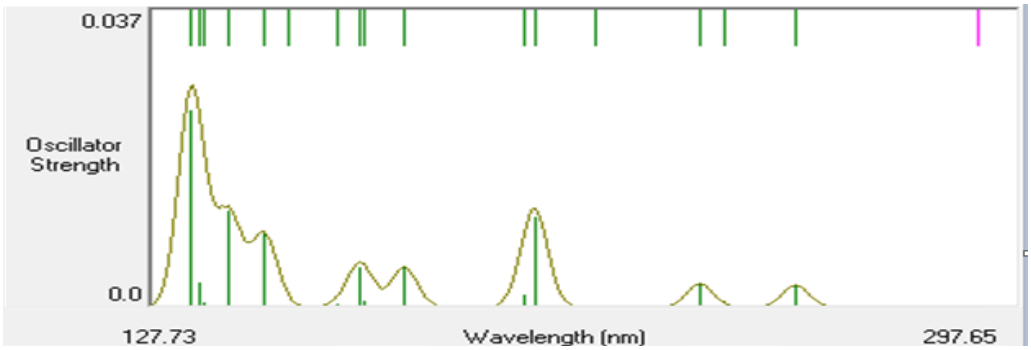
Table 5. Data for vibrational spectroscopy

	Normal Mode	Degeneracy	Frequency	Intensity	Symmetry
IL01	1	1	6.70	0.107	1 A
IL02	1	1	-5.32	0.076	1 A
IL03	1	1	-4016.37	9817.913	1 A
IL04	1	1	-35.39	0.482	1 A

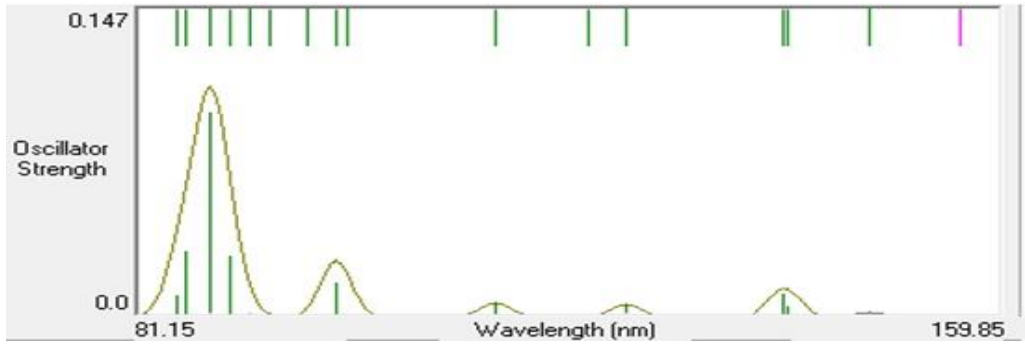
UV-visible spectrum

UV-visible spectroscopy combines the angular concentration located inside the organic resin or compounds. In the case of morpholinium ionic liquids, the conjugation of UV-visible spectroscopy with their opposite conjugation, vibration level conjugation and oxygen-based lone pair of electrons are determined by those of spectrum found in 100-140 nm as a broad peak.

IL01



IL02



IL03

IL04

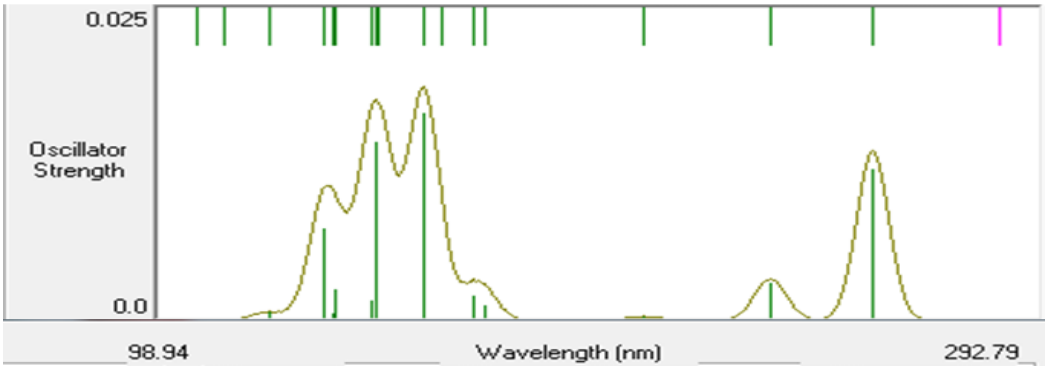


Figure 4. UV-visible spectrum

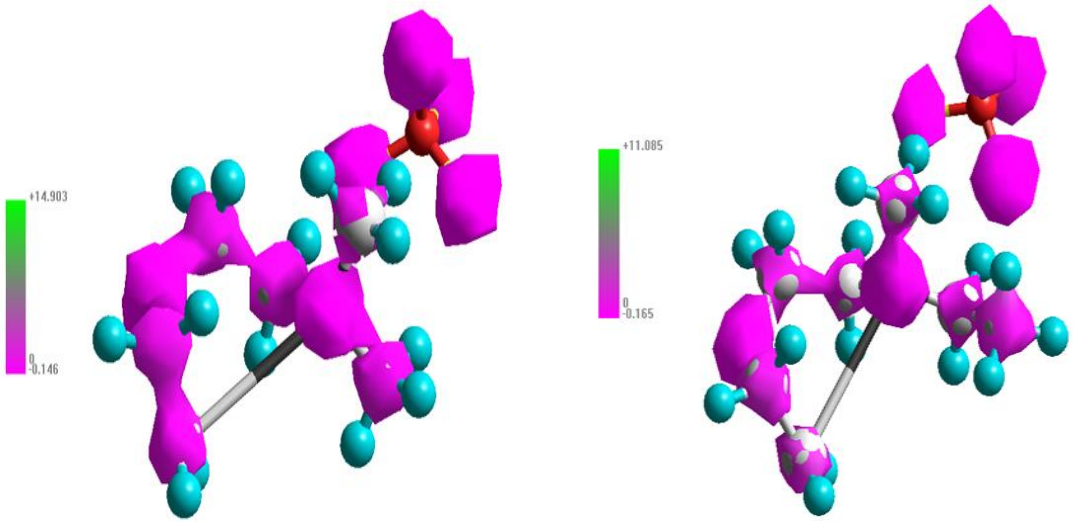
Table 6. Data of UV-visible spectrum

	Transition	Degeneracy	Spin multiplicity	Wavelength	Oscillator strength
IL01	1	1	Triplet	289.92	0.0
IL02	1	1	Triplet	156.27	0.0
IL03	1	1	Triplet	11188.89	0.0
IL04	1	1	Triplet	283.98	0.0

The distribution electrostatic potential due to 3D mapped structure

Electrostatic potential is an important property through which it can be easily detected by a different charge distribution over molecule. Increasing the amount of charge in a single molecule will increase the same biological activity. The three-dimensional geometry of the molecular-electrostatic potential distribution highlights the existence of three regions with increased electronegativity in whole molecule.

IL01 IL02



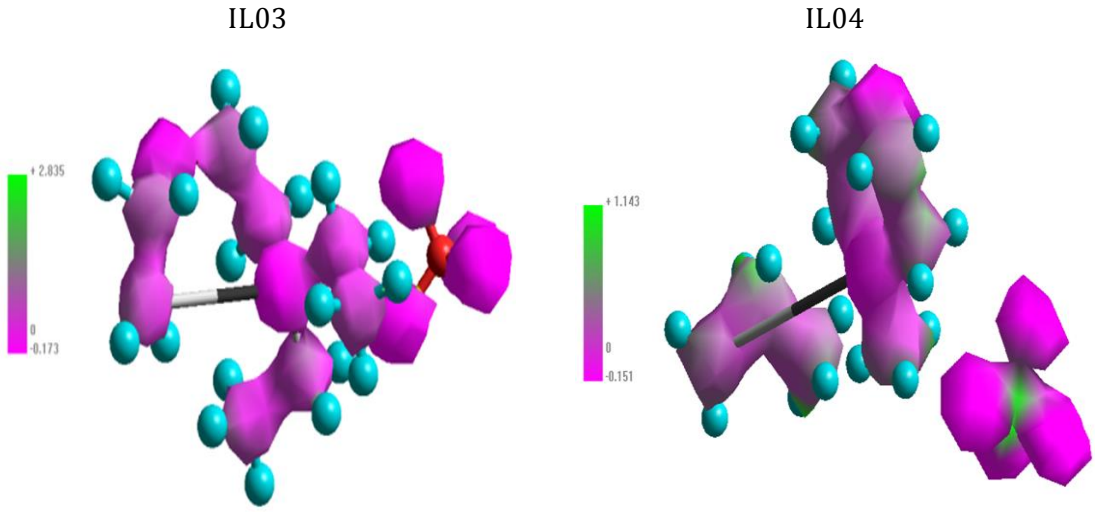


Figure 5. The 3D geometry of the distribution electrostatic potential

Table 7. Data of electrostatic potential energy difference of two levels

	IL01	IL02	IL03	IL04
E1	+14.903	+11.085	+2.835	+1.143
E2	-0.146	-0.165	-0.173	-0.151
ΔE= E2-E1	-15.049	-11.25	-3.008	-1.294

Here, E1=Electrostatic potential energy in positive value, E2=Electrostatic potential energy in negative value and ΔE=Electrostatic potential energy difference of two level

Quantitative structure-activity relationships

Table 8. Data for QSAR study

	IL01	IL02	IL03	IL04
Partial charge (e)	0.0	0.0	0.0	0.0
Surface Area(grid)	380.70	404.82	417.07	458.30
Volume, Å^3	594.68	643.0	676.04	714.79
Hydration Energy kcal/mol	0.30	0.61	0.93	1.37
Log P	1.11	1.35	1.69	1.82
Refractivity Å^3	35.08	40.10	44.85	44.62
Polarizibility Å^3	14.89	16.72	18.56	18.56
Mass (amu)	202.99	217.01	231.04	231.04

Calculation of PIC50

The correlation between the biological activity and descriptor is developed by Zineb Almi *et al.* 2014 [19] for the PIC50 value calculation from the Hyperchem simulation value that is given in following equation as:

$$PIC5 = 3.028 - 0.542logP + 0.352\ HE - 1.272\ Pol + 0.863\ MR - 0.038\ MV - 0.024\ MW + 19.120q01 + 0.024\ SAG$$

Here, HE=hydration energy, Pol=polazibility, MR=molecular refractivity, LogP=partition coefficient, MV=molar volume, MW=molar weight, SAG=surface area grid, q01=atomic net charges.

Table 9. Data of PIC50

	IL01	IL02	IL03	IL04
PIC50	-4.466	-4.077	-3.688	-4.285

Conclusions

Finally, the morpholinium ionic liquids do not change the chemical activity by changing the alkyl chain, but changes in biochemical and biological activity are quite noticeable. The biological activity of IL01, IL02, and IL04 is near -4.00 to -4.40 where the IL03 which has PIC50 is -3.688. The measuring PIC50 and the result are supportive for higher biological active molecule or standard antibiotics. It is noted that the ethyl and ethyl groups makes it more biologically active. However, the design of all the ionic liquids under the standard 4 or less can be established as an ultra-biological active molecule.

Conflict of Interest

We have no conflicts of interest to disclose.

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How to cite this manuscript: Mohammad Jahidul Islam, Ajoy Kumer*, Md. Nuruzzaman Sarker, Sunanda Paul, The Activity of Alkyl Groups in Morpholinium Cation on Chemical Reactivity, and Biological Properties of Morpholinium Tetrafluroborate Ionic Liquid Using the DFT Method. Chemical Methodologies 4(2), 2020, 130-142. DOI:10.33945/SAMI/CHEMM.2020.2.3.