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Effect of External Electric Field and Temperature on Entropy, Heat of Capacity, and Chemical Reactivity with QSAR Study of Morphonium Chloride and Nitrous Ionic Liquids Crystal Using DFT

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ABSTRACT

Due to the great number of medicinal application of morphine in drugs, the morphonium chloride (IL01) and morphonium nitrous (IL02) were investigated using the computational method to assess their biological activity. The quantitative structure activity relationship (QSAR) parameters for instance, charge density, surface area grid, volume, LogP, polarizability, refractivity, and molecular mass were demonstrated through the density functional theory (DFT) for simulation as well as the chemical reactivity like HOMO, LUMO, and HOMO, LUMO gap were also calculated. In addition, the most important thermodynamic properties such as entropy and heat of capacity were calculated using DFT method. The values of the initial entropy and heat of capacity were zero without applying temperature. At 273 K, the entropy and heat of the capacity are 0.117, 0.113, and 0.062, 0.055 kcal/mol-deg for IL01 and IL02, respectively, which finally increased by 0.177, 0.162 and 0.120, 0.099 kcal/mol-deg at 523 K. When electric field was applied on IL01, and IL02, the entropy was decreased by 32.47% and 2.65% whereas the heat of capacity was decreased by 79.03% and 1.81%, respectively. Finally, in same electric field with increasing temperature, the entropy was enhanced by 16.45% and 45.45% besides the heat of capacity was increased about 100% at 523 K and IL02 was found to be less response compared with that of the IL01 at low temperature for electric filed but almost similar response at high temperature.

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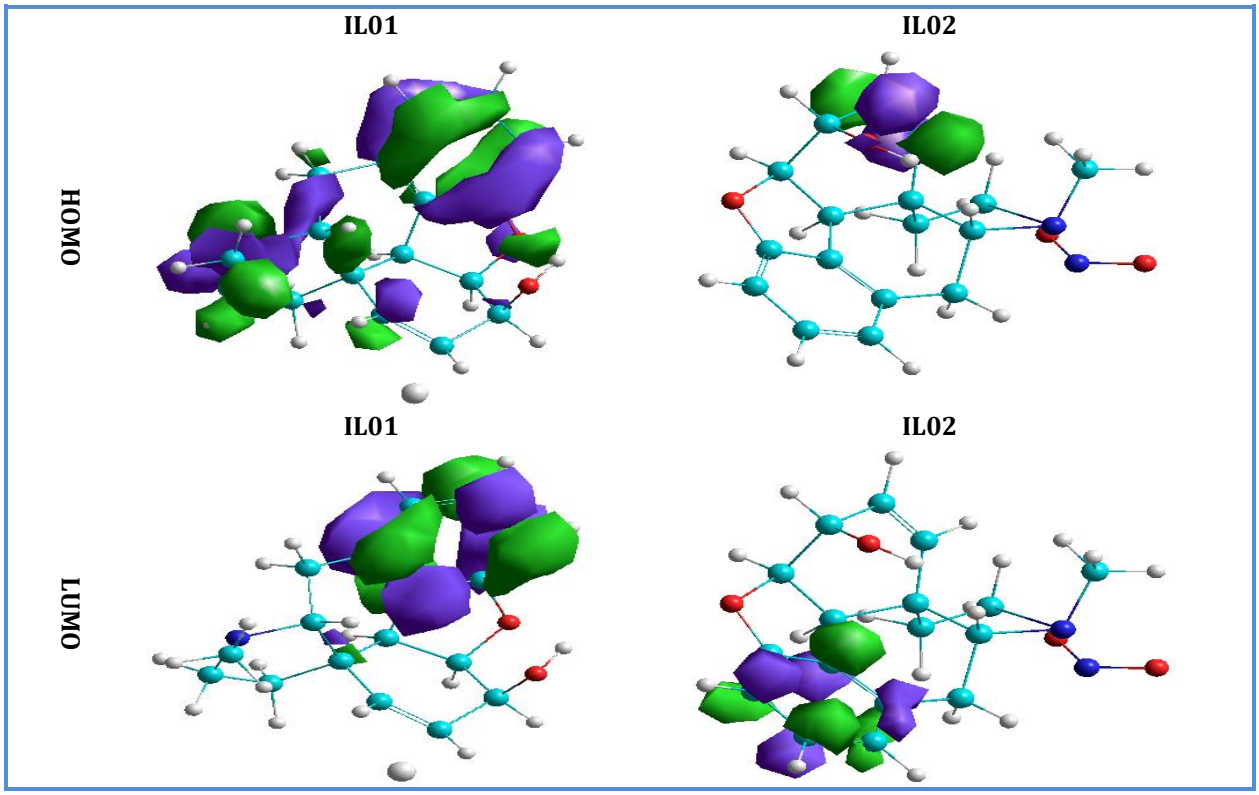
Graphical Abstract



Introduction

Morphine was initially isolated from the poppy seeds in 1805 using as alkaloid of opium [1]. The main beneficial use as pain killer for potent analgesic of chronic pain, however, its use is restricted due to several impacts on human such as the induction of tolerance, severe withdrawal symptoms and high risk of degeneration, and mistreatment [2]. Opium is more potent; however, the pure morphine is ten time more active. Around 400,000 addicted soldiers used extensively morphine drug for giving more concentration in the US civil war [3]. Despite of the bad impact of the morphine in civil war, the scientist searched to produce several efforts to have a less addictive alternative which brought the synthesis of heroin or morphine.

Morphine is prescribed as alternative opium as such codeine, fentanylmethadone, hydrocodone, hydromorphone, meperidine and oxycodone [4]. The initial FDA permitted drug from morphine was developed by the west-ward pharmaceuticals international in 1984 [5]. Morphine has more advantageous in dropping the indicator the tininess of breath due to both cancer and non cancer

causes. In additionally, it was also utilized for the healing for advanced cancer or end-stage cardio respiratory diseases, with regular, and low-dose. In the case of breathlessness conditions, for instance, sustained release, it can be able to reduce and maintain the breathlessness [6].

Due to having a numerous pros as medical value, pain it is restricted by dose limiting for showing side effects such as respiratory depression, sedation, nausea, and constipation, as well as the development of tolerance [7]. Morphine is extended release form, and it is often used to treat pain killer in human body. This form of morphine is not to use on a necessary basis for pain. Opioid medication can damage the breathing, and ultimately it may result in death. If you take a long break to take care of you, slowly or shallow breathing, chest with blue colored lip pain, fast or acute heart rate, extreme thirst, you can feel. Secondly the low correlation levels of the nausea, vomiting, hunger, dizziness, a lantikara fatigue or weakness are also obtained in patient body. In the last decade, allergic efficacy of the peripheral opioid is expressed as evidence of the fact that it offers a new alternative to pain treatment. During the administration of the peripheral opium, chaos medication can be achieved through opioid receptor activation on the orphaned cervical nerve terminals in the peripheral tissue to avoid the negative effects seen on the stimulation of central opioid receptors [7].

For a short time, intense electric field pulsates have been used to absorption for years in applications like electro chemotherapy, drug molecule, antimicrobial agents, and biological active molecules. These are pulses which make cell membranes accessible to some substances, including drugs, filaments, gene, and markers. The implicit process is in comparing to the plasma. In between special liposome's presents a convenient way to provide various solutions containing drug, protein, or nucleus acid cells, as they protect their content from adverse environmental conditions, and reduce toxicity. There are medicines for non-targeted cells, enhancing drug intake in targeted cells.

In this research study, the main goal was to reduce the morphine side effect on the patent body when it is taken as a drug. For this purpose, the morphine is converted to morphonium salts as morphonium ionic liquids which is considered as the designer greener molecules for 21st century. As Ionic liquid is considered as a designer molecule due to its tunable physical and chemical properties, morphine molecule was attached with hydronium ion to form morphonium cation which has to attach with chloride and nitrous ion to produce the morphonium chloride and morphonium nitrous ionic liquids crystal [8, 9]. It is proved that some ammonium carboxylate ionic liquid was found biological active [10-12]. Additionally some morpholinium, palladium, rhodium cation based molecule were simulated for prediction of physical and biological properties [13-18]. From this evaluations, it was found that some molecule have very low binding energy indicating

highly active drugs [8, 9, 19]. In this case, the electric field and temperature effect were calculated for use as a safe drug from UV visible light and in all environments and it revealed a poor implantation on the global descriptor, such as hardness and softness applying -0.020 a.m.u to +0.020 a.m.u [20]. For designing new molecule, the computational software was used though the density functional theory.

Experimental

Computational method

The drawing default was selected to build the target molecule for analyzing the molecular structures, drawing two-dimensional structure and automatically added the hydrogen atom from building module. To determine the thermo-physical and molecular orbital, the geometry optimization was conducted using the DFT, 6G-31G* and B3-LYP [21]. After optimization, entropy, heat of capacity, HOMO, LUMO, and electrostatic potential were recorded. The charge density, surface area grid, volume, LogP, polarizability, refractivity, and molecular mass were premeditated. The main key point of the temperature effect and electric field activity were simulated. The all computing methods were performed though DFT using the Hyperchem 8.0.10 software.

Results and discussion

Optimized structure

The 3D molecular structure after optimization is presented in Figure 1, which includes the values of the reactivity, molecular symmetry, and plane of symmetry. In Figure 1, the white ball is hydrogen, blue is nitrogen, red is oxygen and carbon is cyan.

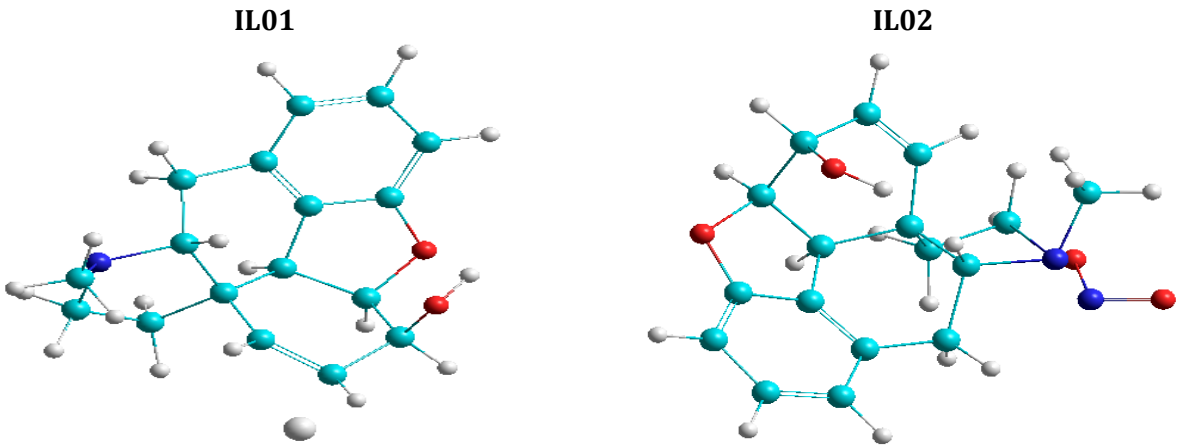


Figure 1. Optimized structure

Quantitative structure-activity relationships (QSAR)

The minimum binding energy indicates the maximum binding affinity with other molecules. The maximum binding affinity indicates as the best molecule for drug molecules targeting computationally. In case of the biological activity of a molecule, the surface area is considered as an important parameter. Greater charge surface area of a molecule can be able to kill more pathogens. The greater positive charge surface area means a higher biological activity.

On the other hand, a negative value of LogP indicated the hydrophilicity and positive LogP indicates the hydrophobicity that plays an important role in biochemical interactions and bioactivity. Hydrophobic drugs tend to be more toxic because, in general, are kept longer, have a wider distribution in the body, are somewhat less selective in their binding to molecules and finally are often extensively metabolized. As seen in Table 1, the LogP is positive which mention as toxic nature, and to introducing the toxicity the nitrous is more effective than chloride in morphonium cation.

Table 1. Data for quantitative structure activity relationships

	Partial charge (e)	Surface Area (grid)	Volume, Å^3	Hydration Energy kcal/mol	Log P	Refractivity, Å^3	Polarizibility, Å^3	Mass (amu)
IL01	0.0	440.24	797.64	-4.07	0.64	87.57	32.27	304.8
IL02	0.0	465.13	803.06	-19.04	1.38	87.52	32.12	315.35

Thermophysical properties with various temperatures

Entropy and enthalpy is an important part of thermodynamics, which allows physics and physical chemistry to participate in any system. Entropy and enthalpy are closely related to each other [22]. Entropy can be understood as the discharge condition of any substance, *i.e.,* whose entropy value is greater than its distortion in the reaction of the participant. Table 2. reveals that, at the temperature o without electric field, the value of entropy of optimized molecule is zero. Therefore, there are no substances in the zero temperature, no substances in any system and will easily participate in the biochemical chemical reaction.

Table 2. Thermophysical properties

	Entropy (kcal/mol-deg)	Heat capacity (kcal/mol-deg)	Dipole moment, D
IL01	0	0	0
IL02	0	0	0

On the other hand, Table 3. is shown that the increase of temperature is mentioned the increase of entropy. That means that the effect of temperature above that system for the reaction occurring is

decreased. From Table 3, it is found that the entropy and heat of capacity of morphonium chloride and morphonium nitrous increase with increasing temperature. At 273 K, the entropy and heat of capacity are 0.117, 0.113 and 0.062, 0.055 kcal/mol-deg and gradually increases by the value 0.177, 0.162 and 0.120, 0.099, respectively at 523 K for IL01, and IL02.

Table 3. Data for entropy and heat capacity with various temperature

	273 K		323 K		373 K		423 K		473 K		523 K	
	Entropy	**Heat capacity (kcal/mol-deg)**	**Entropy**	**Heat capacity (kcal/mol-deg))**	**Entropy**	**Heat capacity (kcal/mol-deg))**	**Entropy**	**Heat capacity (kcal/mol-deg))**	**Entropy**	**Heat capacity (kcal/mol-deg))**	**Entropy**	**Heat capacity (kcal/mol-deg))**
IL01	0.117	0.062	0.129	0.075	0.141	0.088	0.153	0.099	0.165	0.110	0.177	0.120
IL02	0.113	0.055	0.123	0.063	0.133	0.072	0.143	0.081	0.153	0.090	0.162	0.099

Electric field and temperature effect on different axis

The drug release from the conductive nanoparticle is controlled externally by the application of a weak, external electric field. Unlike other drug release systems which involve implantable chips or delivery of drugs with laser pulses, ultrasounds or magnetic field. Several forms of external fields, electric, magnetic, and mechanical, can in principle produce distortions of structures of molecule.

An electric field also has an effect on the entropy of a material. An external electric field would formally change the thermodynamic and molecular dynamic properties of a liquid. The electric field effect with varying temperature was recorded at 20, 40, and 60 mA along X, Y, and Z axis. Tables 4-6. reveal that, the applied electric field, entropy and heat of capacity increased with small portion changing in different axis. The largest entropy and heat of capacity were found in X axis than Z axis. The Y axis shows the smaller magnitude comparison other.

Table 4. Data for entropy and heat capacity with various temperature and electric field in 20 mA on the X axis

	273 K		323 K		373 K		423 K		473 K		523 K	
	Entropy	**Heat capacity (kcal/mol-deg)**	**Entropy**	**Heat capaciy (kcal/mol-deg))**	**Entropy**	**Heat capacity (kcal/mol-deg))**	**Entropy**	**Heat capacity, (kcal/mol-deg))**	**Entropy**	**Heat capacity (kcal/mol-deg))**	**Entropy**	**Heat capacity (kcal/mol-deg))**
IL01	0.079	0.013	0.081	0.016	0.084	0.018	0.087	0.021	0.090	0.024	0.092	0.026
IL02	0.110	0.054	0.120	0.064	0.130	0.073	0.140	0.082	0.150	0.091	0.160	0.10
	Electric field in 20 mA on Y axis											
IL01	0.076	0.012	0.079	0.014	0.082	0.017	0.084	0.020	0.087	0.022	0.089	0.025
IL02	0.109	0.053	0.120	0.062	0.129	0.071	0.140	0.080	0.149	0.090	0.158	0.101
	Electric field in 20 mA on Z axis											
IL01	0.078	0.014	0.081	0.017	0.084	0.019	0.087	0.022	0.090	0.025	0.093	0.027
IL02	0.110	0.054	0.121	0.064	0.131	0.073	0.141	0.082	0.151	0.091	0.166	0.099

From the Table 4, it is found that with increasing the temperature, the entropy and enthalpy have been changed from 0.79 to 0.92 and 0.013 to 0.026, respectively, for IL01 where the entropy is 0.110 to 0.116 and enthalpy is 0.054 to 0.10 along X axis. This change is similar to Y and Z axis on the other hand, the

result of applying 40 and 60 mA current along X, Y and Z axis with increasing temperature has listed in Tables 5 and 6, respectively while the main out is explain that with soaring temperature, the heat capacity and entropy have increased for both IL01 and IL02 but IL02 shows the higher value than IL01.

Table 5. Data for entropy and heat capacity with various temperature and electric field in 40 mA on the X axis

	273 K		323 K		373 K		423 K		473 K		523 K	
	Entropy	**Heat capacity (kcal/mol-deg)**	**Entropy**	**Heat capacity (kcal/mol-deg))**	**Entropy**	**Heat capacity (kcal/mol-deg))**	**Entropy**	**Heat capacity (kcal/mol-deg))**	**Entropy**	**Heat capacity (kcal/mol-deg))**	**Entropy**	**Heat capacity (kcal/mol-deg))**
L01	0.077	0.012	0.079	0.015	0.082	0.017	0.085	0.020	0.087	0.023	0.090	0.025
IL02	0.104	0.049	0.113	0.058	0.122	0.068	0.132	0.077	0.141	0.086	0.154	0.094
Electric field in 40 mA on Y axis												
IL01	0.076	0.012	0.079	0.014	0.081	0.017	0.084	0.019	0.086	0.022	0.089	0.024
IL02	0.106	0.051	0.116	0.060	0.126	0.069	0.135	0.078	0.145	0.087	0.154	0.095
Electric field in 40 mA on Z axis												
IL01	0.078	0.013	0.080	0.015	0.083	0.018	0.086	0.020	0.088	0.023	0.091	0.025
IL02	0.112	0.055	0.122	0.064	0.132	0.073	0.142	0.083	0.153	0.092	0.162	0.100

Table 6. Data for entropy and heat capacity with various temperature and electric field in 60 mA on the X axis

	273 K		323 K		373 K		423 K		473 K		523 K	
	Entropy	**Heat capacity (kcal/mol-deg)**	**Entropy**	**Heat capacity (kcal/mol-deg))**	**Entropy**	**Heat capacity (kcal/mol-deg))**	**Entropy**	**Heat capacity (kcal/mol-deg))**	**Entropy**	**Heat capacity (kcal/mol-deg))**	**Entropy**	**Heat capacity (kcal/mol-deg))**
IL01	0.077	0.012	0.079	0.015	0.082	0.017	0.085	0.020	0.087	0.022	0.090	0.025
IL02	0.105	0.050	0.114	0.059	0.124	0.068	0.133	0.078	0.143	0.086	0.152	0.095
Electric field in 60 mA on Y axis												
IL01	0.076	0.012	0.079	0.014	0.081	0.017	0.084	0.019	0.086	0.022	0.089	0.024
IL02	0.107	0.052	0.117	0.061	0.127	0.070	0.137	0.079	0.146	0.088	0.156	0.096
Electric field in 60 mA on Z axis												
IL01	0.078	0.013	0.080	0.015	0.083	0.017	0.086	0.020	0.088	0.022	0.091	0.024
IL02	0.108	0.052	0.118	0.062	0.128	0.071	0.137	0.080	0.147	0.089	0.157	0.097

HOMO-LUMO

HOMO and LUMO may have accounted about the electronic transition for the lower energy level to higher energy levels as if there had showed the chemical reactivity region regarding the positive and negative part of orbitals. The greater value of the LUMO belongs to the nucleophilic attraction part whereas the positive or nucleophilic group can be easily attracted. The concept for HOMO might be introduced for the electron available part of orbitals and can intense to attract the electrophilic groups. So the LUMO-HOMO gap indicates the chemical reactivity or chemical stability. As seen in Figure 2, the HOMO for IL01 is mentioned the both of aromatic ring while the HOMO for IL02 is only found in alkyl chain. The LUMO for IL01 is appeared at the nitrogen containing part of cyclic region in cation whereas LUMO for IL02 is found in aromatic ring. The LUMO, HOMO gap for IL01 and IL02 are 4.975 and 4.037,

respectively, indicating the chemically less stable and biologically more active as its value may have more than 6 to be chemically stable.

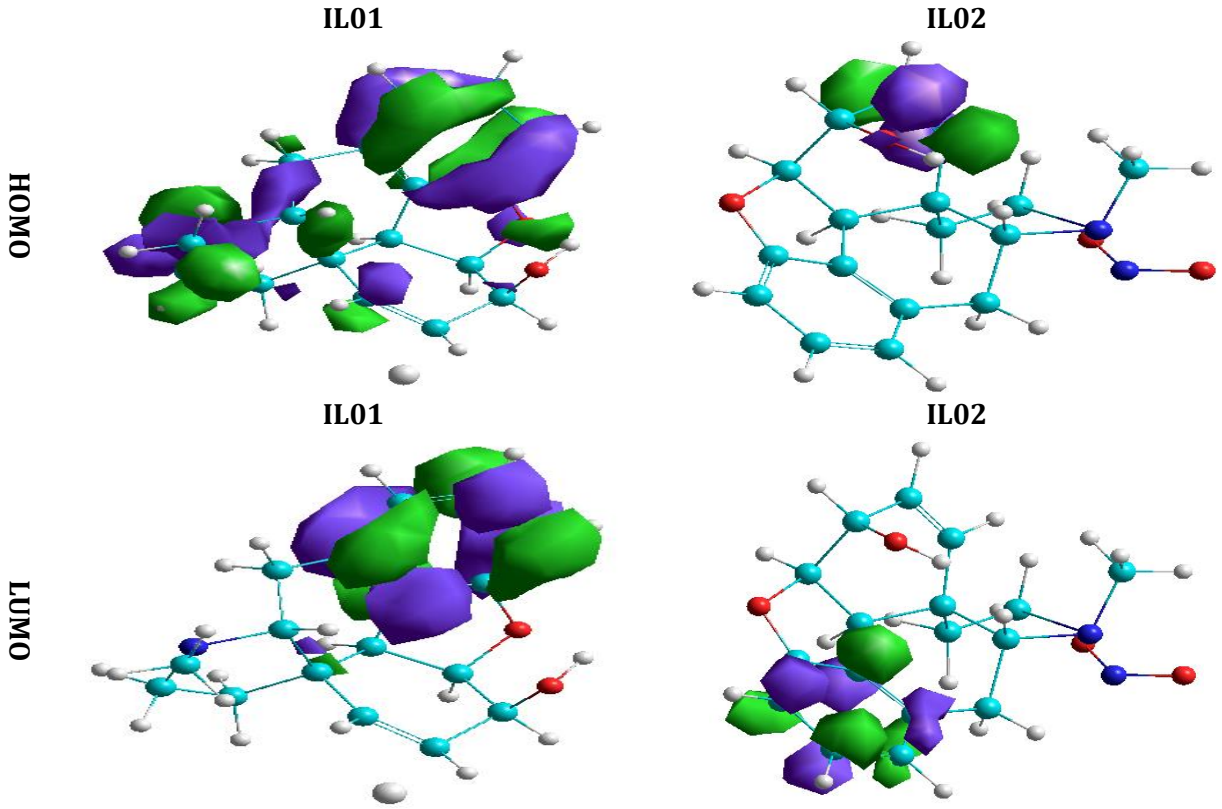


Figure 2. Picture of HOMO, LUMO orbital

Table 7. Data for HOMO & LUMO

	HOMO (0) eV	HOMO (-1) eV	HOMO (-2) eV	LUMO (0) eV	LUMO (-1) eV	LUMO (-2) eV	LUMO- HOMO gap (0)
IL01	-5.068	0.093	0.238	0.093	-5.068	-9.239	4.975
IL02	1.645	5.682	5.820	5.682	1.645	-0.508	4.037

Temperature and electric fields effect on chemical reactivity

As shown in Table 8, by changing the temperature, the magnitude of HOMO, LUMO did not altered. However, by applying the electric fields at various temperatures, the value of HOMO, LUMO was not changed.

Table 8. Temperature and Electric fields effect on chemical reactivity

		HOMO (0) eV	LUMO (0) eV
IL01	Without temperature	-5.068	0.093
	With temperature	-5.068	0.093
	With Temperature and Electric fields	-5.068	0.093
IL02	Without temperature	1.645	5.682

	With temperature	1.645	5.682
	With Temperature and Electric fields	1.645	5.682

Conclusions

In this work, we evaluated the effect of temperature and electric field activity on the morphonium chloride and morphonium nitrous molecule as treating in drug for only thermophysical properties but this case of chemical reactivity shows almost zero effect. The entropy and heat of capacity were increased in all cases by applying an external electric field with various temperatures, whereas chemical reactivity was unchanged. Also, the entropy and heat capacity were decreased comparing the corresponding temperature of without electric field. Finally, it was found that, the IL01, IL02 can show biological active and their poor chemical stability was recognized as more biological active and LogP may indicate the non toxic material for human body.

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