ISNN:2181-1296

SHAROF RASHIDOV NOMIDAGI
SAMARQAND DAVLAT UNIVERSITETI

САМАРКАНДСКИЙ ГОСУДАРСТВЕННЫЙ
УНИВЕРСИТЕТ ИМЕНИ ШАРОФА РАШИДОВА

SAMARKAND STATE UNIVERSITY NAMED
AFTER SHAROF RASHIDOV

ILMIY AXBOROTNOMA

НАУЧНЫЙ ВЕСТНИК
SCIENTIFIC JOURNAL

ANIQ VA TABIIY FANLAR SERIYASI

Matematika, Mexanika, Informatika
Fizika, Kimyo, Biologiya, Geografiya

№ 3/1 (151)
2025

ISSN 2181-1296

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2025-yil, 3-son (151/1) ANIQ VA TABIIY FANLAR SERIYASI

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Samarqand viloyat matbuot boshqarmasida ro‘yxatdan o‘tish tartibi 09-25.
Jurnal 1999-yildan chop qilina boshlagan va OAK ro‘yxatiga kiritilgan.

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Obuna indeksi – yakka tartbidagi obunachilar uchun **- 5583,**
tashkilot, korxonalar uchun **- 5584**

M U N D A R I J A
C O N T E N T S

№	Maqola nomi	Article title	Bet/ page
1	Yemirilishni hisobga olgan holda ikki zonali g‘ovak muhitda degradatsiyalanuvchi modda ko‘chishi **Xo‘jayorov B., Fayziev B., Sagdullaev O., Haydarov O.**	Transport of a degrading solute in a two-zone porous medium taking into account the decay **Khuzhayorov B., Fayziev B., Sagdullaev O., Khaydarov O.**	**5-11**
2	Fizik-kimyoviy usullar yordamida kadmiy ionlarini aniqlovchi ion-selektiv elektrod membranasining tuzilishi **Abduraxmanov E., Salimova Sh., Jumanova G.**	Membrane structure of ion-selective electrode for determining cadmium ion, analyzed by physicochemical methods **Abdurakhmanov E., Salimova Sh., Jumanova G.**	**12-17**
3	Tasodifiy qo‘zg‘alishlarda elastik sterjenning chiziqlimas ko‘ndalang tebranishlarini so‘ndirish masalasi **Dusmatov O., Kasimova F.**	Problem of absorber nonlinear transverse vibrations of an elastic rod under random impacts **Dusmatov O., Kasimova F.**	**18-22**
4	Birjinsli tekis-radial muhitda anomal filtratsiya **Xo‘jayorov B., Maxmudov J., Akramov Sh.**	Plane-radial anomalous filtration of liquid in homogeneous porous medium **Khuzhayorov B., Makhmudov J., Akramov Sh.**	**23-28**
5	Parasetamolning molekulyar xususiyatlariga erituvchining ta’siri **Holikulov U., Jumabaev A., Xudaykulov B., Yormatov Sh., Safarov A.**	Solvent effect on the molecular properties of paracetamol **Holikulov U., Jumabaev A., Khudaykulov B., Yormatov Sh., Safarov A.**	**29-35**
6	Tibbiy tasvirlar asosida teri kasalliklarini tasniflashning mashinaviy o‘qitish va chuqur o‘qitish yondashuvlari **Boboxonov A., Xuramov L., Rashidov A.**	Machine learning and deep learning approaches to classify skin diseases based on medical images **Bobokhonov A., Khuramov L., Rashidov A.**	**36-48**
7	Urbanizatsiya jarayonlarini hududiy tashkil etilishida xorijiy davlatlar tajribasi **Ibragimov L., Baratova G.**	The experience of foreign countries in the territorial organization of urbanization processes **Ibragimov L., Baratova G.**	**49-55**
8	Singulyar sirtlar uchun transversallik sharti **Usmanov S.**	Transversality condition for singular surfaces **Usmanov S.**	**56-60**
9	Tuproq namligini o'lchovchi avtonom sensorlar uchun $KPbBr_3$ nanokompoziti **Rahmonova M., Muxamadiev N., Galyamitdinov Y.**	$KPbBr_3$ nanocomposite for autonomous agro soil moisture sensors **Rahmonova M., Mukhamadiev N., Galyamitdinov Y.**	**61-67**
10	Fotoelektrik modul yuzasi ifloslanishi jarayonining matematik modeli **Muminov R., Utamuradova Sh., Dyskin1 V., Tukfatullin O., Butunbaev B.**	Mathematical model of the soiling process of a photovoltaic module surface **Muminov R., Utamuradova Sh., Dyskin1 V., Tukfatullin O., Butunbaev B.**	**68-74**
11	Landshaft komplekslarini tadqiq etishda landshaft-meliorativ yondashish va baholash **Eshquvvatov B., Xurramova N., Saydullayeva S.**	Landscape-ameliorative approach and assessment in the study of landscape complexes **Eshkuvvatov B., Khurramova N., Saydullaeva S.**	**75-80**
12	Yuklangan Hirota tenglamani sochilish nazariyasining teskari masalalari usulida integrallash **Hoitmetov U., Musoyeva F.**	Integrating the loaded Hirota equation via the inverse scattering method **Hoitmetov U., Musoeva F.**	**81-91**
13	Tebranishlardan himoyalanuvchi mexanik sistemaning chiziqlimas tasodifiy parametrik tebranishlari **Dusmatov O., Xodjabekov M., Ashurov B.**	Nonlinear random parametric oscillations of a vibration-proofed mechanical system **Dusmatov O., Xodjabekov M., Ashurov B.**	**92-100**
14	Qisman-izospektral Shturm-Liuvill operatorlari va ularning tatbiqlari **Mirzaev O., Abdunazarov R., Nosirova G.**	Partially-isospectral Sturm-Liouville operators and their applications **Mirzaev O., Abdunazarov R., Nosirova G.**	**101-111**
15	Texnogen omillarning Ohangaron daryo havzasi landshaftlari ifloslanishiga ta'siri **Fozilov A.**	The influence of technogenic factors on the pollution of landscapes of the Akhangaran river basin **Fozilov A.**	**112-116**
16	Trisiklik 7-дезапуринлар синтези **Kuryazov R.Sh., Shonazarov A.R., Zhao J., Bozorov Kh.A.**	Synthesis of tricyclic 7-deazapurines **Kuryazov R.Sh., Shonazarov A.R., Zhao J., Bozorov Kh.A.**	**117-121**
17	Trisiklik pirrolo[2,3-*D*]pirimidin tizimida karbonil-amin kondensatsiyasi orqali iminlar sintezi **Kuryazov R.Sh.**	Synthesis of imines via carbonyl-amine condensation in the tricyclic pyrrolo[2,3-d]pyrimidine system **Kuryazov R.Sh.**	**122-126**

UDC: 535.012 **DOI:https://doi.org/10.59251/2181-3973.2025.v1.138.1.3416**

SOLVENT EFFECT ON THE MOLECULAR PROPERTIES OF PARACETAMOL

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Received: 16.05.2025
Revised: 26.05.2025
Accepted: 16.07.2025
Published: 31.07.2025

Publisher: Samarkand State University named after Sharof Rashidov.

Abstract. In this study, the effect of different solvent phases (water, DMSO, acetonitrile, ethanol, chloroform and heptane) on the electronic, reactivity and nonlinear optical (NLO) properties of paracetamol was analyzed using quantum mechanical calculations. Quantum mechanical calculations were performed using the density functional theory (DFT) method with the B3LYP function and the 6-311++G(d,p) basis set. The calculation results showed that the smallest dipole moment for the paracetamol molecule is 2.62 D in the heptane phase, and the largest dipole moment is 3.36 D in the water phase. It was found that the polarizability and first-order hyperpolarizability values of paracetamol decrease in different solvent phases in the following order: water > DMSO > acetonitrile > ethanol > chloroform > heptane.

Keywords: paracetamol, solvent, DFT, MEP, reactivity, NLO.

Parasetamolning molekulyar xususiyatlariga erituvchining ta’siri

Annotatsiya. Ushbu tadqiqotda parasetamolning elektron, reaktivlik va nochiziqli optik (NLO) xususiyatlariga turli erituvchi (suv, DMSO, asetonitril, etanol, xloroform va geptane) fazalarning ta’sirini kvant-mexanik hisoblash usullaridan foydalangan holda tahlil qilingan. Kvant-mexanik hisoblashlar zichlik funksional nazariyasi (DFT) usulida B3LYP funksionali va 6-311++G(d,p) bazislar to’plami bilan amalga oshirilgan. Hisoblash natijalari shuni ko'rsatdiki, paratsetamol molekulasi uchun eng kichik dipol momenti geptan fazasida 2,62 D, eng katta dipol momenti esa suv fazasida 3,36 D ga teng. Paratsetamolning qutblanuvchanligi va birinchi darajali giperqutblanish qiymatlari turli erituvchi fazalarida quyidagi tartibda kamayishi aniqlandi: suv > DMSO > asetonitril > etanol > xloroform > geptan.

Kalit so‘zlar: parasetamol, erituvchi, DFT, MEP, reaktivlik, NLO.

Влияние растворителя на молекулярные свойства парацетамола

Аннотация. В данном исследовании влияние различных фаз растворителя (вода, ДМСО, ацетонитрил, этанол, хлороформ и гептан) на электронные, реакционные и нелинейно-оптические (НЛО) свойства парацетамола было проанализировано с помощью квантово-механических расчетов. Квантово-механические расчеты были выполнены с использованием метода теории функционала плотности

(ТФП) с функцией B3LYP и базисным набором 6-311++G(d,p). Результаты расчетов показали, что наименьший дипольный момент для молекулы парацетамола составляет 2,62 D в фазе гептана, а наибольший дипольный момент составляет 3,36 D в водной фазе. Было обнаружено, что значения поляризуемости и гиперполяризуемости первого порядка парацетамола уменьшаются в различных фазах растворителя в следующем порядке: вода > ДМСО > ацетонитрил > этанол > хлороформ > гептан.

Ключевые слова: парацетамол, растворитель, ТФП, МЭП, реакционная способность, НЛО.

Introduction. Paracetamol (acetaminophen) (Figure 1) is a widely used drug worldwide due to its pharmaceutical (analgesic and antipyretic) properties [1, 2]. The study of its molecular structure, reactivity, bioactivity, and electro-optical properties, as well as the influence of the environment on its pharmacological and physico-chemical properties, is of great scientific and practical importance. The crystal structure and vibrational spectra of paracetamol have been reported in several previous studies. M. Haisa et al. [3] and Stasilowicz et al. [4] rationally apply X-ray powder diffraction (PXRD) and FTIR and Raman spectroscopy to study the crystallographic structure of paracetamol.

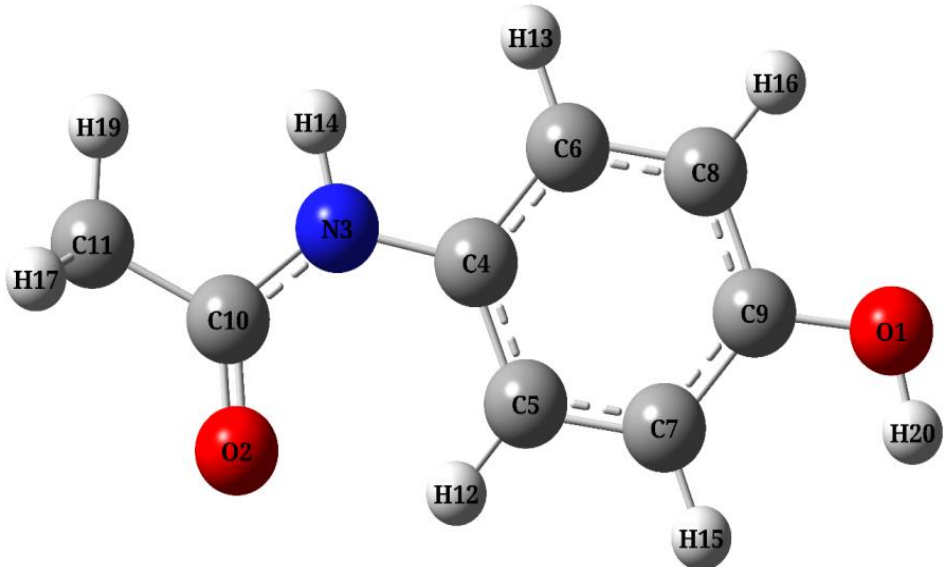


FIGURE 1. The optimized structure of paracetamol calculated at B3LYP/6-311++G(d,p) level

G. Nichols et al. [5] analyzed the method of obtaining paracetamol form II from solution and its physicochemical properties. The most stable and reactive conformers of paracetamol were studied at the B3LYP/6-311++G(d,p) level by Mehdi Yoosefian et al. [6]. They also studied in depth the effects of internal hydrogen bonds and the aqueous phase. The presence of polar functional groups O-H, C=O and N-H in the paracetamol molecule indicates the ability to form intermolecular hydrogen bonds and a significant change in the electro-optical properties of the molecule under the influence of the solvent.

In this study, the effect of solvent polarities on the molecular properties of paracetamol, including electronic, structural, nonlinear optical (NLO) and vibrational spectra, was investigated using the Density Functional Theory (DFT) method.

Methods. The geometry of the paracetamol molecule in the gas and solvent phases with different dielectric constants (water, DMSO, acetonitrile, ethanol, chloroform and heptane) was optimized by the Density Functional Theory (DFT) method using the B3LYP (Becke, 3-parameter, Lee-Yang-Parr) hybrid functional [7, 8] and the 6-311++G(d,p) basis set containing diffusion and polarization functions. To more accurately account for the interaction between paracetamol and the

solvent phase, the IEF-PCM (Integral Equation Formalism Polarizable Continuum Model) model was used. All DFT calculations were performed in the Gaussian 16W program package [9]. The GaussView 6.1 tool [10] was used to visualize the calculation results.

Results and discussion.

Free Energy of Solvation and dipole moment.

To investigate the effect of solvent phases with different dielectric constants (Table 1) on the thermodynamic stability of paracetamol, it is necessary to calculate the change in the free energy of solvation, i.e. the Gibbs free energy. The Gibbs free energy represents the ability of a system to do work at constant temperature and pressure and is given by the following formula [11]:

$$G=H-TS \quad (1)$$

where H is enthalpy, T is temperature, S is entropy.

Free energy of solvent (ΔG_{solv}) is determined using the following formula:

$$\Delta G_{solv}=G_{solv}-G_{gas} \quad (2)$$

where G_{solv}, G_{gas} are the calculated Gibbs free energies in the solvent and gas phases, respectively.

TABLE 1. The dielectric constant of solvents

Solvent	**Dielectric constant (ε)**
Water	78.3553
DMSO	46.826
Acetonitrile	35.688
Ethanol	24.852
Chloroform	4.7113
Heptane	1.9113

The variation of the free energy of solvation of paracetamol in different solvent phases is shown in Figure 2. In water, the solvation energy is approximately 42.59 kJ/mol, showing the highest value. In DMSO and acetonitrile, this value decreases to 41 and 40 kJ/mol, respectively, and in ethanol, it decreases slightly to 39.43 kJ/mol. In chloroform, the energy decreases sharply to 27.17 kJ/mol, and in heptane, the lowest value was found to be 13.2 kJ/mol. This trend indicates a decrease in the solvation energy with decreasing solvent polarity. While in highly polar solvents such as water, the molecule-solvent interaction is strong, in nonpolar solvents such as heptane, this effect is much weaker. The dipole moment of paracetamol changes in parallel with the solvation energy. In water, the dipole moment is around 3.36 Debye, having the highest value. In DMSO and acetonitrile, this value is maintained in the range of 3.34–3.33 Debye, while in ethanol it drops to 3.3 Debye. In chloroform, the dipole moment decreases to 2.99 Debye, and in heptane to 2.62 Debye. These changes depend on the dielectric constant and polarity of the solvent, indicating that the dipole moment of paracetamol is higher in polar solvents.

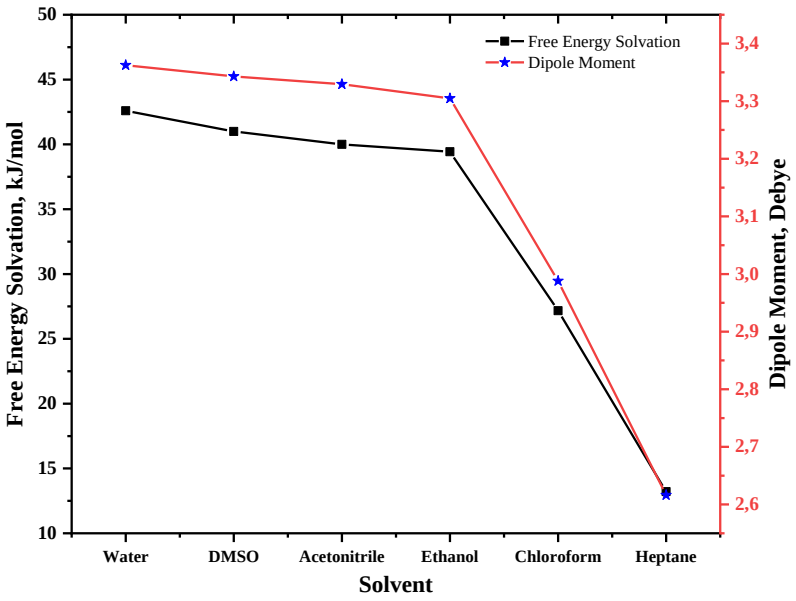


FIGURE 2. The solvent effect on the free energy solvation and dipole moment of paracetamol molecule

Molecular electrostatic potential (MEP) surface.

The molecular electrostatic potential (MEP) maps of the paracetamol molecule were analyzed in different phases. The decreasing order of electrostatic potential in the MEP images is represented by the colors blue > green > yellow > orange > red [12]. Red regions indicate the most negative electrostatic potential, and blue regions indicate the most positive electrostatic potential.

While the electrostatic potential range in the gas phase is from $-6.027 \cdot 10^{-2}$ a.u. to $+6.027 \cdot 10^{-2}$ a.u., in water this range extends from $-7.712 \cdot 10^{-2}$ a.u. to $+7.712 \cdot 10^{-2}$ a.u. A similar extension was observed in DMSO (-7.685·10-2 au / +7.685·10-2 au) and acetonitrile ($-7.659 \cdot 10^{-2}$ a.u. / $+7.659 \cdot 10^{-2}$ a.u.). These results indicate that solvent polarization enhances the electrostatic differences in the molecule and, accordingly, more clearly expresses the electrophilic and nucleophilic reactivity centers.

In the MEP maps, the red and yellow regions are found to be mainly located near oxygen atoms. These regions are described as potential sites for electrophilic reactivity. In contrast, the blue regions are more concentrated around hydrogen atoms bonded to oxygen and nitrogen atoms, indicating their high nucleophilic reactivity potential.

The presence and type of solvent significantly alter the molecular interaction capacity of the paracetamol molecule by increasing or decreasing the electrostatic differences in the MEP map. In particular, strongly polar media such as water and DMSO increase the prominence of electrophilic and nucleophilic centers, which may directly affect the pharmacological and bioactive properties of the paracetamol molecule.

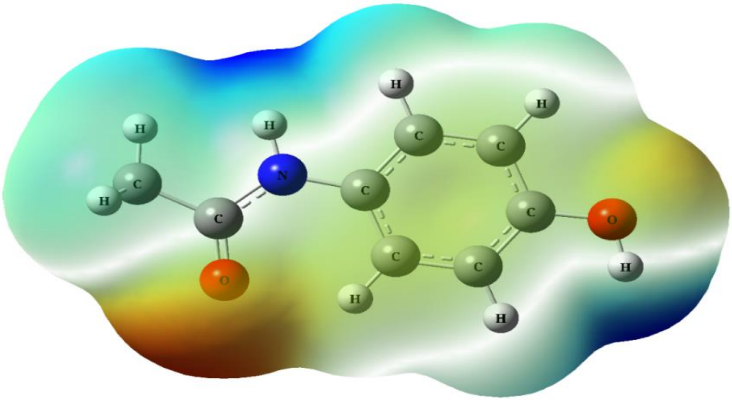


FIGURE 3. Molecular electrostatic potential (MEP) surface of paracetamol in the gas phase

Frontier Molecular Orbitals (FMO) analysis.

Frontier molecular orbital (FMO) analysis is useful for understanding reactivity and electronic transitions [13]. Table 2 presents the chemical reactivity parameters energy gap (E_g), hardness (η), chemical potential (μ), softness (S) and global electrophilic index (ω) calculated for the paracetamol molecule in the various phases using the lowest unoccupied molecular orbital (LUMO) and the highest occupied molecular orbital (HOMO) energies. These values are determined using the following formulas based on Koopman's theorem [14]:

$$E_g = E_{HOMO} - E_{LUMO} \quad (3)$$

$$\eta = \quad (4)$$

$$\mu = \quad (5)$$

$$\omega = \mu^2/2\,\eta \quad (6)$$

The HOMO energy is lowest in water (–6.0322 eV) and highest in the gas phase (–5.9201 eV), indicating that the electron-donating ability of the molecule depends on the polarity of the solvent. The LUMO energy is highest in the gas phase (–0.6822 eV) and lowest in water (–0.7573 eV). This indicates that the electron-accepting ability of paracetamol increases in polar solvents. The Energy Gap is in the range of 5.2744–5.2748 eV in water, DMSO, acetonitrile and ethanol, showing a stable value. In chloroform, this value decreases to 5.2649 eV and in heptane to 5.2518 eV. A smaller Energy Gap indicates a higher reactivity of the molecule [15]. Therefore, paracetamol is relatively more reactive in nonpolar solvents such as heptane. Chemical Hardness is highest in water (2.6375 eV) and lowest in heptane (2.6259 eV), indicating that the molecule is more stable in polar solvents. The Softness parameter, on the contrary, is lowest in water (0.3792 eV^{-1}) and highest in the gas phase (0.3818 eV^{-1}), confirming that the molecule is softer and more reactive in a nonpolar environment. Chemical Potential is lowest in water (–3.3948 eV) and highest in the gas phase (–3.3012 eV), indicating that the electron flow of paracetamol decreases in polar solvents. In heptane, this value is –3.3198 eV. Electronegativity Index is lowest in water (2.1847 eV) and highest in the gas phase (2.0805 eV), indicating that the molecule's electron-withdrawing ability is higher in a nonpolar environment. In heptane, this value is 2.0985 eV. The reactivity parameters of paracetamol vary depending on the polarity of the solvent. In polar solvents (water, DMSO), the molecule is more stable, has a higher Energy Gap and Chemical Hardness, and a lower Softness. In nonpolar solvents (heptane, chloroform), the Energy Gap decreases and the Softness increases, indicating an increased reactivity of the molecule.

TABLE 2. Molecular orbital energy (eV) (HOMO and LUMO) of paracetamol in different solvents

Medium	HOMO	LUMO	Energy Gap E_g	Chemical Hardness η	Softness S	Chemical potential μ	Electrophilicity Index ω
Gas	-5,9201	-0,6822	5,2379	2,6190	0,3818	-3,3012	2,0805
Water	-6,0322	-0,7573	5,2749	2,6375	0,3792	-3,3948	2,1847
DMSO	-6,0284	-0,7540	5,2744	2,6372	0,3792	-3,3912	2,1804
Acetonitrile	-6,0300	-0,7554	5,2747	2,6373	0,3792	-3,3927	2,1822
Ethanol	-6,0257	-0,7519	5,2738	2,6369	0,3792	-3,3888	2,1775
Chloroform	-5,9873	-0,7225	5,2649	2,6324	0,3799	-3,3549	2,1378
Heptane	-5,9457	-0,6939	5,2518	2,6259	0,3808	-3,3198	2,0985

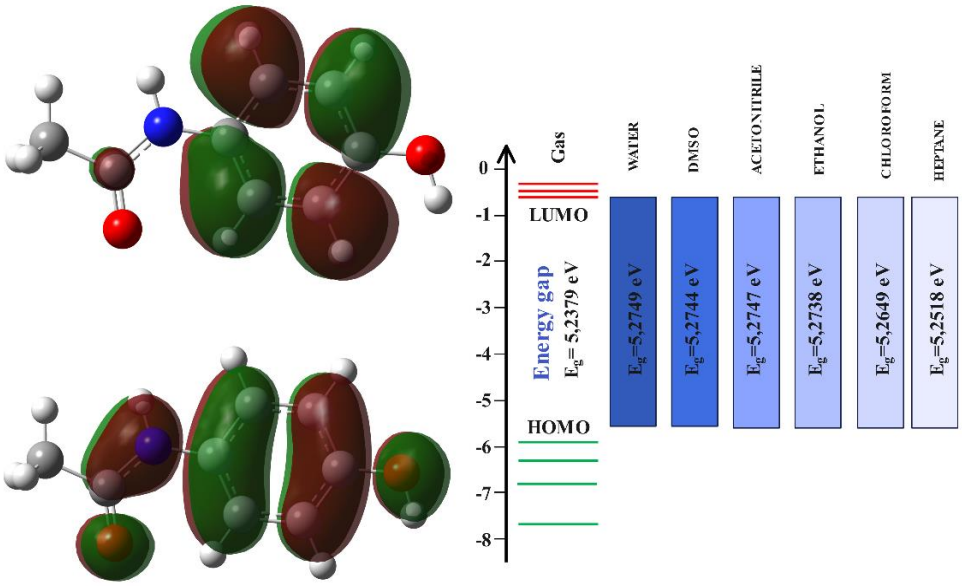


FIGURE 4. Frontier molecular orbitals maps and energy gaps of paracetamol in different phases

Non-linear optical (NLO) properties.

The effect of different solvent environments on the polarization (α) and first-order hyperpolarization (β) properties of the paracetamol molecule was studied. The results of the study show that the degree of polarization of the solvent has a significant effect on the electrical response parameters of the molecule (Table 3).

The average isotropic polarization (α_{iso}) of paracetamol in the gas phase is 16.755×10^{-24} esu, which is significantly higher in water (22.402×10^{-24} esu), DMSO (22.303×10^{-24} esu) and acetonitrile (22.229×10^{-24} esu). The high polarization of these solvents increases the deformation of the electron cloud of the molecule. The α_{aniso} (anisotropic polarization) value is also higher in water (16.305×10^{-24} esu) and DMSO (16.278×10^{-24} esu) compared to the gas phase. In solvents with low polarization, such as heptane (α_{iso}=18.608×10^{-24} esu), the polarization is maintained at a relatively low level.

The total hyperpolarizability (β_{tot}) of the paracetamol molecule also depends significantly on the solvent environment. While in the gas phase β_{tot}=21.949×10^{-30} esu, in water this value almost doubled to 41.919×10^{-30} esu. Similarly high values were observed in DMSO (41.524×10^{-30} esu) and acetonitrile (41.254×10^{-30} esu). Solvents with low polarity, in particular chloroform (34.906×10^{-30} esu) and heptane (28.123×10^{-30} esu), reduce the β_{tot} value.

TABLE 3. Solvent effect on polarizability and first-order hyper-polarizability of paracetamol

Medium	α_{xx}, 10^{-24} esu	α_{yy}, 10^{-24} esu	α_{zz}, 10^{-24} esu	α_{iso}, 10^{-24} esu	α_{aniso}, 10^{-24} esu	β_x, 10^{-30} esu	β_y, 10^{-30} esu	β_z, 10^{-30} esu	β_{tot}, 10^{-30} esu
Gas	23,792	9,753	16,720	16,755	12,911	-21,428	-3,332	3,394	21,949
Water	31,386	12,789	23,031	22,402	16,305	-41,787	-3,032	-1,369	41,919
DMSO	31,272	12,717	22,919	22,303	16,278	-41,391	-3,096	-1,216	41,524
Acetonitrile	31,192	12,659	22,835	22,229	16,259	-41,122	-3,095	-1,129	41,254
Ethanol	31,048	12,557	22,682	22,096	16,224	40,640	-3,092	-0.975	40,769
Chloroform	29,159	11,528	20,885	20,524	15,613	-34,711	-3,529	1,056	34,906
Heptane	26,566	10,529	18,729	18,608	14,452	-27,759	-3,640	2,662	28,123

Conclusion. This study aims to study the effect of solvent phases with different dielectric constants on the molecular properties of paracetamol at the DFT: B3LYP/6-311++G(d,p) theoretical level. The calculation results show that the solvation energy decreases with decreasing solvent polarity.

While the molecule-solvent interaction is strong in highly polar solvents such as water, this effect is much weaker in nonpolar solvents such as heptane. It is also shown that paracetamol has a higher dipole moment in polar solvents. The reactivity parameters of paracetamol vary depending on the polarity of the solvent. It was found that in polar solvents (water, DMSO), the molecule is more stable, while in nonpolar solvents (heptane, chloroform), the reactivity of the molecule increases. It was found that with decreasing dielectric constant of the solvent medium, the NLO parameters such as polarizability and first-order hyper-polarizability of paracetamol decrease.

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