www.dergipark.gov.tr
ISSN:2148-3736
El-Cezerî Fen ve Mühendislik Dergisi
Cilt: 9, No: 2, 2022 (740-747)

El-Cezerî Journal of Science and Engineering
Vol: 9, No: 2, 2022 (740-747)
DOI : 10.31202/ecjse.1000757

ECJSE

Makale / Research Paper

Impact of Solvent Polarity on the Molecular Properties of Dimetridazole

Rebaz Anwar OMER[* 1,2a], Lana Omer AHMED[3b], Pelin Koparir[4c], Jawameer Hama[5d]

[1]Department of Chemistry, Faculty of Science & Health, Koya University, Koya KOY45, Iraq
[2]Department of Chemistry, Faculty of Science, Firat University, 23169, Elazig, Turkey
[3]Department of Physics, Faculty of Science & Health, Koya University, Koya KOY45, Iraq
[4]Forensic Medicine Institute, Department of Chemistry, Firat University, 23169 Elazig, Turkey
[5]Department of Chemistry, College of Science, University of Raparin, Rania, Iraq.
rebaz.anwar@koyauniversity.org

Received/Geliş: 25.09.2021 **Accepted/Kabul:** 28.10.2021

Abstract: Recently molecular activity of dimetridazole (DMZ) gained interested due to medical applications. In this study, a computational investigation of the solvent impact on solvation free energy, dipole moments, polarizability, hyper-polarizability and characteristic atomic properties; hardness and softness quality, chemical potential, electronegativity and electrophilicity have been accounted for DMZ. All forms of the calculation for both gas phase and solution phase used Becke 3-Parameter of Lee-Yang parr (B3LYP) theory with a 631++G basis set. Using the Solvation Model on Density (SMD), the effect of solvent polarity on solvation free energy, dipole moment, polarizability, hyper-polarizability and molecular properties were measured. The dipole moment of the DMZ was lower value in a gas phase comparative with the solution phase. Furthermore, the electronegativity and chemical potential were increased from non-polar to polar solvents, while the electrophilicity index was decreased. However, in the case of chemical hardness & softness, the opposite relationship has been found. The results of this study contribute to an understanding of the molecular activity of DMZ and stimulate its activity in the solution phase.

Keywords: Dimetrizole, Solvation model, Dipole moment, Solvent-free energy, Molecule polarizability.

Çözücü Polaritesinin Dimetridazolün Moleküler Özellikleri Üzerindeki Etkisi

Öz: Son zamanlarda tıbbi uygulamalar nedeniyle dimetridazolün (DMZ) moleküler aktivitesi ilgi görmeye başlamıştır. Bu çalışmada, çözücünün çözünme serbest enerjisi, dipol momentleri, polarize edilebilirlik, hiper-polarize edilebilirlik ve karakteristik atomik özellikler üzerindeki etkisinin hesaplamalı bir araştırması; DMZ için sertlik ve yumuşaklık kalitesi, kimyasal potansiyel, elektronegatiflik ve elektrofilik hesaplanmıştır. Hem gaz fazı hem de çözelti fazı için tüm hesaplama biçimleri, bir 631++G temel seti ile Lee-Yang parr (B3LYP) teorisinin Becke 3-Parametresini kullandı. Çözme Modeli Yoğunluk (SMD) kullanılarak çözücü polaritesinin solvasyon serbest enerjisi, dipol momenti, polarize edilebilirlik, hiper-polarize edilebilirlik ve moleküler özellikler üzerindeki etkisi ölçülmüştür. DMZ'nin dipol momenti, çözelti fazına kıyasla bir gaz fazında daha düşük bir değerdi. Ayrıca, polar olmayan çözücülerden polar çözücülere doğru elektronegatiflik ve kimyasal potansiyel artarken, elektrofiliklik indeksi azalmıştır. Ancak, kimyasal sertlik ve yumuşaklık durumunda tam tersi bir ilişki bulunmuştur. Bu çalışmanın sonuçları, DMZ'nin moleküler aktivitesinin anlaşılmasına katkıda bulunur ve çözelti fazındaki aktivitesini uyarır.

Anahtar kelimeler: Dimetrizol, Solvasyon modeli, Dipol momenti, Solventsiz enerji, Molekül polarize edilebilirliği..

How to cite this article
Omer A., Ahmed LÖ., Koparir P., Hama J., "Impact of Solvent Polarity on the Molecular Properties of Dimetridazole" El-Cezerî Journal of Science and Engineering, 2022, 9 (2); 740-747.

Bu makaleye atıf yapmak için
Omer A., Ahmed LÖ., Koparir P., Hama J., "Çözücü Polaritesinin Dimetridazolün Moleküler Özellikleri Üzerindeki Etkisi" El-Cezerî Fen ve Mühendislik Dergisi 2022, 9 (2); 740-747.
ORCID: [a] 0000-0002-3774-6071, [b] 0000-0003-2181-1972, [c] 0000-0002-0663-4093, [d] 0000-0002-3981-9748

1. Introduction

Dimetridazole (1,2-dimethyl-5-nitroimidazole) (DMZ) (Figure 1) is in the imidazole family drugs[1, 2], and used to manage turkey flock infection with Histomonas meleagridis that develops Histomoniasis (or 'blackhead'), as well as poultry coccidiosis [3]. DMZ residues were found in the tissue of broiler and eggs, due to unintended contamination of the feed or excessive use of the drug [4]. Different analytical methods have been used for the determination of DMZ, including high-performance liquid chromatography with detection of UV or diode-array [5-8] with electrochemical detection[9] and gas chromatography with electron-capture detection [10].

Modern techniques have been used to investigate the role, structure, and interaction of biologically active [11, 12]. DFT has a reasonable cost-accuracy ratio for large systems in terms of the required computational efforts, the calculations are always prohibitive and work best for charged systems [13, 14]. In addition, the DFT methods can fill the gap between existing semi-empirical methods in terms of the cost-accuracy ratio with a physically sound approach. Using DFT has elevated the performance of the systems and eliminate self-interaction error and extended charged systems even when treated unscreened are unproblematic. Also, DFT calculation is performed completely analytical for the computation of gradients to eliminate the problems with numerical noise in geometry optimizations or frequency calculations [15, 16].

In this research, the effect of solvent on solvent-free energy, dipole moment, polarizability, first-order hyper-polarizability, and chemical reactivity of DMZ was assessed, which potentially help to better understand the stability of DMZ in various solution phases, and help to develop new pharmaceutical and (bio)chemical products derived from DMZ.

(a) (b)

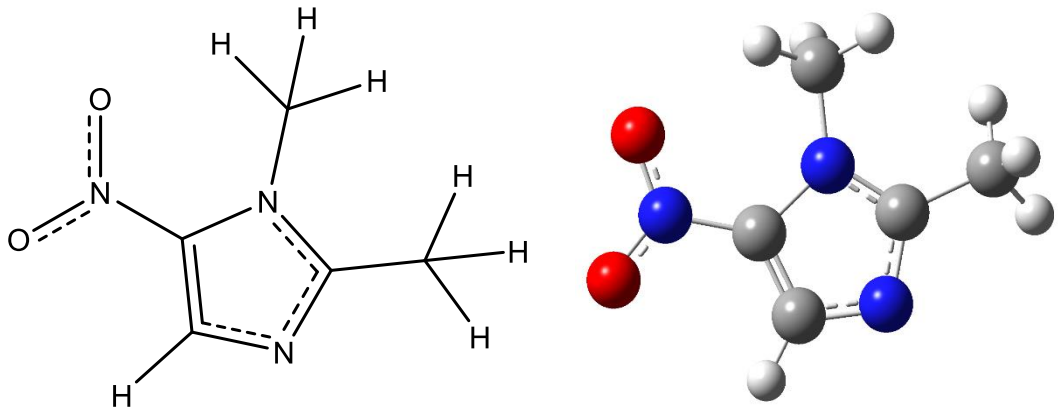

Figure 1. Structure of MDZ in the form of a) Planar structure and b) 3D structure.

2. Computational Methods

All forms of calculations were performed using the Gaussian 09 software package [17, 18]. Becke, 3-parameter, Lee-Yang-Parr (B3LYP) with 6-31++G basis set theory was good agreement with geometries structure of the molecules [19-23]. The geometries of DMZ were optimized at the B3LYP theory level with a 6-31++G basis set. The optimization and frequency of the title molecule were confirmed at lower energy states. Using the Solvation Model on Density (SMD), solvation free energies, dipole moment, and molecular properties were determined. Six solvent such as Water,

Acetonitrile, Acetone, Chloroform, Diethyl ether, and Heptane was used. The optimized solution-phase structures were used to perform all calculations involving solvation.

3. Results and Discussion

Free Energy of Solvent: The SMD model proposed was used for the measurement of solvation-free energy in six different solvents namely Water, Acetonitrile, Acetone, Chloroform, Diethyl ether, and Heptane. The energy of the free solvation (ΔG) is determined by the following equation.

ΔG = (Sum of electronic and thermal energy in solvent phase) – (Sum of electronic and thermal energy in the gas phase).

Free energy of the solvent has steadily decreased from higher to lower dielectric constants continues, which means with the diminishing polarity of the solvent, free energy decreases, Figure 2. This is because of the different degrees of the interaction and stabilization of the HOMO-LUMO orbitals in various solvents. The energy bandgap from HOMO-LUMO increasing with the decreasing of the solvent polarity[24]. The suggestion of the DMZ drugs to higher interaction in a decreasing polarity of the solvents such as Heptane.

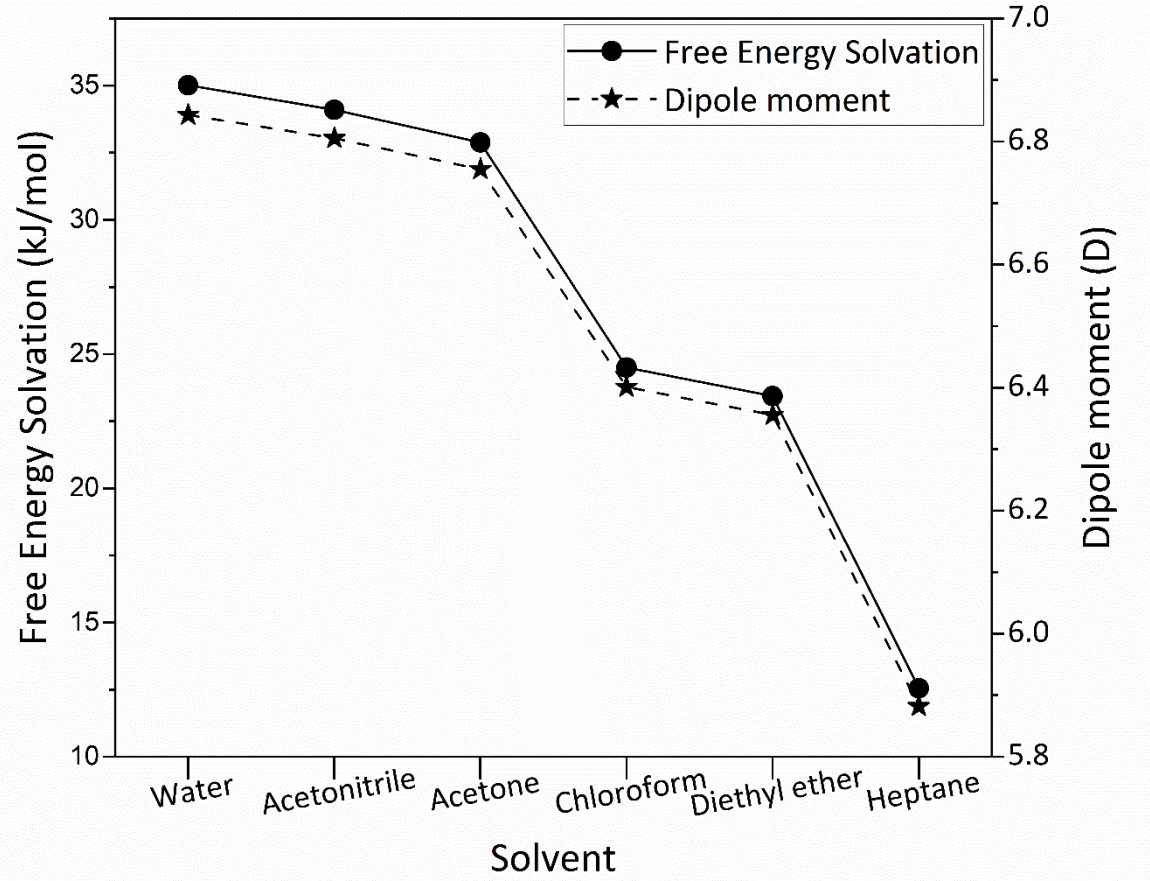

Figure 2. The effect of solvent-free energy salvation and dipole moment of DMZ.

Dipole moment: It is predicted that the dipole moment is greater in solution than the corresponding dipole moment in the gas phase. The dipole moments are measured in the gas phase and various solvents (Water, Acetonitrile, Acetone, Chloroform, Diethyl ether, and Heptane) at the B3LYP theory stage are provided in Figure 2. with 6-31++G as the basis set using the SMD solvation model. In various solvents, the measured dipole moment was discovered in the 6.8431D to 5.882D range. Generally, with the increasing polarity of the solvent, the dipole moment has also been steadily increased in Figure 2.

Polarizability and hyper-polarizability: The measure of distortion of a molecule in an electric field is polarizability. Polarizability is used to assess the frequency of molecular interactions and the optical properties of a system. The following equation was used to determine the polarizability (α).

$$\alpha = 1/3\ (\alpha xx+\alpha yy+\alpha zz) \quad (1)$$

A molecule with a low HOMO-LUMO distance is more polarizable and is known as a soft molecule with high chemical reactivity, low kinetic stability, and high electro-optic reaction [25-29]. The polarizability of DMZ is described in Table 1. The higher polarizability value in a higher dielectric constant i.e. the reactivity increases with increasing the polarity of the solvent, Table 2. This is due to a different degree of solvent interactions HOMO and LUMO orbital in a DMZ molecule. Increasing dielectric constant of the solvent, the HOMO-LUMO energy gap decreases, so the molecule becomes more reactive with increasing solvent polarity, Table 2. However, the polarizability of DMZ varied from 61.48413 to 61.48413 a. u.in different solvents.

Table 1. Effect of the medium on polarizability (a. u.) and first-order hyper-polarizability (a. u.)

Medium	α(xx)	α(yy)	α(zz)	α(mean)	β(x)	β(y)	β(z)	β(mean)
Gas	66.73	58.72	57.585	61.01	55.82	27.59	0.002	62.27
Water	68.12	58.94	57.39	61.48	68.05	37.64	0.002	77.77
Acetonitrile	68.07	58.94	57.39	61.47	67.77	37.36	0.002	77.38
Acetone	68.01	58.92	57.40	61.44	67.38	36.99	0.002	76.87
Chloroform	67.62	58.82	57.44	61.30	64.63	34.48	0.002	73.25
Diethyl ether	67.58	58.81	57.45	61.28	64.27	34.16	0.002	72.79
Heptane	67.15	58.75	57.51	61.14	60.47	31.02	0.002	67.96

Hyper-polarizability (β) of the first order is a nonlinear optical activity measurement that can be of various types, such as βvec, (β vector), βII (β parallel), and βtot (β total). It is a tensor of the third rank that can be defined by a matrix of 3 x 3 x 3. Because of the Kleinman symmetry, the 27 3D matrix components can be reduced to 10 components [30, 31]. 10 components of this matrix are given by GAUSSIAN as βxxx, βyxx, βxyy, βyyy, βxxz, βxyz, βxxz, βyzz, βzzz, and βzzz respectively, from which all x, y, and z components of β can be determined. In this investigation, for all the solvent systems listed in Table 3, we report βtotal.

It is possible to calculate the βtotal variable using the following equation.

$$\beta total = (\beta x^2+\beta y^2+\beta z^2)^{1/2} \quad (2)$$

Where,

$$\beta_x = \beta_{xxx}+\beta_{xyy}+\beta_{xzz} \quad (3)$$

$$\beta_y = \beta_{yyy}+\beta_{xxy}+\beta_{yzz} \quad (4)$$

$$\beta_z = \beta_{zzz}+\beta_{xxz}+\beta_{yyz} \quad (5)$$

The first order hyper-polarizability increased when moving from lower to higher dielectric constant, i.e. with increasing polarity of the solvent, the first order hyper-polarizability increased, Table 1. The hyper-polarizability difference in various solvents ranged from 67.95664 to 77.76577 a. u.

Reactivity Description: The molecular electrical transport properties are determined by the HOMO and LUMO energy difference. The HOMO-LUMO energy gap is used for the measurement of global chemical reactivity. The following formula can be used to measure the hardness (η), chemical potential (μ), and electro-negativity (χ) and softness (S) which was described by Koopman 's theorem for closed-shell molecules [32-36].

$$\eta = \frac{I - A}{2} \tag{6}$$

$$\mu = -\frac{I + A}{2} \tag{7}$$

$$X = \frac{I + A}{2} \tag{8}$$

$$S = \frac{1}{\eta} \tag{9}$$

Where I and A are the molecules' ionization potential and electron affinity of the molecule, respectively and $I=-E_{HOMO}$, $A=-E_{LUMO}$. A large distance gap between HOMO-LUMO is known as hard molecules, whereas small HOMO-LUMO gap molecules are considered soft molecules. It is possible to compare the molecule's stability to hardness and softness. A molecule with a minimum distance between HOMO and LUMO is more reactive and vice versa. Parr et al. 1999 [26] identified a molecule's global electrophilic power as an electrophilicity index (ω) that can be represented by the formula as follows:

$$\omega = \frac{\mu 2}{2\eta} \tag{10}$$

Table 2. Molecular orbital energy (eV) (HOMO and LUMO) of DMZ in different solvents

Medium	**HOMO**	**LUMO**	**ΔE**
Gas	-7.261	-2.759	4.501
Water	-7.194	-2.933	4.261
Acetonitrile	-7.196	-2.929	4.267
Acetone	-7.198	-2.923	4.275
Chloroform	-7.213	-2.882	4.331
Diethyl ether	-7.215	-2.877	4.338
Heptane	-7.234	-2.821	4.413

Table 3. Effect of Medium on molecular properties of MDZ.

Medium	Chemical hardness (η)	Softness (S)	Chemical potential (μ)	Electronegativity (X)	Electrophilicity index (ω)
Gas	5.881	0.170	-5.010	8.640	73.80
Water	5.727	0.175	-5.063	8.660	73.42
Acetonitrile	5.732	0.174	-5.062	8.660	73.44
Acetone	5.737	0.174	-5.060	8.659	73.45
Chloroform	5.772	0.173	-5.047	8.654	73.52
Diethyl ether	5.777	0.173	-5.046	8.653	73.53
Heptane	5.824	0.172	-5.028	8.645	73.60

The above equations are used for calculating the chemical potential, hardness, and electrophilicity index. In terms of their reactivity and site selectivity, this reactivity quantity has been used to recognize the toxicity of different contaminants [37, 38]. Table 3 presents the molecular properties of DMZ in the gas phase and various media. The chemical potential and electronegativity were increased from non-polar to polar solvents, except in gas was the iminium value, Table 3. Were as the electrophilicity index was decreased from higher polar solvent to lower polar solvents the maximum electrophilicity index was in a gas phase, Table 3. On the other hand, with the decreasing polarity of the solvent, chemical hardness increased, in the case of softness, the opposite relation was found.

4. Conclusion

In this study, the effect of the solvent-free energy, dipole moment, and molecular properties have been determined for DMZ drugs by used the B3LYP theory with a 6-31++G basis set. As the dielectric constant was decreased, the solvation energies decreased steadily. With the increasing polarity of the solvent, the dipole moment, polarizability, and first-order hyperpolarizability of DMZ have steadily increased. The chemical potential and electronegativity were increased from non-polar to polar solvents, except for gases, while the Electrophilicity index was decreased from nonpolar to polar solvent. The chemical potential and electronegativity of the DMZ in water are greater than the other solvents, but the value of the Electrophilicity index in Heptane was the greater value compared to the other solvents. On the other hand, with decreasing solvent polarity, chemical hardness increased and the inverse relationship was observed in the case of softness.

It can be concluded that DMZ was more reactive and unstable molecules in a polar solvent, This is evident in the polarizability and chemical softness of various solvents. The finding obtained in this study may help to theoretical evidence for DMZ in a reaction intermediate and pharmaceutical study.

Author(s) Contributions

Each author's contribution to the study is 25%.

Conflicts of Interest

There are no conflicts to declare.

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