Journal of Physical Chemistry and Functional Materials

Home Page of Journal: https://dergipark.org.tr/jphcfum

The Role of the Various Solvent Polarities on Piperine Reactivity and Stability

[a]*Lana Ahmed**, [a]*Rebaz Omer*

[a] *Department of Physics, Faculty of Science, Firat University, 23169, Elazig, Turkey*
[b] *Department of Chemistry, Faculty of Science, Firat University, 23169, Elazig, Turkey*
** Corresponding author: Lana AHMED (E-mail: lana.omer@koyauniversity.org)*

ABSTRACT

Piperine is a natural cytotoxic agent aware of various therapeutic acts. The aim of this study is to look into the effects of solvent polarity on solvent-free energy, dipole moment, polarizability, and hyper-polarizability of the first order, as well as various molecular properties including chemical hardness and softness, chemical potential, electronegativity, and electrophilicity index, in order to gain a better understanding of its reactivity and stability. The Becke, 3-parameter, Lee-Yang-Parr (B3LYP) level of theory with the cc-pVDZ basis set was used to perform all forms of calculations in both the gas phase and in solution. The Solvation Model on Density (SMD) was used to measure the solvation-free energy, dipole moment, and molecular properties of five solvent systems: water, DMSO, ethanol, cyclohexane, and heptane. when the dielectric constant reduced, the solving energies gradually will have decreased, i.e. free energy decreased with declining solvent polarity. Piperine's dipole moment has been found to increase when transitioning from non-polar to polar solvents. The dipole moment of piperine was greater than that of the gas phase in various solvents. PPN's dipole moment and first order hyper-polarizability gradually increased as the solvent polarity increased, while its polarizability decreased. In addition, the hardness, chemical potential and electrophilicity index were decreased from non-polar to polar solvent, but with the rise in solvent polarity for the PPN molecule, softness and electronegativity were increased. The determined free energy solvation, dipole moment, polarizability, hyper-polarizability of the first order, and molecular properties identified in this research may contribute to an understanding of the stability and reactivity of piperine in specific solvent systems.

ARTICLE INFO

Keywords:

PPN,
Solvation effects,
Dipole moment,
Solvation model,
Polarizability

Received: 02-09-2021
Accepted: 15-10-2021
ISSN: 2651-3080
DOI: 10.54565/jphcfum.990410

1. INTRODUCTION

The chemical formula for piperine molecule is C17H19NO3 [1] Piperine (PPN; Figure 1) would be a bioactive phytomedicine/nutrient alkaloid that is found in fruits and roots of Piper nigrum (Black Pepper) and Piper longum (Long Pepper). The existence of PPN in pepper leads to the pungent and bitter taste of pepper [2] PPN is a strong bioactive agent that has been informed to have numerous therapeutic actions [3]. Additionally, PPN has also been documented for many poorly soluble drugs as well as nutrients as a permeation and bioavailability enhancer [4, 5]

Earlier, various theoretical and computational studies of PPN have been shown. Gökalp, 2016 reported the thermodynamical properties of PPN by using DFT and HF at the level of B3LYP/6-31+g(d,p) [6, 7] Zazeri et al., 2019 investigated experimental and computational modeling of rat serum albumin and its interaction with PPN [8] Besides, Choudhary et al., 2020 reported of molecular docking of PPN [9] Alves et al., 2020 explained the experimental and theoretical spectra of PPN [10]

The polarity of the solvent and the mode of solute to solvent interaction can effect on geometry, dipole moment, polarizability, hyper-polarizability, and other molecular properties (s) [11-13] via variable interactions with molecular orbitals of the highest occupied (HOMO) and lowest unoccupied (LUMO) [11, 13, 14] and, thus, could affect the molecule's reactivity and stability. DFT calculations would be used to provide information on molecular characteristics and interactions, which essentially contributes to understanding properties of molecular [15-22]

As part of our continuing study [23-26] but for PPN molecule, the current research was conducted to study the medium impact of PPN on solvation free energy, dipole moment, polarizability, first-order hyperpolarizability and chemical reactivity, which could be beneficial in more understanding the stability of PPN in various solvent systems.

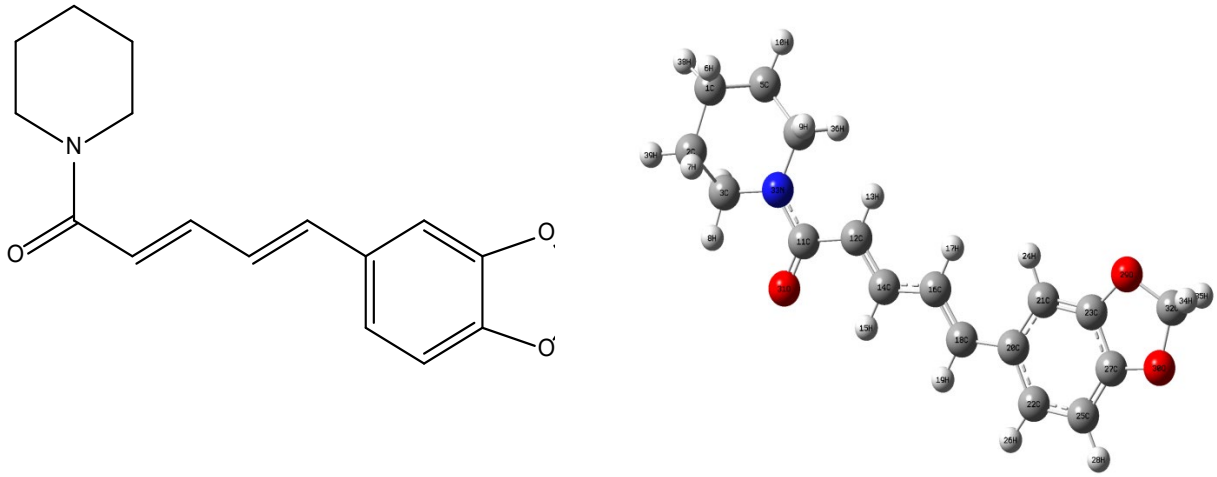

Figure 1. Structure of the PPN molecule

2. COMPUTATIONAL METHOD

The Gaussian 09 program can be used to do many calculations [27-30]. At the B3LYP level of theory with the cc-pVDZ basis set, PPN geometries were optimized. The optimized geometry has been verified by the lack of negative frequency in the molecule's lowest energy state. Then using Density Solvation Model (SMD), the solvation free energies, dipole moment and molecular properties were determined [31, 32] in such solvents, including water, DMSO, ethanol, cyclohexane, and heptane. The optimized solution-phase structures were used to do all solvation calculations.

3. DISCUSSION AND RESULTS

3.1 Energy of free Solvation

In five different solvents, including water, DSMO, ethanol, cyclohexane and heptane, the conceptual SMD model has been used to determine solvent-free energy. According to the bellow equation, the free energy solvation (ΔG) can be determined [25].

$$\Delta G = G(sol) - G(gas) \qquad (1)$$

where:
G (gas) = In the gas phase, the amount of electronic and thermal free energy
G (sol) = In the solvent, the amount of electronic and thermal free energy

Table 1. SMD calculated the solvation free energy (kJ/mol) of PPN in different solvents.

Dielectric Constant in different Medium	B3LYP/ cc-pVDZ
Water (78.54)	-27.833
DMSO (47)	-27.310
Ethanol (24.6)	-26.195
Cyclohexane (2.02)	-13.540
Heptane (1.92)	-12.581

As we can see from Table 1 and Figure 2, From a higher to a lower dielectric constant, the free energy solvation for the PPN molecule decreased dramatically, i.e. free energy decreased as the polarity of the solvent decreased. This would be related to the various degrees of interactions and, thus, the different solvents stabilize the HOMO-LUMO orbital. As illustrated in Table 4 and Figure 6, the bandgap energy of HOMO-LUMO increases with decreasing solvent polarity, implying a higher degree of PPN association with decreasing medium polarity.

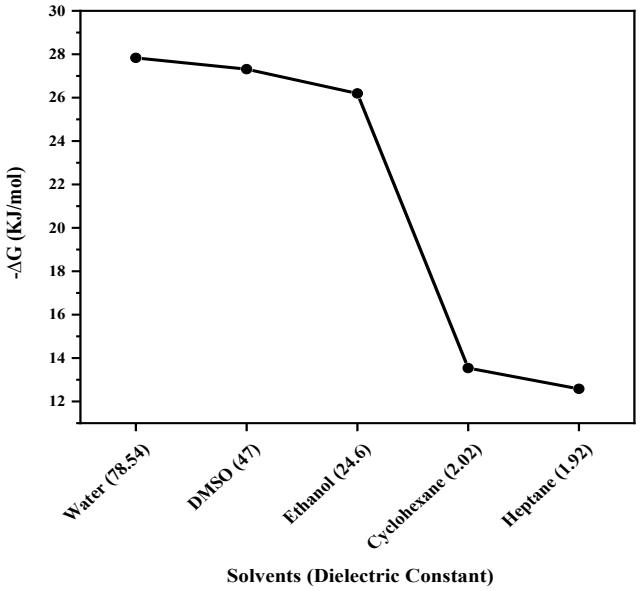

Figure 2. PPN salvation free energy (kJ/mol) is affected by solvent polarity.

3.2. Dipole Moment

The dipole moment in solution should be larger than the dipole moment in the gas phase. Table 2 shows the dipole moments estimated at the B3LYP stage in the gas phase and various solvents (water, DMSO, ethanol, cyclohexane, and heptane) with cc-pVDZ as the basis set using the SMD solvation model. As switching from lower to higher dielectric constant, the dipole moment is progressively increased, as shown in Figure 3, the dipole moment increases as the polarity of the solvent increases.

3.3. Polarizability and First Order Hyper Polarizability

Polarizability refers to a molecule's ability to distort in an electric field. The following equation was used to calculate polarizability (α). [26]:

$$\alpha = \frac{1}{3}(\alpha_{xx} + \alpha_{yy} + \alpha_{zz}) \quad (2)$$

To calculate the frequency of molecular interactions and optical properties of a structure, polarizability will be used [14]. A molecule with a small HOMO-LUMO difference is perhaps more polarizable and is classified as a soft molecule with high chemical reactivity, low kinetic stability and high electro-optic response [14]. The calculated polarizability of PPN is seen in Table 3 and Figure 4, which shows that by moving from the high dielectric constant to the low dielectric constant, polarizability increases steadily, i.e., as the polarity of the solvent decreases, the reactivity increases. This is responsible for a specific level of solvent interaction with the HOMO and LUMO orbital of the PPN molecule. Table 4 and Figure 6 demonstrate that the HOMO-LUMO energy difference reduces as the solvent's dielectric constant rises, rendering the molecule more reactive as the solvent polarity increases. Consequently, PPN polarizability varied from 111.869 to 113.81 a.u. in various solvents.

Table 2. In the gas phase and various solvents with SMD, PPN dipole moment (Debye, (D)) is measured.

Dielectric Constant in different Medium	Dipole Moment (D)
Gas	4.09
Water (78.54)	5.55
DMSO (47)	5.52
Ethanol (24.6)	5.47
Cyclohexane (2.02)	4.61
Heptane (1.92)	4.57

The first order of hyperpolarizability (β) is a nonlinear optical behavior factor that could be of various kinds, such as β_{vec} (β vector), β|| (β parallel) and β_{tot} (β total). It is a third rank tensor that could be represented by a matrix of 3 x 3 x 3. Due to Kleinman symmetry, the 27 components of the 3D matrix can be assumed to be 10 components [33]. 10 parts of this matrix are given by GAUSSIAN as βxxx, βyxx, βxyy, βyyy, βxxz, βxyz, βyyz, βxxz, βyzz, βzzz, respectively, in which all x, y and z parts of β could be determined.

In this study, all solvent systems mentioned in Table 3, we measure βtot. It is possible to calculate the βtot by using the following equation [26].

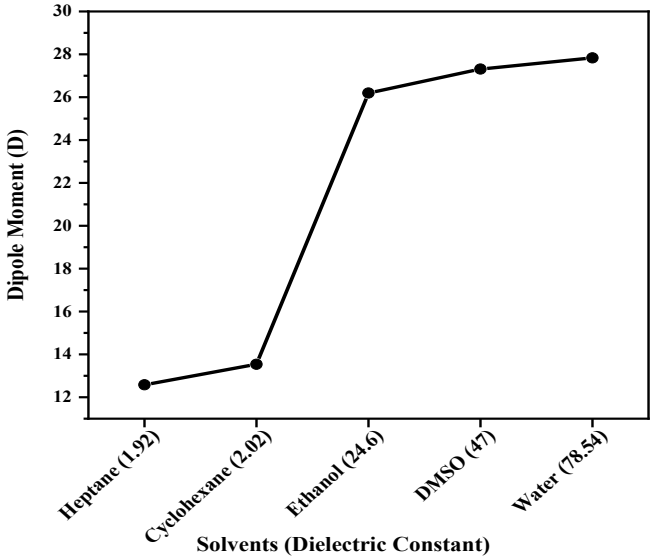

Figure 3. The effect of the polarity of the solvent on the dipole moment (D) of PPN

$$\beta_{tot} = (\beta_x^2 + \beta_y^2 + \beta_z^2)^{\frac{1}{2}} \quad (3)$$

where,

$$\beta_x = \beta_{xxx} + \beta_{xyy} + \beta_{xzz} \quad (4)$$

$$\beta_y = \beta_{yyy} + \beta_{xxy} + \beta_{yzz} \quad (5)$$

$$\beta_z = \beta_{zzz} + \beta_{xxz} + \beta_{yyz} \quad (6)$$

Figure 5 shows that as the dielectric constant increased from lower to higher, the first order hyperpolarizability increased with increasing solvent polarity, i.e., the first order hyperpolarizability increased with increasing solvent polarity. Here for the PPN molecule, the first order hyperpolarizability ranged from 169.966 to 197.229 a.u. in various solvents.

Table 3. In first-order polarizability (a. u.) and hyperpolarizability (a.u.), there is a medium impact on it.

Dielectric Constant in different Medium	α_{xx}	α_{yy}	α_{zz}	α_{tot}	β_x	β_y	β_z	β_{tot}
Gas	96.1881	122.437	126.167	114.931	98.6664	119.5884	-8.8227	155.288
Water (78.54)	87.7072	121.949	125.952	111.869	118.2345	157.4198	-11.7822	197.229
DMSO (47)	87.8279	121.955	125.954	111.913	117.9693	156.8192	-11.7256	196.587
Ethanol (24.6)	88.0884	121.969	125.959	112.006	117.3945	155.5311	-11.6056	195.208
Cyclohexane (2.02)	92.878	122.242	126.07	113.73	106.5025	133.4656	-9.767	171.030
Heptane (1.92)	93.0976	122.255	126.076	113.81	105.9901	132.5156	-9.697	169.966

3.4. Descriptors of Global Reactivity

The energy difference between HOMO and LUMO defines the molecular electrical transport properties. The energy gap of HOMO-LUMO can be used to determine molecules' global chemical reactivity descriptors such as hardness, chemical potential, softness, electronegativity and electrophilicity index [21, 34-38]. Table 4 and Figure 6, demonstrate the energy band gap of HOMO-LUMO for PPN.

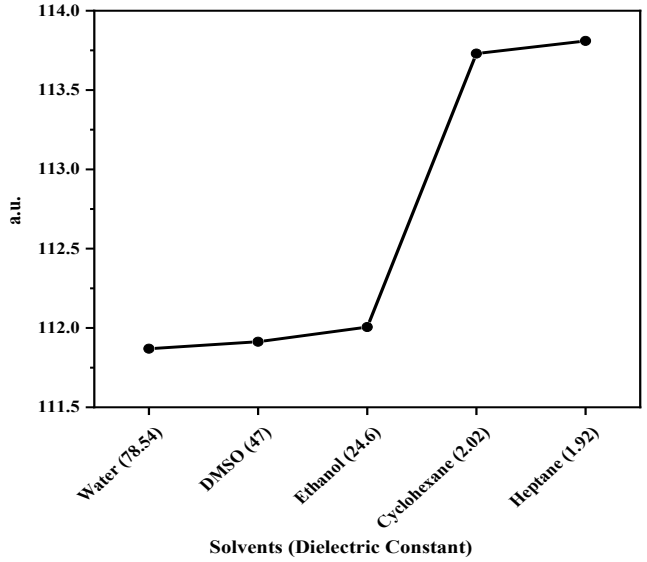

Figure 4. Polarizability is affected by the polarity of the solvent.

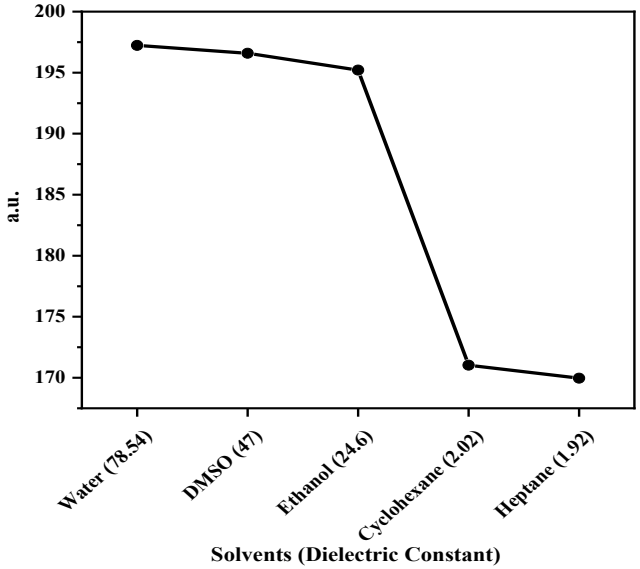

Figure 5. first order hyper-polarizability is affected by the polarity of the solvent.

Table 4. In different solvents, PPN molecular orbital energy (eV) (HOMO and LUMO) was measured with SMD.

Dielectric Constant in different Medium	Orbital Energy of Molecules (eV)		
	HOMO	LUMO	ΔE
Gas	-0.20053	-0.0667	3.642
Water (78.54)	-0.20375	-0.07268	3.567
DMSO (47)	-0.20369	-0.07257	3.568
Ethanol (24.6)	-0.20356	-0.07234	3.571
Cyclohexane (2.02)	-0.20145	-0.06861	3.615
Heptane (1.92)	-0.20137	-0.06846	3.617

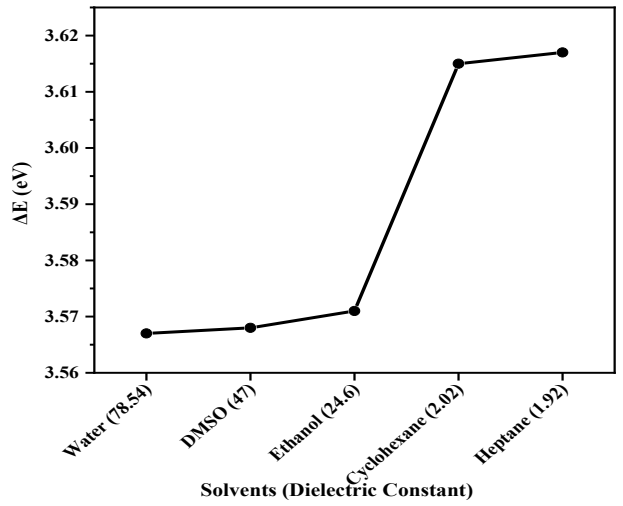

Figure 6. The HOMO-LUMO energy gap of PPN is affected by the polarity of the solvent.

Koopman's theorem for closed-shell molecules can be generalized using the following formula to calculate hardness (η), chemical potential (μ), electronegativity (χ), and softness (S).

$$\eta = \frac{I-A}{2} \quad (7)$$

$$\mu = -\frac{I+A}{2} \quad (8)$$

$$\chi = \frac{I+A}{2} \quad (9)$$

$$S = \frac{1}{\eta} \quad (10)$$

where I and A, respectively, are the molecules' ionization potential and electron affinity which can express by:

$$I = -E_{HOMO} \quad (11)$$

and

$$A = -E_{LUMO} \quad (12)$$

Molecules with a large HOMO-LUMO gap are known as hard molecules, whereas those with a small HOMO-LUMO gap are known as soft molecules. It is possible to correlate the stability of the molecule to hardness and softness. A molecule with a minimum gap

between HOMO and LUMO is more reactive and vice versa. The global electrophilic power of a molecule as electrophilicity index (ω) characterized by Parr *et al.* 1999 which could be signified by the formula as follows [37]:

$$\omega = \frac{\mu^2}{2\eta} \quad (13)$$

For calculation of the chemical potential, hardness and electrophilicity index, the above equations are used. This reactivity quantity was used to characterize the toxicity of various contaminants in terms of their reactivity and site selectivity [39-41]. **Error! Reference source not found.** presents the molecular properties of PPN in the gas phase and five mediums. Ongoing from non-polar to polar solvent the hardness, chemical potential and electrophilicity index were decreased whereas the softness and electronegativity were increased with the increasing of the polarity of the solvents. The effect of solvent polarity on electronegativity and the electrophilicity index of the PPN molecule are seen in Figure 7 and Figure 8, respectively.

Table 5. The effect of Medium on molecular properties of PPN

Dielectric Constant in different Medium	Chemical Hardness (η)	Softness (S)	Chemical Potential (μ)	Electronegativity (χ)	Electrophilicity Index (ω)
Gas	1.821	0.549	-1.821	3.636	3.019
Water (78.54)	1.780	0.561	-1.783	3.761	2.837
DMSO (47)	1.784	0.561	-1.784	3.759	2.839
Ethanol (24.6)	1.785	0.560	-1.785	3.754	2.845
Cyclohexane (2.02)	1.807	0.553	-1.807	3.674	2.952
Heptane (1.92)	1.808	0.553	-1.808	3.671	2.957

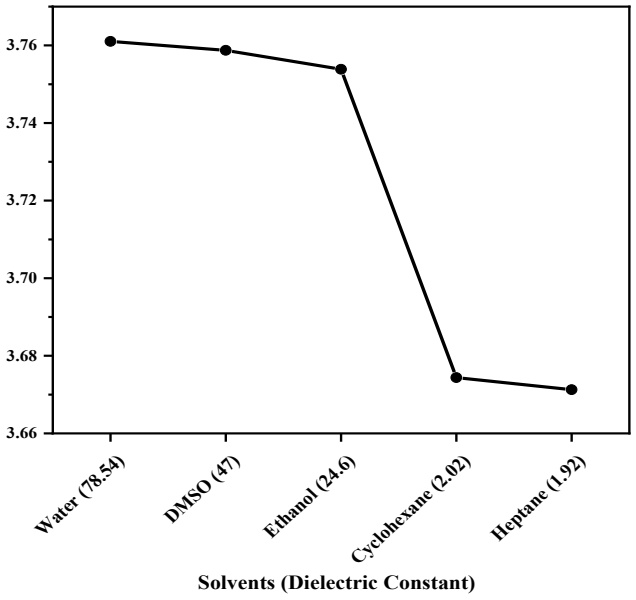

Figure 7. The electronegativity of PPN is affected by the

4. CONCLUSIONS

The B3LYP theory with the cc-pVDZ basis set was used to measure the medium effect on solvation-free energies, dipole moment, and molecular properties in this analysis. As the dielectric constant was decreased, the solvation energies decreased gradually. With the increasing polarity of the solvent, the dipole moment and first-order hyper-polarizability of PPN gradually increased, while the polarizability decreased by increasing the polarity of the solvents. The hardness, chemical potential and electrophilicity index were reduced from non-polar to the polar solvent; however, softness and electronegativity were raised with the increase in solvent polarity for the PPN molecule. It can also be inferred that PPN is more reactive and therefore unstable in a polar solvent, which is obvious in different solvents from polarizability.

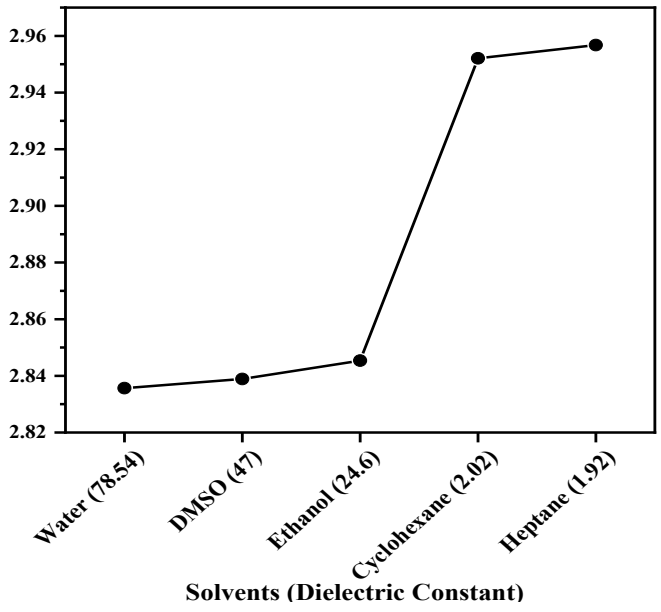

Figure 8. The electrophilicity index of PPN is affected by the polarity of the solvent.

ACKNOWLEDGEMENTS

We would like to thank Firat University, Physics Department and Prof. Dr. Niyazi Bulut at Firat University for his excellent guidance and support

REFERENCES

1. K. Vasavirama and M. Upender, Piperine: a valuable alkaloid from piper species. Int J Pharm Pharm Sci, 2014. 6(4): p. 34-8.
2. L. Gorgani, et al., Piperine—the bioactive compound of black pepper: from isolation to medicinal formulations. Comprehensive Reviews in Food Science and Food Safety, 2017. 16(1): p. 124-140.
3. C. Pradeep and G. Kuttan, Effect of piperine on the inhibition of lung metastasis induced B16F-10 melanoma cells in mice. Clinical & experimental metastasis, 2002. 19(8): p. 703-708.
4. G. Shoba1, et al., Influence of piperine on the pharmacokinetics of curcumin in animals and human volunteers. Planta medica, 1998. 64: p. 353-356.
5. J.J. Johnson, et al., Enhancing the bioavailability of resveratrol by combining it with piperine. Molecular nutrition & food research, 2011. 55(8): p. 1169-1176.
6. F. Gökalp, A study on piperine, active compound of black pepper. Akademik Platform Mühendislik ve Fen Bilimleri Dergisi, 2016. 4(3).
7. P. Koparir, K. Sarac, and R.A. Omar, Synthesis, Molecular Characterization, Biological and Computational Studies of New Molecule Contain 1, 2, 4-Triazole, and Coumarin Bearing 6, 8-Dimethyl. 2021.
8. G. Zazeri, et al., Experimental approaches and computational modeling of rat serum albumin and its interaction with piperine. International journal of molecular sciences, 2019. 20(12): p. 2856.
9. P. Choudhary, et al., Computational studies reveal piperine, the predominant oleoresin of black pepper (Piper nigrum) as a potential inhibitor of SARS-CoV-2 (COVID-19). Current Science (00113891), 2020. 119(8).
10. F.S. Alves, et al., Spectroscopic methods and in silico analyses using density functional theory to characterize and identify piperine alkaloid crystals isolated from pepper (Piper Nigrum L.). Journal of Biomolecular Structure and Dynamics, 2020. 38(9): p. 2792-2799.
11. P. Anbarasan, et al., Geometries, electronic structures and electronic absorption spectra of silicon dichloride substituted phthalocyanine for dye sensitized solar cells. Recent Research in Science and Technology, 2010.
12. P. Lakshmi Praveen and D. Ojha, Substituent and solvent effects on UV-visible absorption spectra of liquid crystalline disubstituted biphenylcyclohexane derivatives–a computational approach. Crystal Research and Technology, 2012. 47(1): p. 91-100.
13. M.F. Khan, et al., Computational study of geometry, solvation free energy, dipole moment, polarizability, hyperpolarizability and molecular properties of 2-methylimidazole. Sultan Qaboos University Journal for Science [SQUJS], 2016. 21(2): p. 89-101.
14. M. Targema, N.O. Obi-Egbedi, and M.D. Adeoye, Molecular structure and solvent effects on the dipole moments and polarizabilities of some aniline derivatives. Computational and theoretical Chemistry, 2013. 1012: p. 47-53.
15. A. Jayaprakash, et al., Vibrational and electronic investigations, thermodynamic parameters, HOMO and LUMO analysis on crotonaldehyde by ab initio and DFT methods. Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy, 2011. 83(1): p. 411-419.
16. R.A. Omer, et al., Theoretical analysis of the reactivity of chloroquine and hydroxychloroquine. Indian Journal of Chemistry-Section A (IJCA), 2020. 59(12): p. 1828-1834.
17. L.A. Omer and R.O. Anwer, Population Analysis and UV-Vis spectra of Dopamine Molecule Using Gaussian 09. Journal of Physical Chemistry and Functional Materials. 3(2): p. 48-58.
18. O. Rebaz, et al., Computational determination the reactivity of salbutamol and propranolol drugs. Turkish Computational and Theoretical Chemistry, 2020. 4(2): p. 67-75.
19. K.F. Al-Azawi, et al., Experimental and quantum chemical simulations on the corrosion inhibition of mild steel by 3-((5-(3, 5-dinitrophenyl)-1, 3, 4-thiadiazol-2-yl) imino) indolin-2-one. Results in Physics, 2018. 9: p. 278-283.
20. L.A. Omer and O. Rebaz, Computational Study on Paracetamol Drug. Journal of Physical Chemistry and Functional Materials, 2020. 3(1): p. 9-13.
21. L. Ahmed and O. Rebaz, Spectroscopic properties of Vitamin C: A theoretical work. Cumhuriyet Science Journal, 2020. 41(4): p. 916-928.
22. A. Hssain and H. Kebiroglu, Serotonin: Structural characterization and determination of the Band Gap Energy. Journal of Physical Chemistry and Functional Materials. 2(2): p. 54-58.
23. M.F. Khan, R.B. Rashid, and M.A. Rashid, Computational study of geometry, molecular properties and docking study of aspirin. World J Pharm Res, 2015. 4: p. 2702-2714.
24. M.F. Khan, et al., In silico molecular docking studies of lichen metabolites against cyclooxygenase-2 enzyme. Bangladesh Pharmaceutical Journal, 2015. 18(2): p. 90-96.
25. M.F. Khan, et al., Effects of solvent polarity on solvation free energy, dipole moment, polarizability, hyperpolarizability and molecular reactivity of aspirin. Int. J. Pharm. Pharm. Sci, 2017. 9(2): p. 217-221.
26. M.F. Khan, et al., Effects of Solvent Polarity on Solvation Free Energy, Dipole Moment, Polarizability, Hyperpolarizability and Molecular Properties of Metronidazole. Bangladesh Pharmaceutical Journal, 2016. 19(1): p. 9-14.
27. A. Tomberg, Gaussian 09w Tutorial An Introduction To Computational Chemistry Using G09w And Avogadro Software.
28. R.A. Omer, et al., Computational and spectroscopy study of melatonin. Indian Journal of Chemistry-Section B (IJC-B), 2021. 60(5): p. 732-741.
29. P. Koparir, et al., Synthesis, Characterization, and theoretical inhibitor study for (1E, 1'E)-2, 2'-thiobis (1-(3-mesityl-3-methylcyclobutyl) ethan-1-one) dioxime. El-Cezeri. 8(3): p. 1495-1510.
30. O. Rebaz, et al., Structure reactivity analysis for Phenylalanine and Tyrosine. Cumhuriyet Science Journal. 42(3): p. 576-585.
31. A.V. Marenich, C.J. Cramer, and D.G. Truhlar, Universal solvation model based on solute electron density and on a continuum model of the solvent defined by the bulk dielectric constant and atomic surface tensions. The Journal of Physical Chemistry B, 2009. 113(18): p. 6378-6396.
32. L. Ahmed and O. Rebaz, A theoretical study on Dopamine molecule. Journal of Physical Chemistry and Functional Materials, 2019. 2(2): p. 66-72.
33. D. Kleinman, Nonlinear dielectric polarization in optical media. Physical Review, 1962. 126(6): p. 1977.

34. R.G. Parr, et al., Electronegativity: the density functional viewpoint. The Journal of Chemical Physics, 1978. 68(8): p. 3801-3807.
35. R.G. Parr and R.G. Pearson, Absolute hardness: companion parameter to absolute electronegativity. Journal of the American chemical society, 1983. 105(26): p. 7512-7516.
36. R.G. Parr and P.K. Chattaraj, Principle of maximum hardness. Journal of the American Chemical Society, 1991. 113(5): p. 1854-1855.
37. R.G. Parr, L.v. Szentpály, and S. Liu, Electrophilicity index. Journal of the American Chemical Society, 1999. 121(9): p. 1922-1924.
38. P.K. Chattaraj, B. Maiti, and U. Sarkar, Philicity: a unified treatment of chemical reactivity and selectivity. The Journal of Physical Chemistry A, 2003. 107(25): p. 4973-4975.
39. R. Parthasarathi, et al., Toxicity analysis of benzidine through chemical reactivity and selectivity profiles: a DFT approach. Internet Electronic Journal of Molecular Design, 2003. 2(12): p. 798-813.
40. R. Parthasarathi, et al., Intermolecular reactivity through the generalized philicity concept. Chemical physics letters, 2004. 394(4-6): p. 225-230.
41. R. Parthasarathi, et al., Toxicity analysis of 33'44'5-pentachloro biphenyl through chemical reactivity and selectivity profiles. Current Science, 2004. 86(4): p. 535.