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Effects of Solvent Polarity on Solvation Free Energy, Dipole Moment, Polarizability, Hyperpolarizability and Molecular Properties of Metronidazole

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Abstract

A computational study of medium effect on solvation free energy, dipole moment, polarizability, hyperpolarizability and different molecular properties like chemical hardness & softness, chemical potential, electronegativity and electrophilicity index of metronidazole have been reported in this paper. Becke, 3-parameter, Lee-Yang-Parr (B3LYP) level of theory with 6-31G (d,p) basis set was applied for gas phase and solution. The effect of solvent polarity on solvation free energy, dipole moment, polarizability, hyperpolarizability and molecular properties were calculated by employing Solvation Model on Density (SMD). The solvation free energies and dipole moment of metronidazole were found to be increased in non-polar to polar solvents. The dipole moment of metronidazole was higher in different solvent than that of the gas phase. Moreover, from non-polar to polar solvents the chemical potential, electronegativity and electrophilicity index were increased. On the other hand, opposite relation was found in the case of chemical hardness and softness. The results obtained in this study may lead to understand the stability and reactivity of metronidazole and the results will be of assistance to use the title molecule as reaction intermediates and pharmaceuticals.

Key words: Metronidazole, solvation free energy, dipole moment, polarizability, solvation model

Introduction

Metronidazole (Figure 1) is a nitroimidazole antiinfective agent which has specific activity against a number of obligate anaerobic organisms and protozoa. It is bactericidal, amoebicidal and trichomoncidal. It is the drug of choice for the first episode of mild to moderate *Clostridium difficile* colitis (Cohen *et al*., 2010). Recently, the structural modifications of metronidazole have received much attention (Mao *et al*., 2009). Several attempts were made to synthesize metronidazole derivatives for improving its potency and efficacy (Mao *et al*., 2009; Bowden *et al*., 1998).The FTIR, FT-Raman and UV-Vis spectroscopic studies of metronidazole using Density functional theory (DFT) and restricted Hartree-Fock (RHF) level of theory have been reported (Harikrisnan *et al*.,2015).

As a part of our ongoing research (Khan *et al*., 2015a; Khan *et al*., 2015b) the present study was undertaken and to the best of our knowledge, the effect of solvent polarity on the solvation free energy, dipole moment, polarizability, hyperpolarizability and global reactivity descriptors (chemical hardness, softness, chemical potential, electronegativity and electrophilicity index) have not been reported, previously.

Computational methods

All calculations were performed in Gaussian09 software package (Frisch *et al*., 2010). The geometry of metronidazole was fully optimized before performing

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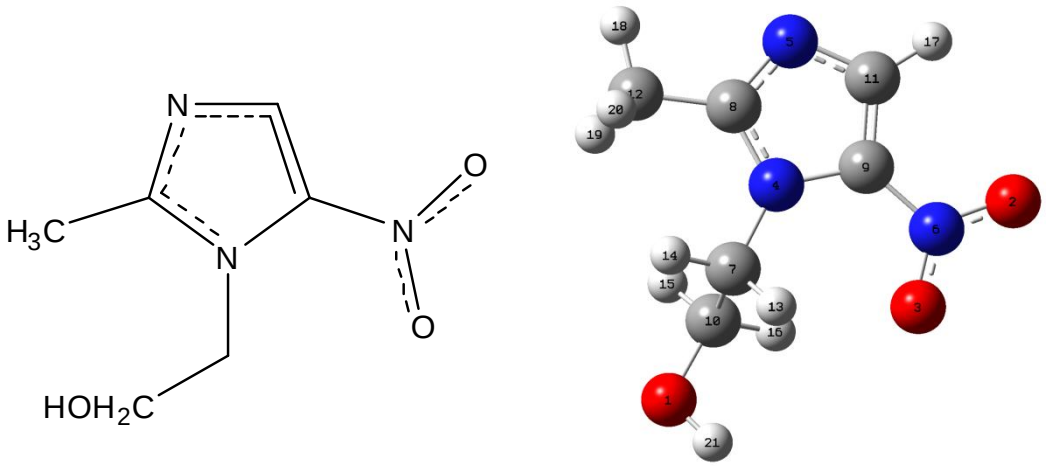
any calculation. The absence of negative frequency confirmed that the geometry is fully optimized. The solvation free energies, dipole moment polarizability, hyperpolarizability and molecular properties were calculated using B3LYP/6-31G (d,p) level of theory. The Solvation Model on Density (SMD) was used to calculate the properties in different solvents.



a) b)

Figure 1. Structure of metronidazole. a) Planar structure b) 3D structure.

Results and Discussion

Solvation free energy: The calculated solvation free energies of metronidazole are presented in table 1. It ranged from -13.61 to 16.17 Kcal/mol. However, the highest solvation free energy was found in water and the lowest in chloroform. The solvation free energy was increased with increasing polarity of the solvent.

Table 1. Solvation free energy (Kcal/mol) and dipole moment (Debye, D) of metronidazole in different solvents with SMD model.

Medium (dielectric constant)	Solvation free energy (Kcal/mol)	Dipole moment (Debye, D)
Gas	-	3.61
Chloroform (4.7)	-13.61	4.83
n-Octanol (9.9)	-14.74	5.39
DMSO (46.8)	-15.19	5.25
Water (78.3)	-16.15	5.89

Dipole moment: The dipole moment is expected to be larger in solution than in the gas phase. Table 1 presents the dipole moments computed in the gas phase and in different solvents namely water, dimethyl sulfoxide (DMSO), *n*-octanol and chloroform. All the dipole moments are calculated with B3LYP level of theory using 6-31G (d,p) basis set. The calculated dipole moment in different solvent was found in the range of 4.83D to 5.89D. Generally, the dipole moment was also increased gradually with increasing polarity of the solvent.

Polarizability and first order hyperpolarizability: Polarizability is the measure of distortion of a molecule in an electric field. The polarizability (α_{tot}) was calculated by using the following equation:

$$\alpha_{tot} = \frac{1}{3}\left(\alpha_{xx} + \alpha_{yy} + \alpha_{zz}\right)$$

The polarizability is used to determine the strength of molecular interactions and optical properties of a system (Targema, 2013). A molecule with a low HOMO-LUMO energy gap is more polarizable (Tables 2 and 3) and possesses high chemical reactivity, low kinetic stability, and high electro-optic response and is known as soft molecule (Targema, 2013). The calculated polarizability of metronidazole is presented in table 2 and figure 2, which indicate that the polarizability gradually decreased when going from higher to lower dielectric constant i.e., the reactivity

increased with increasing polarity of the solvent. The polarizability of metronidazole in different solvent was ranged from 60.8 to 163.3 atomic units (a.u.).

The first order hyperpolarizability (β) is the measure of the nonlinear optical activity which can be of different types such as β_{vec} (β vector), $\beta_{\|}$ (β parallel) and β_{tot} (β total). It is a third rank tensor that can be described by a 3 × 3 × 3 matrix. The 27 components of the 3D matrix can be reduced to 10 components due to the Kleinman symmetry (Kleinman, 1977). GAUSSIAN provides 10 components of this matrix as β_{xxx}, β_{yxx}, β_{xyy}, β_{yyy}, β_{xxz}, β_{xyz}, β_{yyz}, β_{xxz}, β_{yzz} and β_{zzz}, respectively, from which the component of β_{tot} can be calculated with the help of the following equation.

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

Where,

$\beta_x = \beta_{xxx} + \beta_{xyy} + \beta_{xzz}$

$\beta_y = \beta_{yyy} + \beta_{xxy} + \beta_{yzz}$

$\beta_z = \beta_{zzz} + \beta_{xxz} + \beta_{yyz}$

The first order hyperpolarizability was increased with increasing dielectric constant of the medium, i.e. the first order hyperpolarizability increased with increasing polarity of the solvent (Table 2 and Figure 3). The hyperpolarizability in different solvents was found in the range of 37.3 to 44.4 a.u.

Table 2. Effect of solvent polarity on polarizability (a.u.) and first order hyperpolarizability (a,u.).

Medium (dielectric constant)	α_{xx}	α_{yy}	α_{zz}	α_{tot}	β_x	β_y	β_z	β_{tot}
Gas Phase	122.6	134.2	69.2	108.7	-22.5	-13.9	13.8	29.8
Water (78.3)	174.0	215.9	99.9	163.3	-37.1	6.1	23.6	44.4
DMSO (46.8)	163.7	192.7	96.6	151.0	-34.8	-4.4	20.5	40.6
n-Octanol (9.9)	164.5	198.5	92.7	151.9	-34.9	0.8	20.2	40.3
Chloroform (4.7)	81.9	67.9	32.7	60.8	-32.0	-5.6	18.3	37.3

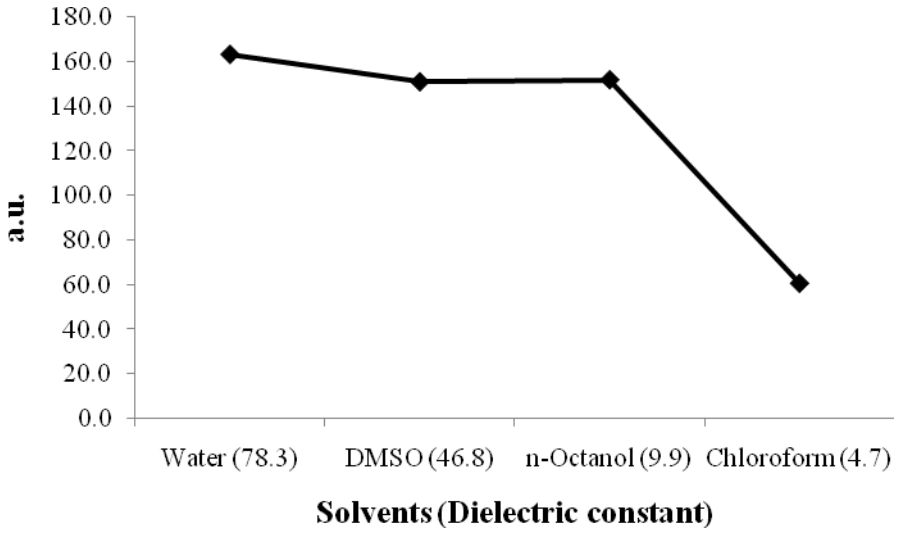


Figure 2. Medium effect on polarizability of metronidazole.

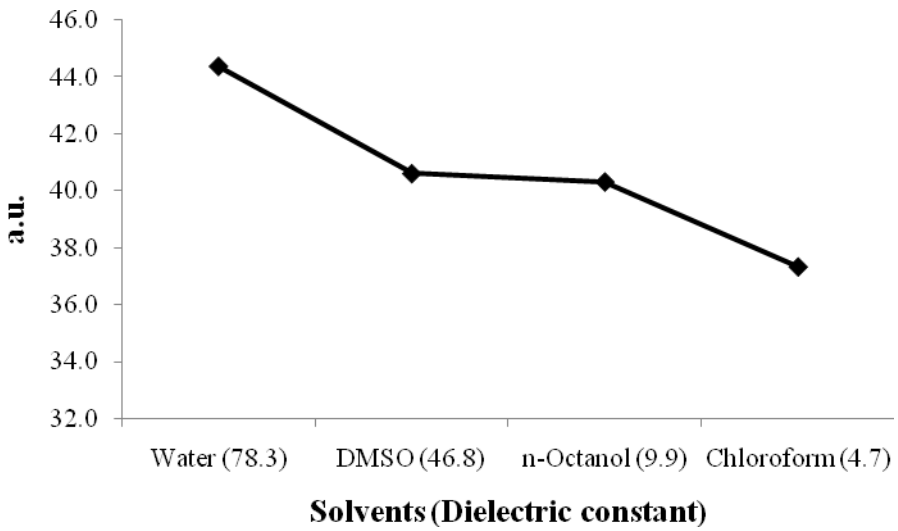


Figure 3. Medium effect on first hyperpolarizability of metronidazole.

Global reactivity descriptors: The energy gap between HOMO and LUMO is a critical parameter to determine molecular electrical transport properties. By using HOMO and LUMO energy values for a molecule, the global chemical reactivity descriptors of molecules such as hardness, chemical potential, softness, electronegativity and electrophilicity index have been defined (Parr *et al*., 1978; Parr *et al*., 1983; Parr *et al*., 1991; Parr *et al*., 1999; Chattarar*et al*., 2003). Pauling introduced the concept of electronegativity as the power of an atom in a molecule to attract electrons to it. Using Koopman's theorem for closed-shell molecules the hardness (η), chemical potential (μ), electronegativity (χ) and softness (S) are defined as follows.

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

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

$$\chi = \frac{I + A}{2}$$

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

where, and A are the ionization potential and electron affinity of the molecules, respectively. The ionization energy and electron affinity can be expressed through HOMO and LUMO orbital energies as I = $-E_{HOMO}$ and A = $-E_{LUMO}$.

Considering the chemical hardness, large HOMO–LUMO gap means a hard molecule and small HOMO–LUMO gap indicates a soft molecule. One can also relate the stability of the molecule to hardness and softness. Molecule with least HOMO–LUMO gap is more reactive and *vice versa.* The electrophilicity index (ω), a new descriptor used to quantify the global electrophilic power of a molecule (Parr *et al*., 1999). Electrophilicity index (ω) was defined as follows (Parr *et al*., 1999):

$$\omega = \frac{\mu^2}{2\eta}$$

By using the above equations, the chemical potential, hardness and electrophilicity index were calculated. These reactivity quantities are very useful in understanding the toxicity of compounds in terms of their reactivity and site selectivity (Parthasarathi *et al*., 2003; Parthasarathi *et al*., 2004a; Parthasarathi *et al*., 2004b). The molecular properties of metronidazole in different solvents are presented in Table 4. When moving from non-polar to polar solvent, the chemical potential, electronegativity and electrophilicity index were increased. On the other hand, opposite relation was found in the case of chemical hardness and softness.

Table 3. HOMO, LUMO and energy gaps of metronidazole in different solvents with SMD.

Medium (dielectric constant)	Molecular orbital energy (eV)		
	HOMO (eV)	*LUMO (eV)*	*ΔE (eV)*
Gas Phase	-7.352	-2.916	-4.437
Water (78.3)	-7.088	-3.000	-4.088
DMSO (46.8)	-6.988	-2.776	-4.212
n-Octanol (9.9)	-7.102	-2.946	-4.156
Chloroform (4.7)	-7.098	-2.843	-4.255

Table 4. Medium effect on molecular properties of metronidazole in different solvents with SMD.

Medium (dielectric constant)	Chemical hardness (η)	Softness (S)	Chemical potential (μ)	Electronegativity (χ)	Electrophilicity index (ω)
Water (78.3)	2.04	0.489	-5.04	5.04	6.22
DMSO (46.8)	2.11	0.475	-4.88	4.88	5.66
n-Octanol (9.9)	2.08	0.481	-5.02	5.02	6.07
Chloroform (4.7)	2.13	0.470	-4.97	4.97	5.81

Conclusion

In the present work, the effect of solvent polarity on solvation free energy, dipole moment, polarizability, hyperpolarizability and global reactivity descriptors have been determined from B3LYP/ 6-31G (d,p) level of theory. The calculated molecular properties may lead to understand the stability and reactivity of metronidazole and the results will be of assistance to use the title molecule as reaction intermediates and pharmaceuticals.

Competing interests

The authors declare no competing interests.

References

Bowden, K. and Izadi, J. 1998. Multifunctional derivatives of metronidazole. II *Farmaco*. **53**, 58-61.

Chattaraj, P.K., Maiti, B. and Sarkar, U. 2003. Philicity: a unified treatment of chemical reactivity and selectivity. *J. Phys. Chem. A.* **107**, 4973-4975.

Cohen, S.H., Gerding, D.N., Johnson, S., Kelly, C.P., Loo, V.G., McDonald, L.C., Pepin, J. and Wilcox, M.H. 2010. Clinical practice guidelines for infection in adults: 2010 Update by the Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA). *Infect. Control Hosp. Epidemiol.* **31**, 431-455.

Frisch, M.J., Trucks, G.W., Schlegel, H.B., Scuseria, G.E., Robb, M.A., Cheeseman, J.R., Scalmani, G., Barone, V., Mennucci, B.G., Petersson, A., Nakatsuji, H., Caricato, M., Li, X., Hratchian, H.P., Izmaylov, A.F., Bloino, J., Zheng, G., Sonnenberg, J.L., Hada, M., Ehara, Toyota, M.K., Fukuda, R., Hasegawa, J., Ishida, M., Nakajima, T., Honda, Y., Kitao, O., Nakai, H., Vreven, T., Montgomery Jr., J.A., Peralta, J.E., Ogliaro, F., Bearpark, M., Heyd, J.J., Brothers, E., Kudin, K.N., Staroverov, V.N., Kobayashi, R., Normand, J., Raghavachari, Rendell, K.A., Burant, J.C., Iyengar, S.S., Tomasi, J., Cossi, M., Rega, N., Millam, J.M., Klene, M., Knox, J.E., Cross, J.B., Bakken, V., Adamo, C., Jaramillo, J., Gomperts, R., Stratmann, R.E., Yazyev, O., Austin, A.J., Cammi, R., Pomelli, C., Ochterski, J.W., Martin, R.L., Morokuma, K., Zakrzewski, V.G., Voth, G.A., Salvador, P., Dannenberg,J.J., Dapprich, S., Daniels, A.D., Farkas,O., Foresman, J.B., Ortiz, J.V., Cioslowski, J. and Fox, D.J. 2009. Gaussian 09, Revision A.02, Gaussian, Inc., Wallingford, CT.

Harikrishnan, S. and Bhoopathy, T.J. 2015. Density functional theory restricted Hartree-Fock simulations and FTIR, FT-Raman and UV-Vis spectroscopic studies on metronidazole. *Int. J. Chem. Tech. Res.* **07**, 460-473.

Khan, M.F., Nabila, S.A., Rashid, R.B., Rahman, M.S., Chowdhury, A.A. and Rashid, M.A. 2015a. *In silico* molecular docking studies of lichen metabolites against cyclooxygenase-2 enzyme. *Bangladesh Pharm. J.* **18**, 90-96.

Khan, M.F., Rashid, R.B. and Rashid, M.A. 2015b. Computational study of geometry, molecular properties and docking study of Aspirin. *World J. Pharm. Res.* **4**, 2702-2714.

Kleinman, D.A. 1962. Nonlinear dielectric polarization in optical media. *Phys. Rev*. **126**, 1977.

Mao, W.J., Lv, P.C., Shi, L., Li, H.Q. and Zhu, H.L. 2009. Synthesis, molecular docking and biological evaluation of metronidazole derivatives as potent *Helicobacter pylori* urease inhibitors. *Bioorg. Med. Chem.* **17**, 7531-7536.

Parr, R.G., Donnelly, R.A., Levy, M. and Palke, W.E. 1978. Electronegativity: The density functional viewpoint. *J. Chem. Phys.* **68**, 3801-3807.

Parr, R.G. and Pearson, R.G. 1983. Absolute hardness: companion parameter to absolute electronegativity, *J. Am. Chem. Soc.* **105**, 7512-7516.

Parr, R.G. and Chattraj, P.K. 1999. Principle of maximum hardness. *J. Am. Chem. Soc*. **113**, 1854-1855.

Parr, R.G., Szentpály, L.V. and Liu, S. 1999. Electrophilicity Index. *J. Am. Chem. Soc.* **121**, 1922-1924.

Parthasarathi, R., Padmanabhan, J., Subramanian, V., Sarkar, U., Maiti, B. and Chattaraj, P. 2003. Toxicity analysis of benzidine through chemical reactivity and selectivity profiles: a DFT approach. *Int. Electron. J. Mol.* **2**, 798-813.

Parthasarathi. R., Padmanabhan. J., Subramanian. V., Sarkar, U., Maiti, B. and Chattaraj, P. 2004a. Intermolecular reactivity through the generalized philicity concept. *Chem. Phys. Lett*. **394**, 225-230.

Parthasarathi, R., Padmanabhan, J., Subramanian, V., Sarkar, U., Maiti, B. and Chattaraj, P. 2004b. Toxicity analysis of 33'44'5-pentachloro biphenyl through chemical reactivity and selectivity profiles. *Curr. Sci.* **86**, 535-542.

Targema, M., Obi-Egbedi, N.O. and Adeoye, M.D. 2013. Molecular structure and solvent effects on the dipole moments and polarizabilities of some aniline derivatives. *Computation. Theoret. Chem.* **1012**, 47-53.