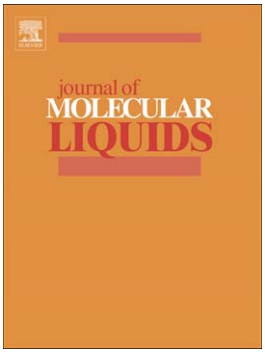

Solubility study of cefpodoxime acid antibiotic in terms of free energy of solution- insights from polarizable continuum model (PCM) analysis

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PII: S0167-7322(16)31384-8
DOI: doi:10.1016/j.molliq.2016.10.019
Reference: MOLLIQ 6423

To appear in: *Journal of Molecular Liquids*

Received date: 31 May 2016
Revised date: 8 September 2016
Accepted date: 4 October 2016

Please cite this article as: V. Sathyanarayanamoorthi, S. Suganthi, V. Kannappan, R. Kumar, Solubility study of cefpodoxime acid antibiotic in terms of free energy of solution- insights from polarizable continuum model (PCM) analysis, *Journal of Molecular Liquids* (2016), doi:10.1016/j.molliq.2016.10.019

Solubility study of cefpodoxime acid antibiotic in terms of free energy of solution- Insights from Polarizable Continuum Model (PCM) analysis

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Abstract

The polarizable continuum model (PCM) analysis has been carried out on a third generation cephalosporin antibiotic, cefpodoxime acid (CA) in ten solvents with wide range of dielectric constant using the B3LYP method with 6-311++G (d,p) basis set. The present investigation is aimed to assess the solubility of the drug in these solvents and an attempt to predict the bioavailability of this commercially important drug. We report the electrostatic, dispersion, and repulsive interaction components of Gibb's free energy of solvation (ΔG_{soln}) of the antibiotic along with cavitation energies in ten solvents. The induced dipole moments of CA in these solvents are calculated and discussed in terms of physical properties of the solvents. The interaction energies of the systems are discussed in terms of dielectric constant, index of refraction and surface tension of the solvents. The free energy of solution of CA in aqueous environment is used to predict the bioavailability of the antibiotic.

Keywords: cefpodoxime acid, PCM analysis, components of ΔG_{soln}, induced dipole moment, solubility

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1. Introduction

The limiting factor for the applicability as well as bioavailability of drugs is their solubility. Solubility enhancement of the antibiotic compounds is an important task in pharmaceutical formulations. Better understanding of solubility leads to higher bioavailability and to more efficient application, connected with a diminished environmental stress [1, 2, 3]. The intra and inter molecular interactions in biological molecules control the secondary structure and binding and play a vital role on their biological activity. The drug molecules can effectively be hydrogen bonded to receptor groups through their appropriate donor-acceptor groups in mostly aqueous environment [4]. In accessing the relative importance of the H – bonding in solution, it is necessary to consider the solvation effect on the solute component. Thus, it is important to identify the effect of solvent environment on the structure and charge distribution of solute molecule [5]. The theoretical methods comprised quantum chemical computations through which the electrophilicity, nucleophilicity, and lipophilicity parameters of drugs can be determined. The electrostatic potential on the surface a drug molecule indicates the number of electron donor or acceptor sites as a measure of the electrostatic interactions of the molecules with the solvent and possible formation of hydrogen bonds, the free energy of solution of the molecule [6, 7]. Drug analysis reports that it highly challenging to synthesize any new molecule that is pharmacologically active. The liberation and absorption of antibiotic molecules determine their bioavailability. Drugs that are orally administered and have poor solubility in aqueous environment show low bioavailability due to their limitation on its absorption in the intestinal tract [8]. Antibiotic compounds that are currently under development have high permeability but poor solubility [9]. Arora et al. [10] found that inclusion of urea in aqueous solution of Cefpodoxime Proxetil with a rapidly adducible endocyte such as stearic acid enhanced its

solubility leading to better bioavailability. The PCM study of drug molecule may be helpful for the pharmaceutical industry in designing novel drugs that may enhance the efficacy and bioavailability of drugs. This model does not take into account specific interactions but only considers the average effect of solvation, which the coulomb forces simulate and is affected by dipole – induced dipole interactions [11, 12, 13]. The third generation antibiotic, cefpodoxime acid is a metabolite of Cefpodoxime Proxetil (CP) and it also has in vitro antibacterial activity like CP against many common Gram-positive and Gram-negative pathogens associated with common pediatric infections. It is considered to be very effective antibiotic of recent years because of its broad spectrum activity and minimal side effect. Rigorous research and development efforts by the pharmaceutical industry have resulted in some success in both these aspects with the availability of molecules like cefpodoxime free acid [10, 11]. The drug action mechanism of β-lactam antibiotics is not completely established. Recently, we established through quantum mechanical study that CA acts more as a nucleophile than an electrophile and found that CA molecule has very low chemical potential (μ) and electrophilicity index (ω) by DFT calculations [7]. In this paper we report the free energy of solution of CA in ten different solvents and its component interaction energies and compare the solubility of CA in these solvents. The interaction energies are correlated with the physical properties of solvents. The induced dipole moments of CA in these solvents are also reported and discussed.

2. Computation method

The molecular geometries are optimized by the ab initio method [16]. The optimized geometries are solvated with the solvent of various ranges of dielectric constant. Computation has been performed both in the gas phase and in the solvent medium using polarizable continuum model (PCM) by the B3LYP method with 6-311++G(d, p) basis set to interpret the

solvent effect on the behavior of the solute molecules [16]. The computer program GAUSSIAN 03 [17] was used for this purpose. The general structure of the drug molecular CA used in the present investigation is depicted in Fig. 1. In the correlation of free energy of solution and dispersive interaction energy, we used the polarizability function [F(ε)] which is a function of dielectric constant and these values are calculated using the Clausius–Mossotti equation

$$F(\varepsilon) = [(\varepsilon-1)/(\varepsilon+2)]\,(M/\rho) \qquad (1)$$

Where,

ε = dielectric constant, M = molar mass and ρ= density of solvent. The physical properties of ten solvents employed in the present investigation are presented as supplementary data (Table A-1).

3. Results and Discussion

Polarizable Continuum Model generally attempts to solve the electrostatic as well as non-electrostatic components in dielectric medium. For this purpose, the electrostatic interaction, dispersion energy and repulsion energy of cefpodoxime acid in ten different solvents are evaluated by PCM. These quantities typically converge quickly during a simulation and thus can provide a good assessment of the computational approach in describing solvent–solute interaction. Electrostatic interaction energy is a type of strong dipole–dipole interaction between the solute and solvent species and hence it depends mainly on the dielectric constant of the medium [16]. The electrostatic interaction energy values for CA in different media at 298 K are given in Table 1. Electrostatic energy values are negative for CA in the ten solvents suggesting the presence of attractive electrostatic force in these systems. It may be seen from the data that electrostatic interaction energy values are less in less polar solvents; but high in more polar solvents. Fig. 2(a) contains plot of electrostatic force of attraction against dielectric constant (ε) of the solvent. It is evident from the plot that electrostatic force of attraction value increases with

ε of the solvent. The values corresponding to benzene and CCl_4 solvents are very low because these two are non-polar in nature. Further, the electrostatic interaction is significantly high in the case of hydroxyl solvents such as water, methanol and ethanol. This is because CA molecule contains carbonyl, amino and imido groups which are polar besides the hydrophilic –COOH group. These groups can interact with hydroxyl solvent molecules through strong intermolecular hydrogen bond which is also a strong dipole-dipole attraction. Since the hydrogen bond is strong in aqueous medium, electrostatic energy in water is found to be the highest. Increase in polarity of solvent increases electrostatic force of attraction value and it may increase the induced dipole moment of CA. This is evident from the plot of electrostatic force of attraction against induced dipole moment (Fig. 2(b)) of CA in different solvents at 298K.

Polarization of the solute molecules by the solvent molecules causes attractive force and the resulting energy of interaction is dispersion energy. The calculated dispersion energy values for CA in ten solvents are given in Table 1. It is observed that dispersion energy for CA is negative in all the ten investigated solvents. It is evident from the data presented in Table 1 that there is no significant difference in the dispersion energy in protic solvents (except water) of varying dielectric constants. The dispersion energy is influenced by ε of the solvent to some extent. The dispersive energy is high for CA in benzene and toluene among the organic solvents, although their dielectric constants are small. This suggests that dispersion energy cannot be directly correlated with ε. Further, these data also indicate that the dispersion energy is influenced by the polarizability of the solvent which in turn depends upon the size. We calculated polarizability function from ε, molar mass and density of solvent using equation (1) and these values for ten solvents are given in Table 1. It may be seen from the data in Table 1 that negative value of dispersion energy increases with increase in F(ε). Thus, among organic

solvents CCl_4 and $CHCl_3$ have smaller F(ε) values and their dispersion energies are low. Ethanol and nitromethane have high F(ε) values and their dispersion energies are also high. It may be pointed out that dispersion energy for CA in benzene and toluene are high although their F(ε) values are less. This may be due to the high quadrupole moments of benzene and toluene. Similar observation was made in the PCM analysis of isoquinoline derivatives in our earlier study [18]. It may also be noted that dispersion energy is large negative in aqueous medium, though its polarizability function is small. This indicates that hydrogen bond interaction between CA and solvent influences dispersion energy in aqueous solution.

The repulsive energy between solute and solvent molecules is another important parameter to be considered in solvation analysis. Table 1 contains computed values of repulsive energies for the CA antibiotic in ten different media. It is found that the repulsive energies of CA–solvent interactions in all the investigated solvents have positive values. Plot of repulsive energy against refractive index of the solvent is given for CA in ten solvents in Fig. 3. The repulsive energy of CA can be correlated with refractive index of the solvent. It is found that there is a uniform decrease in repulsive energy with increase in refractive index of the solvent (except water). This may be due to the presence of strong intermolecular hydrogen bond between water and CA. The assumption in PCM is that the solute molecule is surrounded by a cavity with a molecular shape and it is possible to calculate the free energy difference between a solute molecule in gas phase and in solution. The energy difference between gas phase energy and solution phase energy of solute is called cavitation energy [19]. The magnitude of cavitation energy will affect value of free energy of solution hence the solubility. The values of cavitation energy are calculated for cefpodoxime acid in ten different solvents at 298 K by the B3LYP

method with 6-311++G(d,p) basis set and they are listed in Table 2. Damian et al. suggested that the cavitation energy is linearly related to surface tension and area of cavity as

$$\Delta G_{cav} = \gamma\, S(\rho_0) \qquad (2)$$

where γ is the surface tension and $S(\rho_0)$ is the surface of the same cavity employed in the electrostatic part of the solvation energy and is defined by an iso-surface of the charge density [20]. Hence, the cavitation energy of CA can be correlated with the macroscopic surface tension of the solvent. It can be seen that cavitation energy is positive for CA in all the ten solvents. Thus, the cavitation energy of CA is high in water which has higher surface tension and it is low in methanol, ethanol, acetone, dichloromethane and chloroform which have lower surface tension. The surface tension values for benzene and toluene are higher than the other organic solvents and hence cavitation energy of CA is larger in aromatic solvents. Plot of cavitation energy against surface tension of solvent is given in Fig. 4. This plot establishes that the cavitation energy for CA increases with increase in the surface tension of solvent.

The Gibbs energy (ΔG_{sol}) of solution is the change of the Gibbs energy when a molecule of the solute is transferred from a fixed position in the gas phase into a fixed position in solution at constant temperature. Of course, the energy value is reported per mole of solute. Since temperature is constant in solubility study, the energy due to thermal motion may be assumed to be constant is all the systems. Neglecting the entropy contribution due to molecular motion, ΔG_{sol} can be defined as

$$\Delta G_{sol} = \Delta G_{ele} + \Delta G_{disp} + \Delta G_{rep} + \Delta G_{cav} \qquad (3)$$

Thus, ΔG_{ele} collects the components of electrostatic origin, namely, those related to the usual *ab initio* molecular Hamiltonian and to the solute-solvent electrostatic polarization effects, ΔG_{disp} the short range solute-solvent interactions and ΔG_{rep} the short range solute-solvent

repulsive forces. ΔG_{cav} is the work needed to form the cavity. Dispersion-repulsion forces and cavitation contribution to the energy normally comes with opposite signs, thus reducing the total contribution. In many cases, specifically for the case of charged or highly polar solutes, electrostatic forces play the dominant role in solvation. Solubility (S) of a compound is related to free energy of solution [21] by equation (4)

$$\log S = (-\Delta G_{sol}/2.303RT) \qquad (4)$$

In equation (4), ΔG_{sol} is free energy of solution; R is molar gas constant and T is temperature in K.

ΔG_{sol} values for CA in ten solvents are calculated by summing up the component energies and these values are presented in Table 2. It may be pointed out that the values of free energy of solution for CA in eight solvents are negative suggesting that the dissolution process is thermodynamically feasible for CA in these solvents under specified conditions. However, ΔG_{sol} values for CA in C_6H_6 and CCl_4 are positive at 298 K and hence dissolution of CA in these two solvents is not a feasible process at the specified temperature. These data also indicate that properties of solvents influence the free energy of solution. Plot of ΔG_{sol} for CA against dielectric constant of solvent is given in Fig. 5. The plot shows that the influence of ε on ΔG_{sol} is significant in hydroxyl solvents such as water, methanol and ethanol and ΔG_{sol} values are more negative in these three solvents. This shows that intermolecular hydrogen bond between solute and solvent plays key role in determining the solubility of the drug molecule. By comparing the free energies of CA in aprotic organic solvents, the dissolution process is more favored in acetone and nitromethane than in chloroform and toluene. This may due to larger contribution of electrostatic and dispersion energies and relatively smaller repulsive and cavitation energies of CA in these two solvents. It may be inferred that dissolution process is more favourable in

solvents with higher Abraham's hydrogen bond acidity and basicity values. This can be established by comparing the values of free energy of solution and hydrogen bond acidity and basicity values. If we compare the values of ΔG_{sol} of CA in different solvents, we find that the ΔG_{sol} value is more negative in water and alcohols and less negative in other organic solvents. It may be noted that water, methanol and ethanol have relatively larger Abraham's hydrogen bond acidity and basicity functions.

Electrical properties of a solute are influenced by solvation by changing its geometry and also by polarizing its charge distribution[19]. Hence, dipole moment of a solute may be influenced in a solvent environment. Induced dipole moments for CA in ten investigated solvents are computed and the values are given in Table 2. The induced dipole moment of CA increases slightly with dielectric constant of solvent. Fig. 6 contains plot of induced dipole moment of CA against dielectric constant of solvent. The plot indicates that the induced dipole moment of CA is large in all the investigated solvents

4. Conclusions

Solubility study and PCM analysis has been carried out on CA in e ten solvents using the B3LYP method with 6-311++G (d,p) basis set. The electrostatic, dispersion and repulsive components of Gibb's free energy of solvation of the antibiotic along with cavitation energies in various solvents are reported and discussed. Electrostatic force of attraction correlates satisfactorily with ε of solvent. The electrostatic interaction is significantly high in the case of hydroxyl solvents which may be attributed to solute-solvent hydrogen bonding. Dispersion energy of CA is largely influenced by the polarizability function. Quadrupole moment of solvent molecule also influences the dispersion energy component. The repulsive energy decreases with increase in refractive index of the solvent (except water). It is found that cavitation energy is

positive for CA in all the ten solvents and it increases with increase in macroscopic surface tension of solvent. The present study shows that high dielectric constant of solvent and intermolecular hydrogen bond formation between solute and solvent favor dissolution of CA. The induced dipole moments of CA in these solvents are significant and increases with dielectric constant of solvent. This study establishes that, ΔG_{sol} for CA in water is large negative and the drug may be more soluble in water than in other solvents. It is established that the solubility and bioavailability of CA may be higher in aqueous medium than in non-aqueous media.

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Figure Legends

Figure 1 Optimized structure of cefpodoxime acid

Figure 2 (a) Plot of electrostatic force of attraction versus dielectric constant (ε) of solvent and (b) plot of electrostatic force of attraction versus induced dipole moment of CA in different solvents at 298K

Figure 3 Plot of (a) repulsion energy of CA vs refractive index of solvent and (b) repulsion energy vs radius of solvent molecule for ten systems at 298 K

Figure 4 Plot of cavitation energy versus surface tension for cefpodoxime acid in different solvents at 298 K

Figure 5 Plot of negative free energy of solution vs dielectric constant for cefpodoxime acid in different solvents versus at 298 K

Figure 6 Plot of induced dipole moment vs dielectric constant for cefpodoxime acid in different solvents at 298 K

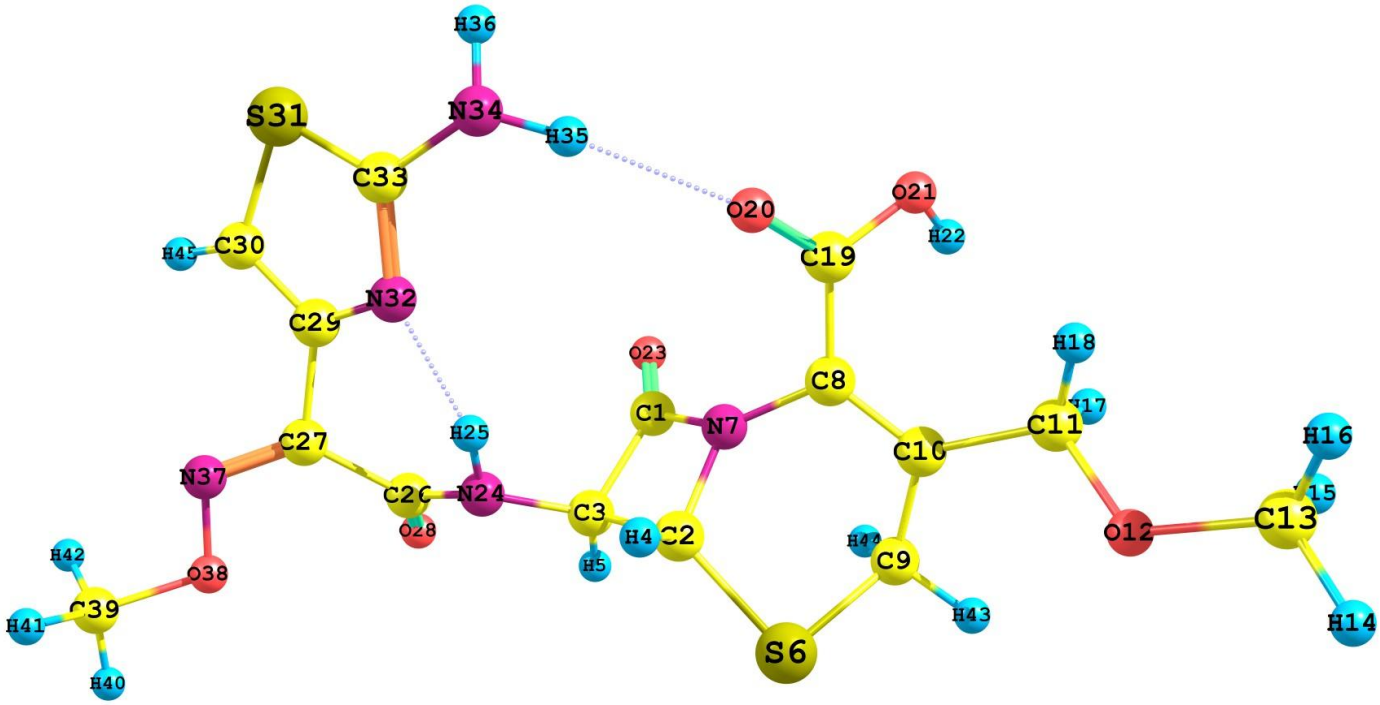
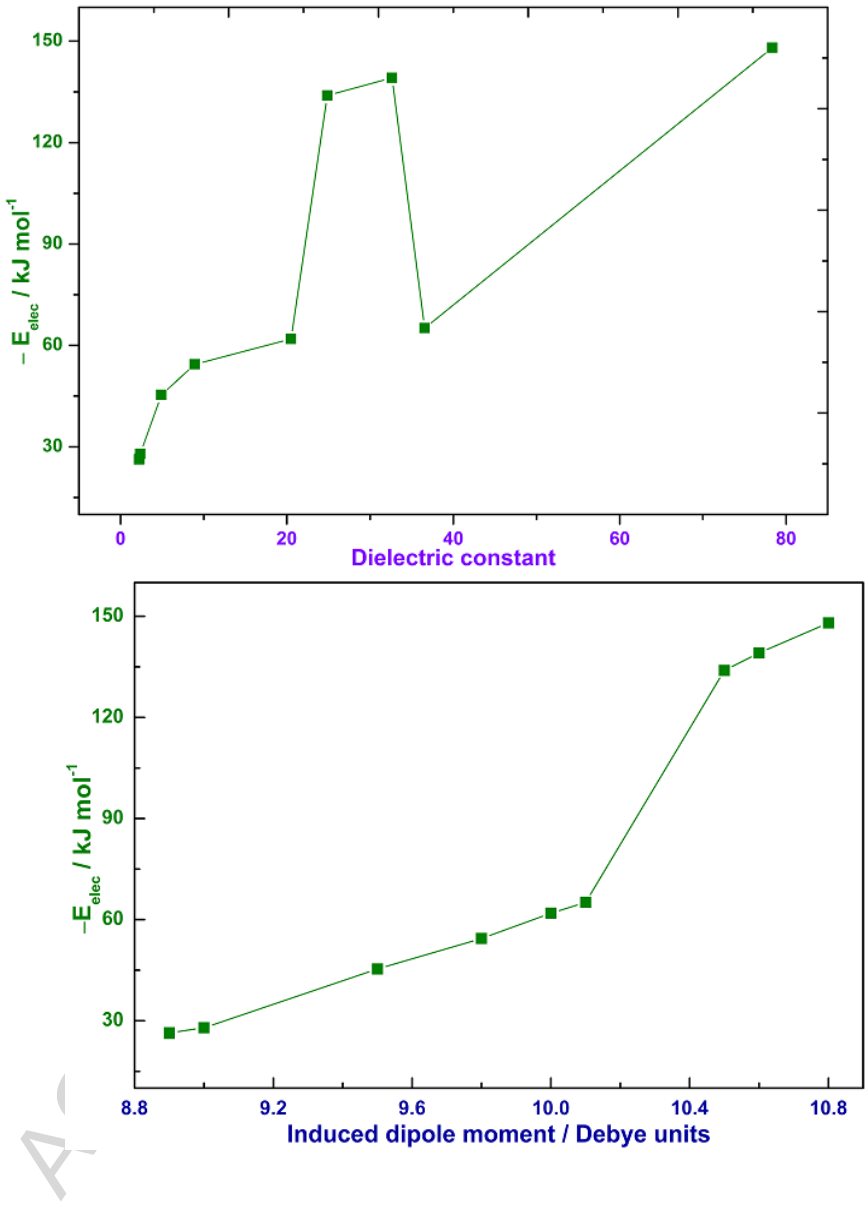


Figure 1 Optimized structure of cefpodoxime acid



(a)

(b)

Figure 2 (a) Plot of negative electrostatic energy versus dielectric constant (ε) of solvent and (b) plot of negative electrostatic energy versus induced dipole moment of CA in different solvents at 298K

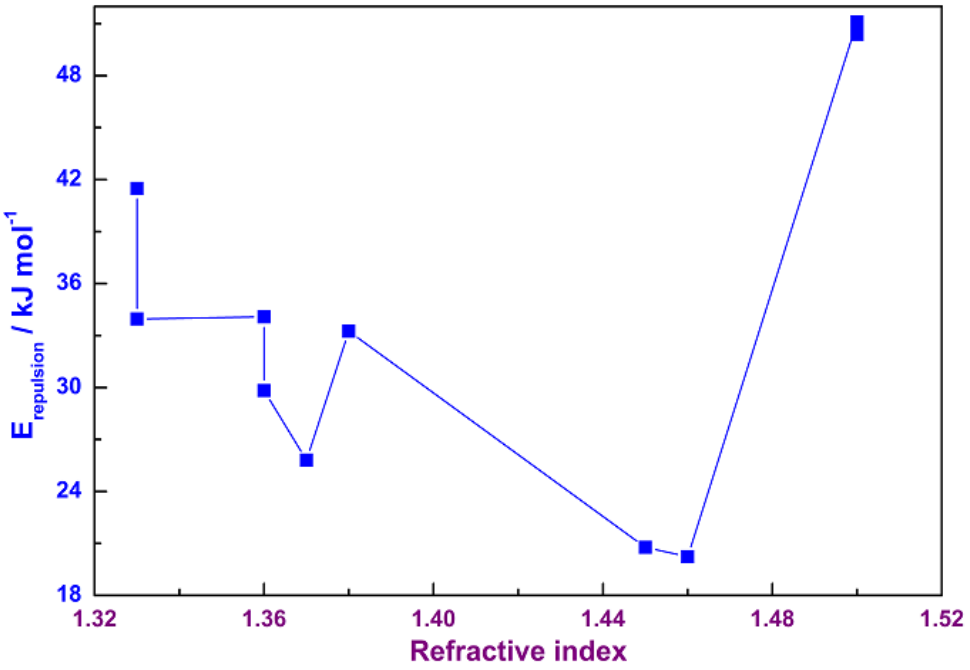


Figure 3 Plot of (a) repulsion energy versus refractive index of solvent (b) repulsion energy versus radius of solvent molecule for ten systems at 298 K

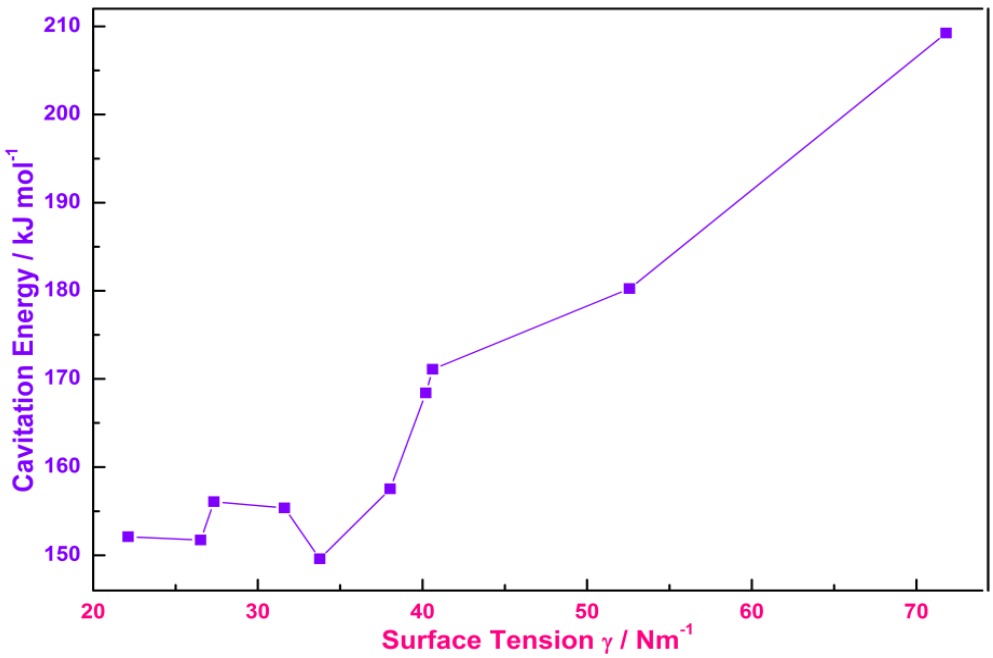


Figure 4 Plot of cavitation energy versus surface tension in different solvents for ten systems at 298 K

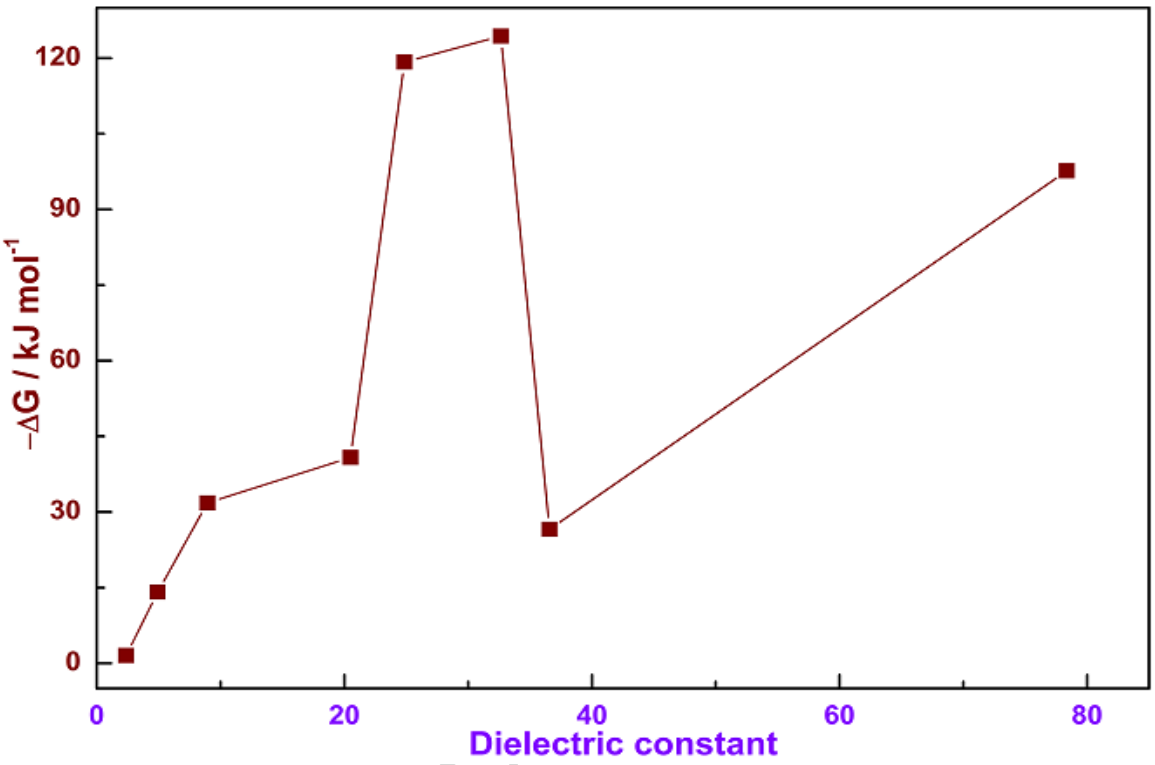


Figure 5 Plot of negative free energy of solution versus dielectric constant in different solvents for ten systems at 298 K

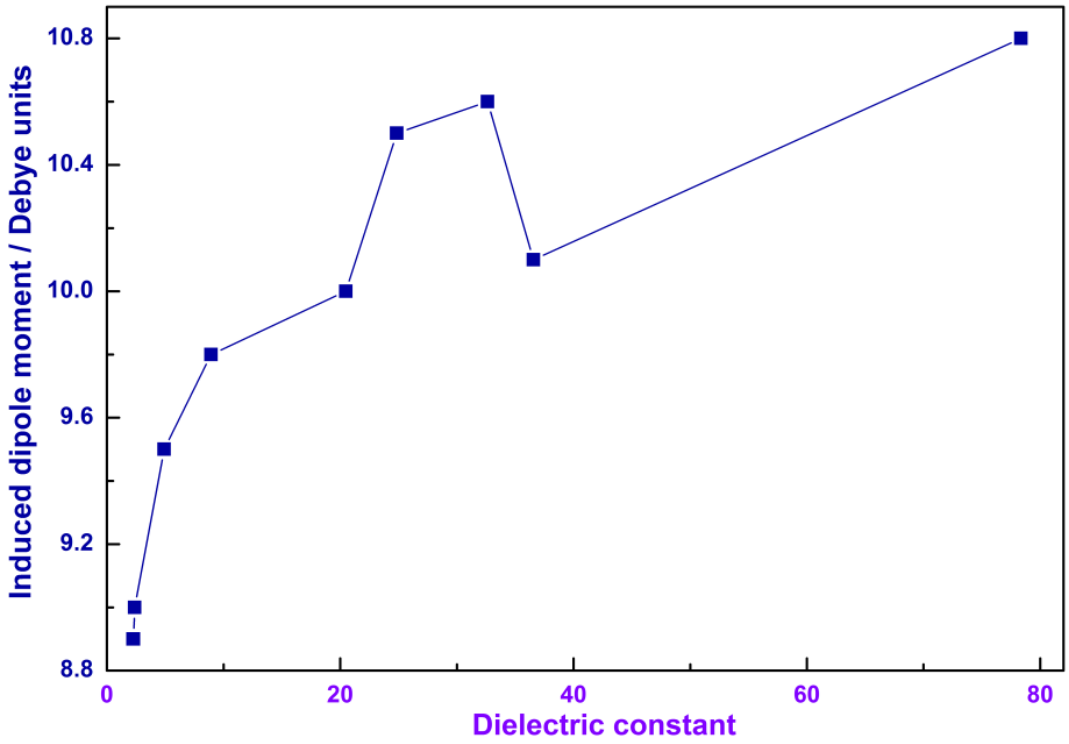


Figure 6 Plot of induced dipole moment versus dielectric constant in different solvents for ten systems at 298 K

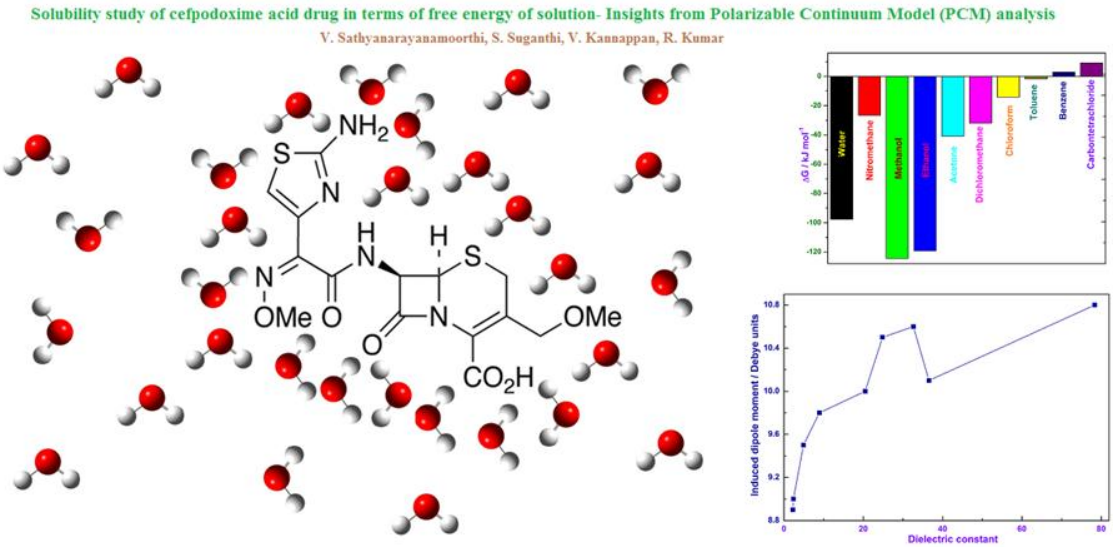
Table 1 – Polarizability function [F (ε)], dispersion energy, repulsion energy, electrostatic energy for CA in different solvents at 298K

Solvent	F(ε), cc mol^{-1}	Dispersion energy, kJ mol^{-1}	Repulsion energy, kJ mol^{-1}	Electrostastic energy, kJ mol^{-1}
Water	17.38	-200.32	41.49	-148.04
Nitromethane	49.38	-174.93	33.25	-65.11
Methanol	37.00	-171.29	33.96	-139.14
Ethanol	51.87	-174.77	34.08	-133.91
Acetone	63.63	-158.33	29.82	-61.89
Dichloromethane	46.33	-159.25	25.80	-54.41
Chloroform	45.59	-141.31	20.78	-45.33
Toluene	33.36	-193.12	51.10	-27.94
Benzene	26.52	-192.00	50.39	-26.43
Carbon-tetrachloride	28.20	-142.23	20.24	-26.26

Table 2 - Dielectric constant (ε), free energy of solution (ΔG), cavitation energy and induced dipole moment of CA in different solvents at 298K

Solvent	Dielectric constant, ε	ΔG_{sol}, kJ/mol	Cavitation energy, kJ/Mol	Dipole moment, Debye
Water	78.35	-97.65	209.23	10.8
Nitromethane	36.56	-26.56	180.24	10.1
Methanol	32.63	-124.37	152.10	10.6
Ethanol	24.85	-119.23	155.36	10.5
Acetone	20.49	-40.82	149.59	10.0
Dichloromethane	8.93	-31.78	156.07	9.8
Chloroform	4.9	-14.14	151.72	9.5
Toluene	2.37	-1.55	168.41	9.0
Benzene	2.27	3.05	171.09	8.9
Carbontetrachloride	2.23	9.28	157.54	8.9

Graphical abstract



PCM analysis is carried out on cefpodoxime acid (CA) in the ten solvents using B3LYP method. Electrostatic, dispersion, cavitation energy and repulsive components of ΔG_{sol} of CA are correlated with solvent properties.

Solubility study of cefpodoxime acid drug in terms of free energy of solution- Insights from Polarizable Continuum Model (PCM) analysis

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Journal : Journal of Molecular Liquids

Highlights

- PCM analysis is carried out on cefpodoxime acid (CA) in the ten solvents using B3LYP method
- E_{elec}, E_{disp}, E_{cav} and E_{rep} components of ΔG_{sol} of CA are correlated with solvent properties.
- High dielectric constant of solvent and intermolecular hydrogen bond favor dissolution process
- CA is found to be more soluble in water than in other organic solvents
- Induced dipole moments of CA are large in the investigated ten systems