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Polarizable continuum model solvation analysis of certain 5-substituted isoquinoline derivatives

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ABSTRACT

The polarizable continuum model (PCM) analysis has been carried out using the B3LYP method with 6-311++G(d,p) basis set for 5-bromoisoquinoline (5-BIQ), 5-aminoisoquinoline (5-AIQ), 5-nitroisoquinoline (5-NIQ), 5-methylisoquinoline (5-MIQ), 5-chloroisoquinoline (5-CIQ) and 5-methoxyisoquinoline (5-MXIQ) in ten solvents with a wide range of dielectric constants. In this paper, we report electrostatic, dispersion and repulsive interaction components of Gibb's free energy of solvation along with cavitation energies for these six systems. The induced dipole moments of these six compounds in ten solvents are calculated for the three solutes. The interaction energies of the systems are discussed in terms of dielectric constant, index of refraction and surface tension of the solvents. The influence of substituent at 5-position of isoquinoline molecule on the solubility property is investigated.

1. Introduction

Isoquinoline is an important nitrogen containing heterocyclic aromatic compound. Quinoline and isoquinoline derivatives are used as effective and efficient anesthetics [1]. Its anesthetic activity is similar to those of procaine or cocaine when injected. In pharmaceutical synthesis, 5-bromoisoquinoline is used as a synthetic intermediate. It is a starting material employed in metal-catalyzed aminomethylation and amination reactions [2–4]. 5-Nitroisoquinoline derivatives are versatile heterocyclic building blocks. In 6-methyl 5-nitroisoquinoline the ortho-substituted nitroisoarene motif present is amenable to the Leimgruber–Batcho indole synthesis. Alternatively, the nitro group can be reduced to an amino group, thereby allowing access to further functionalization [5,6]. It has been demonstrated that 5-aminoisoquinoline (5-AIQ) can reduce ischemia/reperfusion injury of the heart, intestine and liver and 5-AIQ has also been shown to provide beneficial effects in rodent models of lung injury [7–9]. 5-AIQ possesses interesting photo physical properties and it enhanced the intensity of luminol–H_2O_2 chemical luminescence in the presence of horseradish peroxidase enzyme [10]. There are few reports on the use of quinoline, isoquinoline and some of their derivatives as corrosion inhibitors in different media [11–16]. The effects of pyridine, pyrimidine, 2-picoline, quinoline, 2:6-lutidine and isoquinoline on the corrosion inhibition of 1060 aluminum in a 0.1 N trichloroacetic acid at varying temperatures of 30 °C and 40 °C have been investigated [17]. Thus solvation analysis of isoquinoline derivatives in different solvents will be helpful in pharmaceutical preparations and in corrosion studies. It may be pointed out that there are some computational and spectral studies on quinoline and isoquinoline derivatives in recent years [18,19]. An extensive literature survey revealed that there are no reports on the solvation study of 5-substituted isoquinoline derivatives, although these compounds are biologically and industrially important. In this paper we report the results obtained in the quantum mechanical study of solubility properties of six isoquinoline derivatives and correlated the contributing interaction energies with the physical properties of solvents.

2. Computation method

The molecular geometries are optimized by the ab initio method [20]. 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 [20]. The computer program GAUSSIAN 03 [21] was used for this purpose. The general structure of the six isoquinoline derivatives 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

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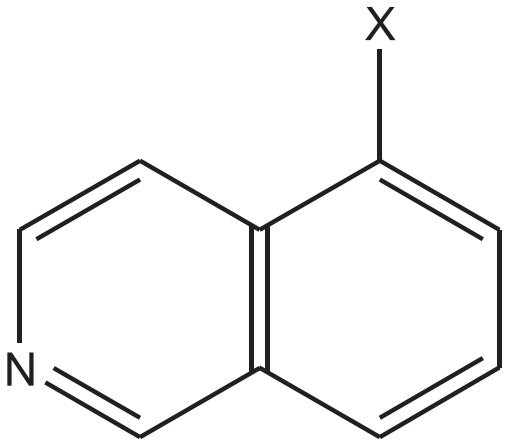

Fig. 1. General structure of 5-substituted isoquinolines. X = Br, NH_2, NO_2, CH_3, Cl, OCH_3.

Table 1
Solvent descriptors.

Solvent	ε	n	γ/dyn cm^{-1}	α	β	r/nm
H_2O	78.35	1.33	71.81	0.82	0.35	0.277
CH_3NO_2	36.56	1.38	52.58	0.06	0.31	0.431
CH_3OH	32.63	1.33	22.12	0.43	0.47	0.371
C_2H_5OH	24.85	1.36	31.62	0.37	0.48	0.472
Acetone	20.49	1.36	33.77	0.04	0.49	0.476
CH_2Cl_2	8.93	1.37	27.33	0.11	0.05	0.454
$CHCl_3$	4.91	1.45	26.53	0.15	0.02	0.496
Toluene	2.37	1.51	40.22	0	0.14	0.564
C_6H_6	2.27	1.50	40.62	0	0.14	0.526
CCl_4	2.23	1.46	38.04	0	0	0.537

ε — dielectric constant at 298 K.
n — index of refraction at optical frequencies at 298 K.
γ — macroscopic surface tension at liquid–air interface.
α — Abraham's hydrogen bond acidity.
β — Abraham's hydrogen bond basicity.
r — molecular radius.

of dielectric constant and these values are calculated using the Clausius–Mossotti equation

$$F(\varepsilon) = (\varepsilon - 1/\varepsilon + 2)\ (M/\rho) \quad (1)$$

where, ε = dielectric constant, M = molar mass and ρ = density of solvent.

3. Results and discussion

The use of nitrogen-containing organic compounds, such as amines and diamines in the study of corrosion of many metals in acidic solutions offers good protection of metallic materials [22,23]. The behavior of some pyridine derivatives towards the inhibition of corrosion has been investigated for 1060 aluminum alloys [17] in a 0.1 N trichloroacetic acid at 30° and 40 ° C. Investigation of solubility parameters and study of components of solute–solvent interactions are of immense help in the formulation of these medicinally important compounds. Inter-molecular interactions of molecules control the structure and binding and hence they play an important role to communicate and control their activities. Such interactions include several components. Among the various components, electrostatic interactions are of special importance because of their long range and their influence on polar or charged molecules. Continuum model for polar and non-polar solvation generally attempts to solve the electrostatics in a dielectric medium. For this purpose, the electrostatic interaction, dispersion energy and repulsion energy of six isoquinoline derivatives 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 the solvent–solute interaction. The free energy of solvation is calculated by the B3LYP method with 6-311++G(d,p) basis set for a group of solvents which include protic and aprotic solvents. The solvent descriptors such as dielectric constant (ε), index of refraction (n), macroscopic surface tension (γ), hydrogen bond acidity parameter (α) and hydrogen bond basicity parameter (β) are listed in Table 1. The solvents are selected such that there is a wide range of polarity.

Solvation analysis is carried out for 5-bromoisoquinoline, 5-aminoisoquinoline, 5-nitroisoquinoline, 5-chloroisoquinoline, 5-methylisoquinoline and 5-methoxyisoquinoline in ten solvents and the general structure of these compounds is given in Fig. 1. Table 2 contains the electrostatic interaction energies of the six isoquinoline derivatives in different media. Electrostatic interaction energy is due to the dipole–dipole interaction between the solute and solvent molecules and hence it depends mainly on the dielectric constant of the medium. It may be pointed out that electrostatic interaction energy values are less in less polar solvents and large in more polar solvents in the case of all the six isoquinoline compounds. Thus, the electrostatic interaction energy values are relatively high in polar solvents (water, nitro methane, methanol, ethanol and acetone) for the six solutes. In solvents like water and alcohols there is a possibility of intermolecular hydrogen bonding and it is also a type of strong dipole–dipole interaction. The data in Table 2 suggest that the electrostatic contribution in a given solvent depends on the structure of the solute. Halogen substituent at position 5 of isoquinoline reduces the electrostatic energy in a given solvent indicating less polar nature of these compounds. Both 5-BIQ and 5-CIQ have almost same electrostatic energy in a given medium. 5-MIQ also has less electrostatic energy in these solvents because methyl group is a less polar group. 5-AIQ and 5-NIQ molecules contain polar amino and nitro groups at position 5 and hence the dipolar character of these solutes is enhanced. Consequently, the electrostatic energy is increased in the case of these two solutes in almost all the ten solvents. The electrostatic interaction contribution to the free energy depends on the dielectric constant of the solvent [24]. Thus the electrostatic interaction increases from CCl_4 to water. Plots of electrostatic energy against dielectric constant for the six systems are depicted in Fig. 2. These plots indicate that the electrostatic energy is negative for all the six solutes in all the solvents investigated. Further, the negative value increases with increase in ε of the solvent. It may pointed out that the dip in the plot in the region of ε values 25–35 in all the six solutes shows that the electrostatic contribution is relatively high for all six solutes in alcoholic solvents.

The dispersion energy is due to the polarization of the solute molecules by the solvent molecules. The dispersion energy values for the six isoquinoline derivatives in various solvents are presented in Table 3. It is evident from the data presented in Table 3 that there is no significant difference in the dispersion energies in protic solvents of varying dipole moments while the dispersive energy is high for the

Table 2
Electrostatic energy of 5-substituted isoquinolines in different solvents at 298 K (kJ/mol).

Solvent	5-BIQ	5-AIQ	5-NIQ	5-MIQ	5-CIQ	5-MXIQ
H_2O	−39.81	−51.73	−60.93	−41.53	−39.60	−46.84
CH_3NO_2	−18.69	−24.21	−31.49	−19.99	−18.57	−22.42
CH_3OH	−38.27	−49.77	−58.51	−39.81	−38.06	−45.00
C_2H_5OH	−37.39	−48.72	−57.29	−38.89	−37.22	−43.99
Acetone	−17.90	−23.21	−30.28	−19.15	−17.77	−21.50
CH_2Cl_2	−15.89	−20.62	−27.18	−16.98	−15.77	−19.03
$CHCl_3$	−13.30	−17.23	−22.92	−14.14	−13.22	−15.89
Toluene	−8.36	−10.87	−14.72	−8.91	−8.32	−9.99
C_6H_6	−7.90	−10.25	−13.97	−8.41	−7.86	−9.41
CCl_4	−7.82	−10.16	−13.84	−8.32	−7.78	−9.33

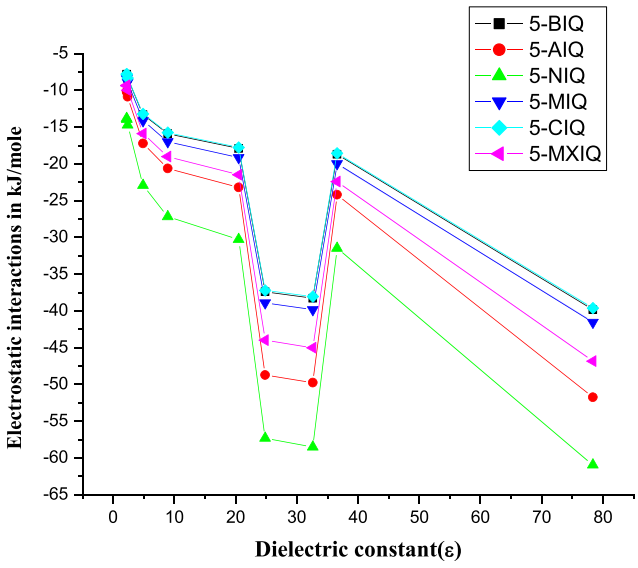

Fig. 2. Plot of electrostatic energy of 5-substituted isoquinoline vs dielectric constant of various solvents.

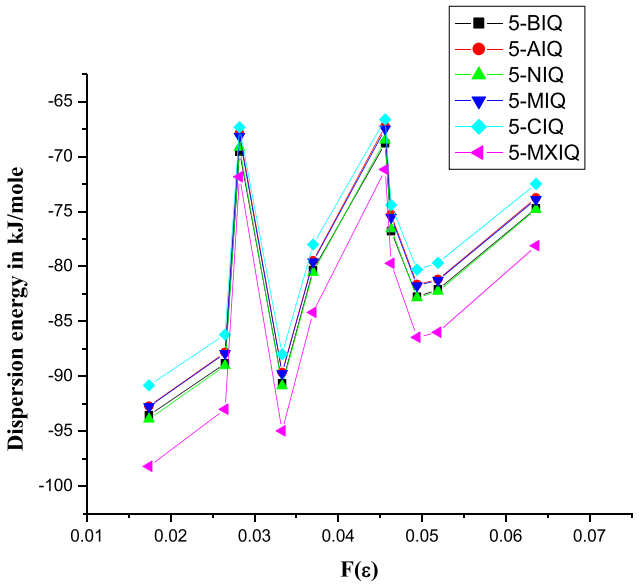

Fig. 3. Plot of dispersion energy of 5-substituted isoquinoline vs F(ε) of various solvents.

six molecules in benzene and toluene among organic solvents. This may be due to the high quadrupole of benzene and toluene. These data also suggest that the dispersion energy is influenced by the polarizability of the solvent which in turn depends upon the size. The plot of dispersive energy vs the polarizability function (F(ε)) is depicted in Fig. 3. The plots for different solutes almost overlap indicating that a structural variation in solute does not affect the dispersion energy significantly. The dispersion energy increases with an increase in F(ε) value and the deviation is observed in alcoholic and chlorinated solvents. For a given solute, the dispersive energy also depends on the dipole moment of solvent molecule. The dispersion energy increases with an increase in the dipole moment of solvent molecule. Thus the dispersive energy of a given isoquinoline derivative is larger in CH_2Cl_2 and $CHCl_3$ than in CCl_4. It may be noted that the dipole moment of CCl_4 is zero while other two chlorinated solvents have net dipole moments.

The repulsive energy between solute and solvent molecules is another important parameter to be considered in solvation analysis. Table 4 contains computed values of repulsive energies for the six solute molecules in ten different media. It is observed that the repulsive energies due to solute–solvent interactions in all the solvents have positive values. Plots of repulsive energy against refractive index of the solvent are given for the three solutes in Fig. 4. By relating the refractive index of the solvents with the repulsive energy, it is found that there is a uniform variation in repulsive energy with the refractive index of the aliphatic solvents. However, in the case of aromatic solvents, there is an abrupt increase in the repulsion energy in all the solutes. The repulsive energy is more positive in benzene and toluene solutions for all the six isoquinoline compounds. This may be due to the fact that both the solute and aromatic hydrocarbon solvents contain π-electrons and there may be a repulsive force between them. It may be pointed out that the repulsive energy is high in benzene and toluene for the six solutes suggesting that these solute compounds may be less soluble in aromatic hydrocarbons.

In PCM the molecule is surrounded by a cavity with a molecular shape and it is possible to calculate the free energy difference between a molecule in gas phase and in a liquid solvent which is called cavitation energy [25]. If the cavitation energy is more positive it will reduce the negative value of free energy of solution and will influence the solubility. The values of cavitation energy are computed for the six solutes in various solvents at 298 K by the B3LYP method with 6-311++G(d,p) basis set and they are listed in Table 5. It can be seen that cavitation energy is positive for the six isoquinoline derivatives in all the ten solvents at 298 K. Analysis of cavitation energy data in Table 5 reveals that the cavitation energy depends on the structure of solute as well as nature of solvent. Damian et al. suggested that the cavitation energy is linearly related to surface tension and area of cavity as

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

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 isosurface of the charge density [26]. Hence, the cavitation energy of a given isoquinoline derivative can be correlated with the macroscopic surface tension of the solvent. Thus the cavitation energy of a particular isoquinoline compound is high in water which has high surface tension and it is low in chloroform which has low surface tension. In a

Table 3
Dispersion energy of 5-substituted isoquinolines in different solvents at 298 K (kJ/mol).

Solvent	5-BIQ	5-AIQ	5-NIQ	5-MIQ	5-CIQ	5-MXIQ
H_2O	−93.55	−92.71	−93.89	−92.76	−90.83	−98.19
CH_3NO_2	−82.76	−81.63	−82.85	−81.76	−80.29	−86.44
CH_3OH	−80.34	−79.50	−80.55	−79.58	−77.99	−84.18
C_2H_5OH	−82.09	−81.17	−82.26	−81.26	−79.67	−85.98
Acetone	−74.73	−73.77	−74.82	−73.90	−72.47	−78.12
CH_2Cl_2	−76.78	−75.28	−76.57	−75.53	−74.40	−79.71
$CHCl_3$	−68.79	−67.25	−68.50	−67.50	−66.62	−71.18
Toluene	−90.67	−89.66	−90.87	−89.75	−87.99	−94.97
C_6H_6	−88.83	−87.82	−89.03	−87.91	−86.19	−93.01
CCl_4	−60.55	−60.87	−61.17	−61.10	−60.33	−62.85

Table 4
Repulsion energy of 5-substituted isoquinolines in different solvents at 298 K (kJ/mol).

Solvent	5-BIQ	5-AIQ	5-NIQ	5-MIQ	5-CIQ	5-MXIQ
H_2O	18.48	20.87	18.23	19.45	18.36	20.87
CH_3NO_2	15.35	17.06	15.06	15.93	15.18	17.06
CH_3OH	15.22	17.15	14.97	15.98	15.10	17.10
C_2H_5OH	15.35	17.23	15.06	16.06	15.18	17.19
Acetone	13.59	15.18	13.34	14.14	13.47	15.14
CH_2Cl_2	12.63	13.63	12.25	12.80	12.38	13.63
$CHCl_3$	10.41	11.12	10.08	10.50	10.20	11.17
Toluene	23.54	26.01	23.17	24.38	23.25	26.10
C_6H_6	23.29	25.68	22.88	24.09	23.00	25.76
CCl_4	9.53	10.96	9.99	10.33	10.12	11.00

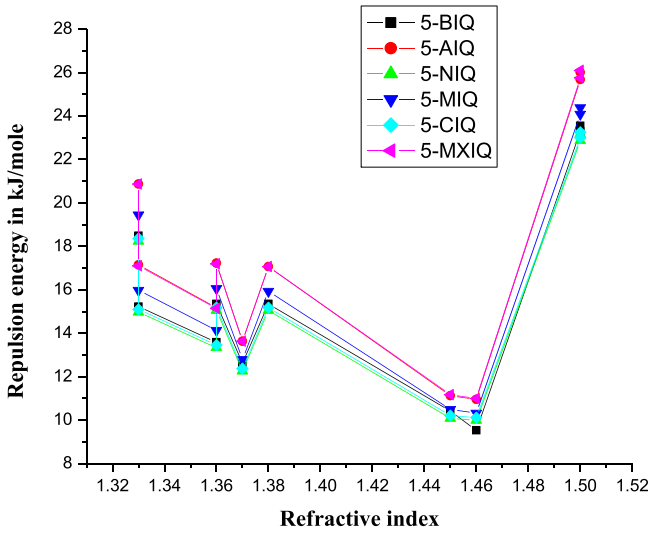

Fig. 4. Plot of repulsion energy vs refractive index of various solvents.

given solvent, the order of repulsion energy is 5-NIQ > 5-MXIQ > 5-BIQ ≈ 5-CIQ > 5-MIQ > 5-AIQ. These results indicate that the presence of electron withdrawing group (except OCH_3) increases the cavitation energy while the presence of electron releasing groups like methyl and amino decreases cavitation energy.

The free energy of solution for the PCM solvated molecule is defined as

$$\Delta G_{sol} = \Delta G_{el} + \Delta G_{cav} + \Delta G_{disp} + \Delta G_{rep} \quad (3)$$

where ΔG_{el} is the electrostatic contribution, ΔG_{cav} is the work needed to form the cavity, ΔG_{disp} is the short range solute–solvent interactions and ΔG_{rep} is the short range solute–solvent repulsive forces. Dispersion–repulsion forces and cavitation contribution to the energy normally come with opposite signs, therefore, reducing the total contribution. Since temperature is constant, the energy due to thermal motion may be assumed to be constant in all the systems. In many cases, specifically for the case of charged or highly polar solutes, electrostatic forces play the dominant role. The free energy of solution for the six solutes in different media is computed by summing up the component energies. These values are presented in Table 6. It may be pointed out that the free energy of solution for the six solutes in all the ten solvents is negative suggesting that the dissolution process is thermodynamically feasible for the six solutes in the investigated solvents. This may be due to the presence of polar groups in position 5 and heterocyclic ring in the solute. The data in Table 6 show that properties of solvents affect the free energy of solution and components of selected molecules. By comparing the free energies of solution of the isoquinoline molecules, the dissolution process is more favored in protic solvents like water and alcohols but less favorable in aromatic hydrocarbons and CCl_4. This may be due to the

Table 5
Cavitation energy of 5-substituted isoquinolines in different solvents at 298 K (kJ/mol).

Solvent	5-BIQ	5-AIQ	5-NIQ	5-MIQ	5-CIQ	5-MXIQ
H_2O	85.31	80.42	90.33	81.97	83.43	87.86
CH_3NO_2	73.10	69.09	77.74	70.17	71.43	75.36
CH_3OH	61.73	58.21	65.62	59.26	60.35	63.61
C_2H_5OH	62.90	59.38	67.04	60.39	61.52	64.90
Acetone	60.47	57.13	64.53	58.09	59.13	62.40
CH_2Cl_2	63.15	59.64	67.33	60.64	61.77	65.16
$CHCl_3$	61.31	57.92	65.45	58.88	59.97	63.27
Toluene	68.00	64.28	72.60	65.32	66.49	70.22
C_6H_6	69.17	65.36	73.77	66.41	67.62	71.39
CCl_4	63.61	60.14	67.92	61.10	62.23	65.66

Table 6
Free energy of solution of 5-substituted isoquinolines in different solvents at 298 K (kJ/mol).

Solvent	5-BIQ	5-AIQ	5-NIQ	5-MIQ	5-CIQ	5-MXIQ
H_2O	−114.88	−123.58	−136.58	−114.84	−112.08	−124.16
CH_3NO_2	−86.11	−88.78	−99.28	−85.81	−83.68	−91.79
CH_3OH	−103.38	−112.12	−124.08	−103.42	−100.95	−112.08
C_2H_5OH	−104.13	−112.66	−124.50	−104.09	−101.71	−112.79
Acetone	−79.04	−81.80	−91.75	−78.91	−76.78	−84.48
CH_2Cl_2	−80.04	−82.26	−91.50	−79.71	−77.79	−85.10
$CHCl_3$	−71.68	−73.35	−81.34	−71.14	−69.63	−75.90
Toluene	−75.49	−74.52	−82.43	−74.27	−73.06	−78.87
C_6H_6	−73.44	−72.39	−80.13	−72.22	−71.05	−76.66
CCl_4	−67.83	−67.08	−73.02	−66.16	−64.99	−70.17

large contribution of electrostatic and dispersion energies and relatively small repulsive energies and cavitation energies of the six solutes in protic solvents. In CCl_4 the solubility is less favored as evident from the small negative ΔG_{sol} for all the six solutes in this solvent. This is mainly due to the low dispersion energy contribution in CCl_4 solvent. It is interesting to note that the solution process is favorable for the six solutes in water. It may be due to the presence of intermolecular hydrogen bond between water and the heteroatom nitrogen which is a part of isoquinoline molecule. This is established by relatively large values of electrostatic and dispersion contribution for the six solutes which exceed the positive values of repulsive and cavitation energies in an aqueous medium. Further, the solution process is more favorable in solvents with higher Abraham's hydrogen bond acidity (α) and basicity (β) values. This can be inferred by comparing the values of free energy of solution (Table 6) and hydrogen bond acidity and basicity values (Table 1). If we compare the values of ΔG_{sol} of different solutes in a given solvent, we find that the solubility is favored in the order, 5-NIQ > 5-MXIQ ≈ 5-AIQ > 5-BIQ ≈ 5-MIQ ≈ 5-CIQ. Thus, the presence of highly polar groups at position 5 of isoquinoline molecule enhances the solubility in a given solvent. Plots of free energy of solution against dielectric constant for the six systems are depicted in Fig. 5. These plots indicate that the free energy of solution is negative for all the six solutes in all the solvents investigated. Further, the negative value increases with an increase in ε of the solvent. It may pointed out that in the region of ε values 25–35 for all solutes the dissolution process is favored in alcoholic solvents.

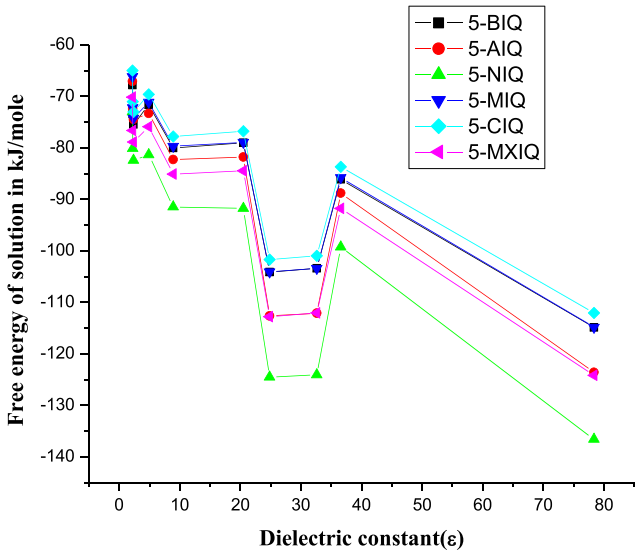

Fig. 5. Plot of free energy of solution of 5-substituted isoquinolines vs dielectric constant of solvents.

Table 7
Induced dipole moments (Debye units) of 5-substituted isoquinolines in different media at 298 K.

Solvent	5-BIQ	5-AIQ	5-NIQ	5-MIQ	5-ClQ	5-MXIQ
H_2O	3.57	4.59	6.03	4.42	3.57	5.21
CH_3NO_2	3.31	4.32	5.72	4.16	3.32	4.86
CH_3OH	3.52	4.55	6.00	4.38	3.53	5.15
C_2H_5OH	3.50	4.52	5.97	4.35	3.51	5.12
Acetone	3.28	4.29	5.68	4.12	3.28	4.82
CH_2Cl_2	3.19	4.19	5.57	4.02	3.20	4.71
$CHCl_3$	3.08	4.05	5.44	3.89	3.09	4.56
Toluene	2.87	3.80	5.18	3.64	2.87	4.29
C_6H_6	2.84	3.78	5.15	3.63	2.85	4.26
CCl_4	2.84	3.77	5.14	3.62	2.85	4.26

Solvation alters the electrostatic properties of a solute by changing its geometry and by polarizing its charge distribution [27]. The polarization effect by the solvent is reflected by the change in the molecular dipole moment of the solute, when it moves from the gas phase into a solution. Induced dipole moments for the six isoquinoline molecules in ten tested solvents are calculated by the B3LYP method with 6-311++G(d,p) basis set and the values are given in Table 7. From the values of the induced dipole moment, we observe that the solvation effect leads to the systematic increase in the induced dipole moment value. Fig. 6 contains the plot of induced dipole moment against the dielectric constant of solvent. The induced dipole moment of a given solute is high in a solvent of high dielectric constant and less in a solvent with low dielectric constant. In a given solvent, 5-nitroisoquinoline has a high induced dipole moment suggesting that solute–solvent interaction is high in this solute molecule. It may be due to highly polar nature of nitro group.

4. Conclusions

The polarizable continuum model (PCM) is used to investigate the solvation of six isoquinoline derivatives in ten solvents with a wide range of dielectric constants. The B3LYP method with 6-311++G(d,p) basis set was employed and GUASSIAN 03 program was used. We report the results obtained in the computation of electrostatic, dispersion and repulsive interaction components of Gibb's free energy of solvation along with cavitation energies for these systems. The induced dipole moments of these three compounds are also calculated for six solutes in all the ten solvents. The electrostatic interaction contribution to the free energy can be satisfactorily correlated with the dielectric constant of the solvent. Dispersion energy in all the systems is influenced by the polarizability of the solvent, which in turn depend upon its molecular size. There is a satisfactory correlation between the repulsion energy and refractive index of the solvent. The cavitation energy of the six isoquinoline derivatives in different solvents can be correlated with the macroscopic surface tension of the solvent. The data for free energies of solution of six isoquinoline compounds in ten solvents indicate that the dissolution process is more favored in water, alcohols and nitromethane but less favorable in aromatic hydrocarbons and CCl_4. Induced dipole moments for the six isoquinoline derivatives in ten chosen solvents are reported and discussed.

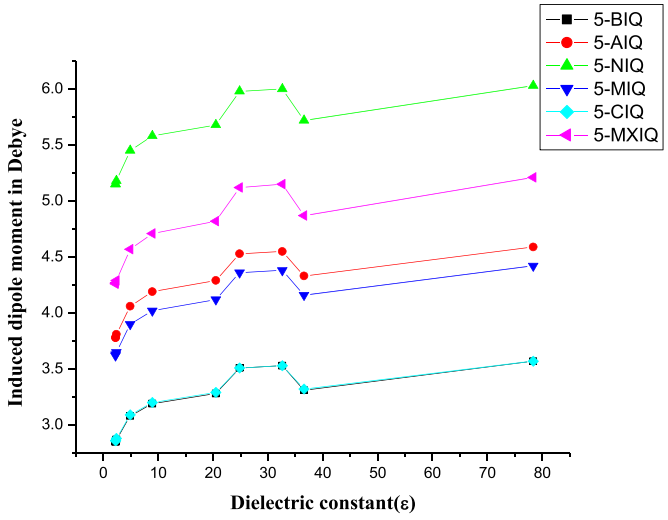

Fig. 6. Plot of induced dipole moment of 5-substituted isoquinolines vs dielectric constant of various solvents.

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