



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.

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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–H₂O₂ 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 $[F(\epsilon)]$ which is a function

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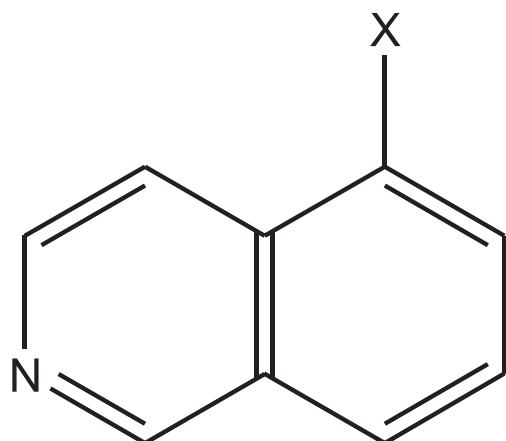


Fig. 1. General structure of 5-substituted isoquinolines. X = Br, NH₂, NO₂, CH₃, Cl, OCH₃.

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

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

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

Table 1
Solvent descriptors.

Solvent	ϵ	n	$\gamma/\text{dyn cm}^{-1}$	α	β	r/nm
H ₂ O	78.35	1.33	71.81	0.82	0.35	0.277
CH ₃ NO ₂	36.56	1.38	52.58	0.06	0.31	0.431
CH ₃ OH	32.63	1.33	22.12	0.43	0.47	0.371
C ₂ H ₅ OH	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 ₂ Cl 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 ₆ H 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.

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-ClIQ 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 CCl₄ 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 be 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-ClIQ	5-MXIQ
H ₂ O	−39.81	−51.73	−60.93	−41.53	−39.60	−46.84
CH ₃ NO ₂	−18.69	−24.21	−31.49	−19.99	−18.57	−22.42
CH ₃ OH	−38.27	−49.77	−58.51	−39.81	−38.06	−45.00
C ₂ H ₅ OH	−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 ₂ Cl 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 ₆ H 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

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