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Quantum mechanical study of solvation analysis on some nitrogen containing heterocyclic compounds

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ABSTRACT

Quantum mechanical investigation has been carried out using B3LYP procedure with 6-311++G(d,p) basis set for quinazoline (QH), quinazoline 4(3H)one (QK), 2-(mercapto) quinazoline-4(3H)one (QM), 2-(chloromethyl) quinazoline-4(3H)one (QC) and 2-(bromomethyl) quinazoline-4(3H)one (QB) in ten solvents to compute free energy of solution and its components by polarizable continuum model (PCM) analysis. The solvents selected have 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 five systems. The induced dipole moments calculated for the five compounds in ten solvents are reported. The interaction energies of the systems are discussed in terms of dielectric constant, index of refraction and surface tension of the solvents. The structural effect on different components of free energy of solution of quinazolines is investigated.

1. Introduction

Quinazoline derivatives belong to the N-containing heterocyclic compounds and they have caused universal concerns due to their widely and distinct biopharmaceutical activities. Researchers have already determined many therapeutic activities of quinazoline derivatives, including anti-cancer [1–4], anti-inflammation [5,6], anti-bacterial [7–10], analgesia [5,9], anti-virus [11], anti-cytotoxin [12], anti-spasm [9,13], anti-tuberculosis [14], anti-oxidation [15], antimalarial [16], anti-hypertension [17], anti-obesity [18], anti-psychotic [19], anti-diabetes [20], etc. Medicinal chemists synthesized a variety of quinazoline compounds with different biological activities by installing various active groups to the quinazoline moiety using developing synthetic methods. And the potential applications of the quinazoline derivatives in fields of biology, pesticides and medicine have also been explored.

Bioavailability depends on several factors, drug solubility in an aqueous environment and drug permeability through lipophilic membranes being the important ones [21]. Thus, solubility in different solvents is an important parameter for assessing the bioavailability of pharmaceutically important organic compounds as well as in the synthesis of these compounds. Realizing the importance of the quinazoline derivatives we carried out solvation analysis of five quinazoline compounds. The standard state free energy of solvation is a fundamental quantity that describes the energy of interaction between a solute and solvent molecules [22]. One of the simplest methods to perform solvation analysis is the polarizable continuum model (PCM). This model envisages a solute in a cavity formed by the union of spheres centered on each atom. The procedures provide computation of the electrostatic interaction of the solute with the apparent surface charges as well as cavitation, dispersion and repulsion contribution [23,24]. PCM was first proposed by Miertus, Scrocco and Tomasi [25] and it has proved to be a reliable tool for the description of electrostatic solute–solvent interactions [26–31]. In this paper, we report the results obtained in the quantum mechanical study of solvation of quinazoline derivatives by PCM analysis and correlated the free energy of solution and its components with the physical properties of solvent.

2. Method of computation

The molecular structures are optimized and the optimized structures are solvated with the solvent of various dielectric constants. The physical properties such as dielectric constant, refractive index, and macroscopic surface tension of solvents are listed Table 1. Computation has been performed with the B3LYP method with 6-311++G(d, p) basis set to interpret the solvent effect on the behavior of the solute molecules [32]. The computer program GAUSSIAN03 [33] was used for this purpose. The general structure of the five quinazolines and its derivatives used in the present investigation is depicted in Fig. 1. In the correlation of free energy of solution and electrostatic

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Table 1
Solvent descriptors.

Solvent	D	n	γ	α	β	F(D)
H_2O	78.35	1.33	71.99	0.82	0.35	17.38
CH_3NO_2	36.56	1.38	37.48	0.48	0.41	49.36
CH_3OH	32.63	1.33	22.12	0.43	0.47	37.02
C_2H_5OH	24.85	1.36	31.62	0.37	0.48	51.87
Acetone	20.49	1.36	33.77	0.04	0.49	63.63
CH_2CL_2	8.93	1.37	27.33	0.10	0.05	46.33
$CHCL_3$	4.90	1.45	26.53	0.15	0.02	45.59
Toluene	2.37	1.50	40.20	0	0.14	33.36
C_6H_6	2.27	1.50	40.62	0	0.14	26.52
CCL_4	2.23	1.46	38.04	0	0	28.20

D — dielectric constant at 298 K.
n — index of refraction at optical frequencies at 298 K.
γ — macroscopic surface tension at a liquid air interface in dyne/cm at 298 K.
α — Abraham hydrogen bond acidity.
β — Abraham hydrogen bond basicity.
F(D) — polarizability function in cc/mol.

interaction energy we used the polarizability which is a function of dielectric constant and these values are calculated using Claussius–Mosotti equation

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

where, D = dielectric constant, M = molar mass and ρ = density

3. Results and discussion

In the fast growing research on novel anticancer agents with 4-anilinoquinazoline scaffolds, a series of novel 2-chloromethyl-4(3H)-quinazolinones were needed as key intermediates. 2-Chloromethyl-4(3H)-quinazolinones are valuable intermediates in the preparations of a wide range of biologically active compounds such as anticancer, anti-inflammatory and hedgehog antagonist agents [34–37]. Solvation analysis and free energy of solution data of pharmaceutically important complex solutes in different solvents are useful for synthetic organic chemists as well as biochemists. It gives an idea about the solute–solvent interaction and it can be related to the work which necessarily builds up a solute in the solvent environment. The solvation effects of quinazoline derivatives are investigated using ab initio method by the B3LYP method with 6-311++G(d, p) basis set. For this purpose the components of free energy of solution, namely, electrostatic interaction, dispersive energy, repulsive energy, and cavitation energy are computed. These quantities typically converge quickly during a simulation and thus can provide a good assessment of the computational approaches in describing solvent–solute interaction [38]. The induced dipole moments are also calculated for the solute molecules in order to correlate solvation effect with the properties of the solvent.

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 [32]. The electrostatic energy values are computed in ten solvents and presented in Table 2. 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 five quinazoline compounds. Thus, the electrostatic energy values are relatively high in polar solvents (water, nitro methane, methanol, ethanol and acetone) for the five solutes. In solvents like water and alcohols there is a possibility of intermolecular hydrogen bonding which is also a type of strong dipole–dipole interaction. This may be the reason for the high electrostatic interaction of the quinazoline derivatives in water and alcoholic solvents. The data in Table 2 suggest that the electrostatic contribution in a given solvent depends on the structure of the solute. In a given solvent, QK has higher electrostatic energy than QH. This may be due to the presence of polar keto group in the pyrimidine ring of quinazoline. It is interesting to note that the presence of substituent in quinazolin-4(3H)one reduces the electrostatic energy. Thus, three solutes QM, QC and QB have smaller electrostatic interaction than QK. Plots of electrostatic energy against dielectric constant for the five 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 dielectric

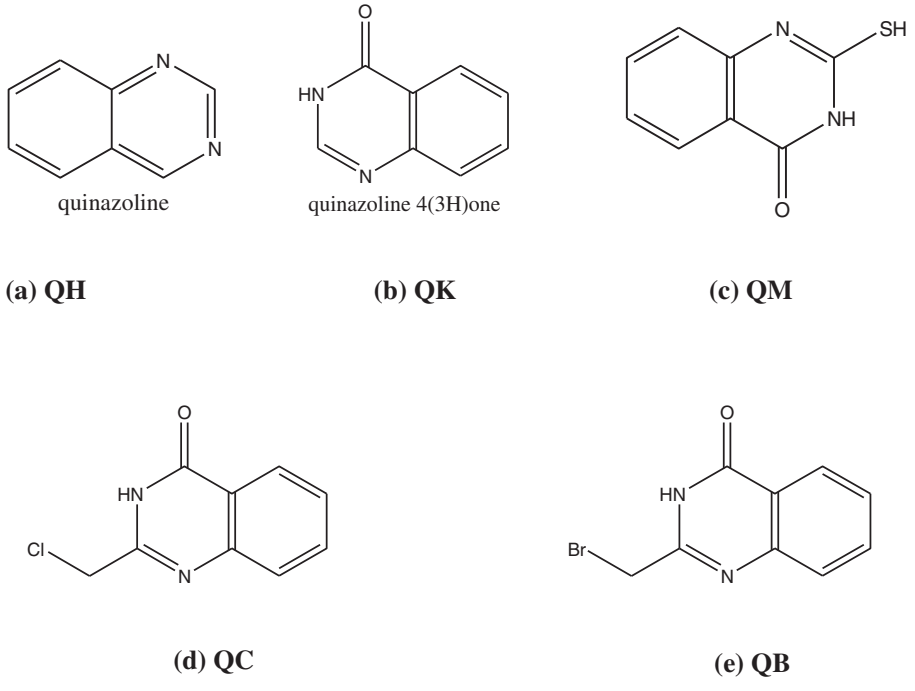

Fig. 1. Structures of quinazoline derivatives.