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Studies on free energy and its components of 2-Phenylindole and its derivatives

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Abstract

Free energy of solvation plays an important role in solvation analysis. Quantum mechanical studies are used to calculate free energies and thermodynamic quantities like cavitation enthalpies. Solvation analysis is done on 2-Phenylindole, Methyl 2-Phenylindole and Ethyl 2-Phenylindole with a set of protic and aprotic solvents. The systematic comparisons of the free energies and its components are carried out from the self-consistent field. The dipole moments and induced dipole moments are calculated and discussed.
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1. Introduction

2-Phenylindole and its derivatives are widely used in industries like chemical and pharmaceutical industries. They are used as medicine for the treatment of adverse conditions of central nervous systems, a photo conductor on electro-photography, anti-estrogenic pharmaceutical agents and also intermediate products in various chemical reactions like nitration, lipid peroxidation, acid induced reactions and electron transfer reactions [1–3].

The solvation models are widely used to predict the solvent effects including free energies of solvation. Quantum mechanics is coupled with Monte Carlo or Molecular dynamics simulations offer the opportunity to study chemical process in solutions and in enzymes [4–7]. Solvent effects can significantly influence the function and reactivity of the organic molecules. The theoretical study of solvation is made very difficult by the very large molecules involved, with the difficulty proceeding from the problem of the simultaneous evaluation of their mutual interactions. Even though various methods such as statistical Monte Carlo and Molecular dynamics simulations to model solute–solvent interactions explicitly, the continuum solvation models that treat the solvent as a structureless medium with a characteristic dielectric constant have been successfully used for studying solvent effects. The polarizable continuum solvation model (PCSM) is a more sophisticated method, which envisages a solute in a cavity formed by the union of spheres centred on each atom. This model also includes a more exact treatment of the electrostatic interactions with the surrounding medium as the electrostatic

Table 1
Solvent descriptors

Solvent	ε	n	γ	α`	β
H_2O	78.35	1.33	71.99	0.82	0.35
CH_3OH	32.63	1.33	22.12	0.43	0.47
C_6H_5Cl	5.62	1.52	32.69	0	0.17
$CHCl_3$	4.90	1.45	26.53	0.15	0.02
C_6H_6	2.27	1.50	40.62	0	0.14
CCl_4	2.23	1.46	38.04	0	0

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Table 2
Electrostatic interactions of the Phenylindole and its derivatives in kJ/mol

Solvent	2-Phenylindole	Methyl 2-Phenylindole	Ethyl 2-Phenylindole
1. H_2O	−33.72	−32.76	−32.51
2. CH_3OH	−31.97	−31.13	−30.88
3. C_6H_5Cl	−23.18	−22.64	−22.26
4. $CHCl_3$	−24.39	−57.45	−100.25
5. C_6H_6	−12.55	−12.18	−11.97
6. CCl_4	−12.43	−12.05	−11.84

Table 3
Dispersion energies of the Phenylindole and its derivatives in kJ/mol

Solvent	2-Phenylindole	Methyl 2-Phenylindole	Ethyl 2-Phenylindole
1. H_2O	−73.09	−78.87	−84.56
2. CH_3OH	−72.97	−78.83	−84.39
3. C_6H_5Cl	−72.76	−78.66	−84.06
4. $CHCl_3$	−48.49	−52.43	−55.94
5. C_6H_6	−72.80	−78.70	−84.14
6. CCl_4	−72.80	−78.70	−84.14

potential of the solute generates as apparent surface charge on the cavity's surface.

The most fundamental thermodynamic quantity, characterizing solubility is the free energy of solvation. The calculation of free energies and cavitation enthalpies are performed with polarizable continuum solvation model (PCSM). A set of polar and non-polar solvents like water, CH_3OH, C_6H_5Cl, $CHCl_3$, C_6H_6 and CCl_4 was used for this solvation analysis.

2. Method of computation

The molecular structures are optimized by ab initio method [8]. The optimized geometries are solvated with the solvent of various range of dielectric constant using STO 6-31G basis set. The computer program GAMESS [9] was used for this purpose.

3. Results and discussion

Solvation analyses are done for 2-Phenylindole, Methyl 2-Phenylindole and Ethyl 2-Phenylindole with a set of polar and non-polar solvents having different dielectric constants. Free energies are calculated from STO-6-31G level of theory. The solvents exhibit wide range of dielectric constant (ε), refractive index (n), macroscopic surface tension (γ), hydrogen bond acidity parameter (α) and hydrogen bond basicity parameter (β). They are tabulated in Table 1.

Tables 2–8 show how the different characteristics as each solvent affect the free energy and its components of selected molecules. The macroscopic surface tension of a particular solvent represents the energy required to make a surface in the solvent, a contribution to the free energy of a solvation is always unfavourable. By comparing the free energies of the molecules, it is more favoured in chloroform than that of other solvents listed here. It may be because of increased favourable electrostatic interactions between the solvent and solute. For solvent chlorobenzene, the index of refraction is larger than CCl_4 and similar to benzene. In addition to that, the hydrogen bond basicity parameter of chlorobenzene is larger than that of benzene and CCl_4. However the free energy of solvation is similar to that of benzene.

For water, the free energies of the solvation of 2-Phenylindole, Methyl 2-Phenylindole and Ethyl 2-Phenylindole are significantly different from those in all other solvents because of the hydrophobic character. Therefore, in water, the solvation free energy is least favourable out of the solvents listed. Since the favourable interactions are outweighted by the hydrophobic contribution. Plots of dielectric constant vs electrostatic interaction are given in Fig. 1.

The electrostatic interaction contribution to free energy depends on the dielectric constant of the solvent [8]. Thus the electrostatic interaction increases from CCl_4 to water except in

Table 4
Repulsion energies of the Phenylindole and its derivatives in kJ/mol

Solvent	2-Phenylindole	Methyl 2-Phenylindole	Ethyl 2-Phenylindole
1. H_2O	24.69	28.28	30.17
2. CH_3OH	13.77	15.73	16.78
3. C_6H_5Cl	19.62	22.47	23.89
4. $CHCl_3$	21.13	−2773.24	−4577.51
5. C_6H_6	18.74	21.46	22.80
6. CCl_4	17.82	20.42	21.67

Table 5
Free energies of the Phenylindole and its derivatives in kJ/mol

Solvent	2-Phenylindole	Methyl 2-Phenylindole	Ethyl 2-Phenylindole
1. H_2O	0.0	0.0	0.0
2. CH_3OH	40.88	46.11	48.91
3. C_6H_5Cl	6.99	10.46	11.33
4. $CHCl_3$	−11421.77	−10643.30	−10402.68
5. C_6H_6	6.87	10.88	12.55
6. CCl_4	15.36	20.38	22.59

Table 6
Dipole moments of the Phenylindole and its derivatives in Debye

Molecule	AM1	PM3	MNDO	Ab initio
1. 2-Phenylindole	2.17	2.31	2.07	2.26
2. Methyl 2-Phenylindole	2.43	2.44	2.33	2.51
3. Ethyl 2-Phenylindole	2.49	2.49	2.37	2.54

Table 7
Induced dipole moments of the Phenylindole and its derivatives in Debye

Solvent	2-Phenylindole	Methyl 2-Phenylindole	Ethyl 2-Phenylindole
1. H_2O	2.98	3.73	3.84
2. CH_3OH	2.95	3.70	3.81
3. C_6H_5Cl	2.77	3.50	3.57
4. $CHCl_3$	3.03	4.05	7.90
5. C_6H_6	2.55	3.22	3.27
6. CCl_4	2.55	3.22	3.27

Table 8
Thermodynamic quantities of cavitations calculated at 298 K(kJ/mol)

Solvent	2-Phenylindole			Methyl 2-Phenylindole			Ethyl 2-Phenylindole		
	ΔG	ΔH	ΔS	ΔG	ΔH	ΔS	ΔG	ΔH	ΔS
i) In terms of microscopic surface tension									
H_2O	64.86	10.88	−0.18	68.87	11.57	−0.19	72.00	12.12	−0.20
CH_3OH	44.70	35.79	−0.03	47.37	38.04	−0.03	49.46	39.79	−0.03
C_6H_5Cl	52.36	49.70	−0.009	76.60	74.29	−0.008	57.86	55.26	−0.009
$CHCl_3$	43.04	43.63	0.002	45.57	46.34	0.003	47.54	48.46	−0.003
C_6H_6	48.80	60.10	0.04	51.67	63.87	0.04	53.91	66.80	0.04
CCl_4	44.43	48.87	0.01	47.03	51.91	0.02	49.06	54.29	0.02
ii) In terms of Pierotti formula									
H_2O	88.09	14.92	−0.25	96.44	16.37	−0.27	101.60	17.27	−0.28
CH_3OH	60.18	48.80	−0.04	65.74	53.49	−0.04	69.17	56.38	−0.04
C_6H_5Cl	70.21	67.78	−0.008	76.60	74.29	−0.008	80.55	78.31	−0.08
$CHCl_3$	57.63	59.36	0.006	62.86	65.02	0.007	66.09	68.52	−0.008
C_6H_6	65.41	81.90	0.06	71.37	89.75	0.06	75.05	94.60	0.07
CCl_4	59.44	66.50	0.02	64.82	72.84	0.03	68.15	76.76	0.03
iii) In terms of Sinanoglu formula									
H_2O	96.09	153.64	0.19	16.37	169.15	0.51	111.81	178.77	0.22
CH_3OH	33.18	63.67	0.10	36.17	69.41	0.11	38.02	72.97	0.12
C_6H_5Cl	22.97	18.49	−0.08	27.39	22.05	−0.02	30.12	24.25	−0.02
$CHCl_3$	22.09	16.58	−0.02	25.67	19.27	−0.02	27.90	20.94	−0.02
C_6H_6	31.11	68.27	0.12	34.91	76.62	0.14	37.27	81.81	0.15
CCl_4	28.65	62.56	0.11	32.18	70.27	0.13	34.37	75.06	0.14

$CHCl_3$. This may be due to hydrogen bond acidity and the least polarity activity of $CHCl_3$ in solution. In the case of methanol, a solvent with a similar index of refraction with large range of dielectric constant, methanol with Ethyl 2-Phenylindole afford more electrostatic interaction and this result can be attributed to a balance between solute–solvent dispersion interactions. The molecules have more favourable free energy in $CHCl_3$ than in other solvents studied here, because of increased favourable electrostatic interactions.

The dispersion energy is due to polarization of the solvent molecules by the solute molecules [10]. This polarization in turn may depend on dipole moment of the solvent molecule. From the data in Table 3, it is found that the dispersion energy is maximum of all the molecules with $CHCl_3$. Thus, the dispersion energy contribution of the 2-Phenylindole and its derivatives' minimum different solvent may be correlated with the dipole moment of the solvent. However, there is not much change in the dispersion energies in protic solvent of varying dipole moment. The refractive index of the solvent is related to the solvent's polarizability, which in turn is related to the dispersion energy of the solvent. From Fig. 2, we observe that the dispersion energy increases with the increase in the refractive index of the solvent except in chloroform. This may be due to the more electronegative atoms involved in the solvent–solute interactions.

The repulsion energy varies from one solvent to another. It has a minimum value in CCl_4 with 2-Phenylindole indicating minimum repulsion between CCl_4 and 2-Phenylindole and also

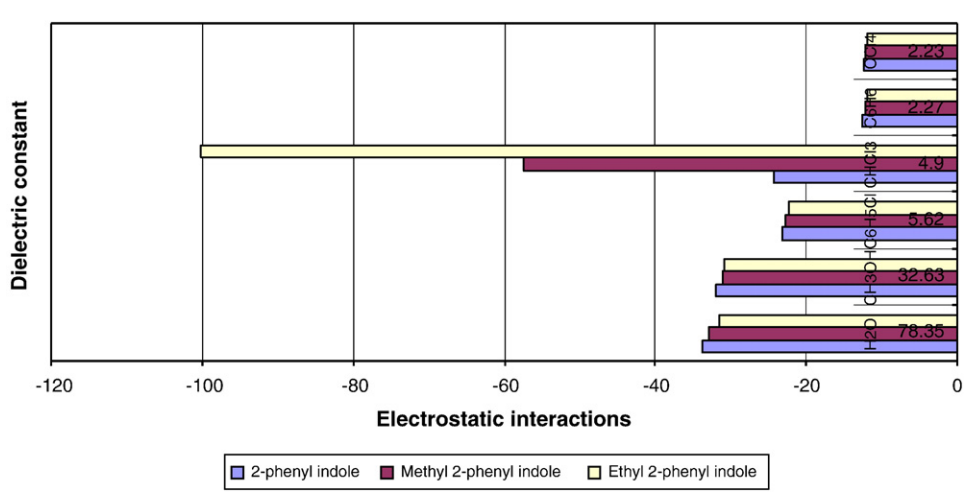

Fig. 1. Dielectric constant vs electrostatic interactions.

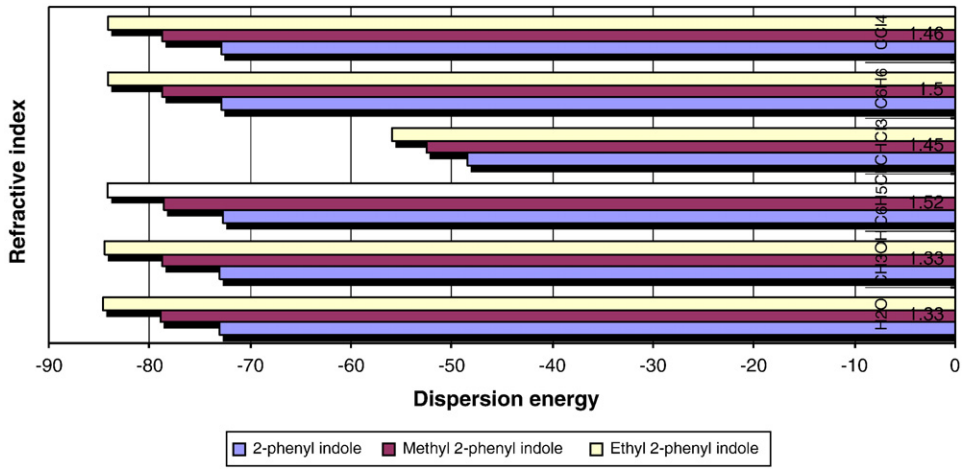

Fig. 2. Refractive index vs dispersion energy.

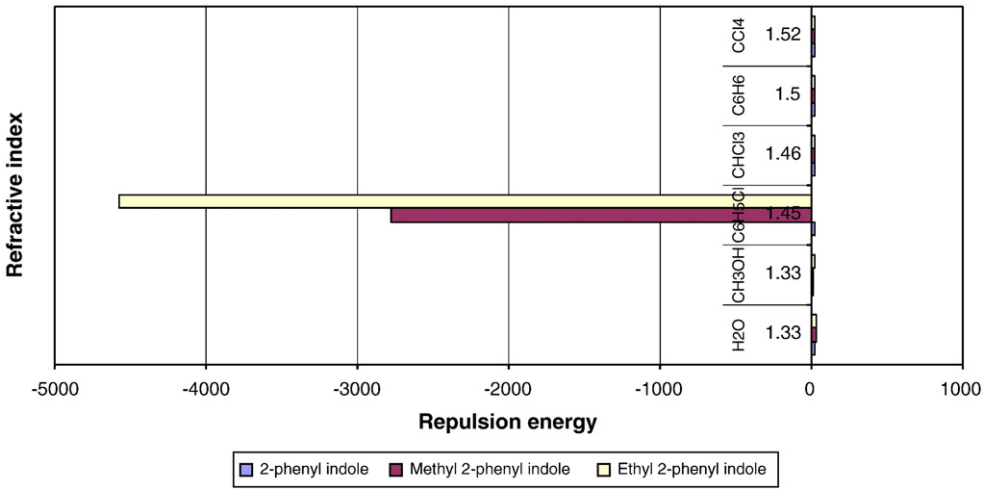

Fig. 3. Refractive index vs repulsion energy.

has a negative value in $CHCl_3$ with Methyl 2-Phenylindole and Ethyl 2-Phenylindole. This may be due to the polarizability effect of the solvent and attached methyl groups in the solute. The repulsion energy is more positive in aqueous solution. This may be due to the hydrophobic character of Phenylindole and its derivatives. By relating the refractive index of the solvents with

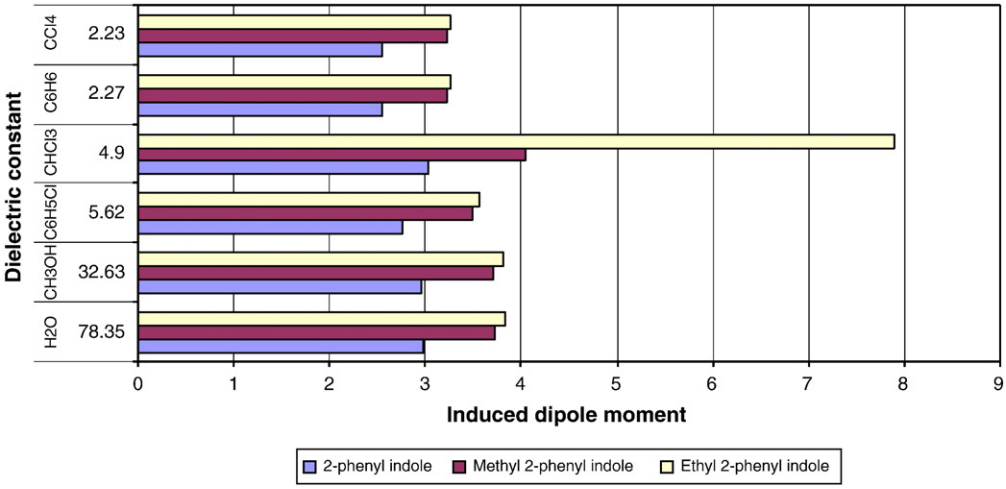

Fig. 4. Dielectric constant vs induced dipole moment.

the repulsion energy, there are uniform changes except in the chloroform. This may due to the more non-hydrogenic atoms present in the interactions. Plots of refractive index vs repulsion energy are given in Fig. 3.

Cavitation enthalpies of molecules in different solutions are the measure of enthalpy contribution to the free energy of salvation [11]. There are several methods for the calculation of cavitation thermodynamic quantities. These quantities in Table 8 obtained in the present calculations are expected to have reasonable accuracy from the formulas given by the macroscopic surface tension method, Sinanghu and Pierotti [12,13]. These three methods do not give the same value for a system. Since the assumption involved is different. The cavitation free energy is positive. The cavitation enthalpies are also positive. But the cavitation entropies are positive or negative depending on the system and method of calculation. These observations show that there is a strong interaction between solvent and solute and it is directly related to the polarity of the medium.

The range of dielectric constants leads to as much as difference in polarization energy. The polarization effect by the solvent is reflected by the change in molecular dipole moment of the solute ongoing from gas phase into solution [14,15]. Tables 5 and 6 list the dipole moments calculated by semi-empirical and ab initio methods and induced dipole moments in various solvents. These variations with dielectric constants are shown in the Fig. 4. The solvation effect leads to a systematic increase in the dipole moments which is similar to that reported in the previous calculations of other types of molecules in the present investigation. [16,17] There are appreciable changes in the dipole moment in all the solvent. However, in the case of chloroform, there is a high variation in the induced dipole moment.

4. Conclusions

We have presented the quantum mechanical solvation analysis for 2-Phenylindole; methyl and ethyl substituted 2-Phenylindole. The physical reasonability of this method is confirmed by its generality. By comparing the free energy of the molecules studied here is in the order of increasing volume, thus, the free energy tends to increase. A direct comparison of the free energies of the molecular interactions reveals the systematic tendency to increase with increasing molecular volume of the solute molecules. The calculated solute properties, like solution phase dipole moments are sensitive to the division of the solvent effects into electrostatic and others, because it is only the treated self-consistency in terms of electronic structure.

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