Solvation Analysis of Halogenated 4-Oxoimidazo[5,1-d][1,2,3,5]tetrazine-8-carboxamide

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Solvation analysis have been carried out for 3-bromomethyl-4-oxoimidazo[5,1-d][1,2,3,5]tetrazine-8-carboxamide, 3-chloromethyl-4-oxoimidazo[5,1-d][1,2,3,5]tetrazine-8-carboxamide and 3-fluoromethyl-4-oxoimidazo[5,1-d][1,2,3,5]tetrazine-8-carboxamide in polar and non-polar solvents having a wide range of dielectric constants. The test set consists of water, ethyl alcohol, methyl alcohol, chlorobenzene, chloroform, benzene and carbon tetrachloride. The physical properties of the systems, such as free energies, electrostatic interaction, cavitation energy and induced dipole moments are discussed. Quantum mechanical self consistent fields explain the properties of the compounds satisfactorily.

Key Words: Solvation analysis, Electrostatic, Free energy, Cavitation.

INTRODUCTION

The polarizable continuum model (PCM) is a more sophisticated method^{1,2}, which envisages a solute in a cavity formed by the union of spheres centered on each atom. This model also includes a more exact treatment of the electronic interaction with the surrounding medium, as the electrostatic potential of the solute generates an 'apparent surface charge' on the cavity's surface. The computational procedure divides this surface into small tesserae, on which the charges are evaluated. Typically, the spheres define the cavity are taken to be 1.2 times the van der Waals radii. A technical difficulty caused by the preparation of the solute charge density outside this cavity is dealt with by a renormalization. The solvents are characterized by its dielectric constant, surface tension, molecular size and density. The standard state free energy of solvation is a fundamental quantity that describes the energy of interaction between a solute and solvent molecules³⁻⁸. Procedures are provided not only for the computation of the electrostatic interaction of the solute with the apparent surface charges, but also for the cavitation energy⁹, dispersion and repulsion contribution to the solvation free energy¹⁰. The polarizable continuum model is extended to halogenated 4-oxoimidazo [5,1-d] [1,2,3,5]tetrazine-8-carboxamide such as 3-bromomethyl-4-oxoimidazo[5,1-d][1,2,3,5]tetrazine-8-carboxamide, 3-chloromethyl-4-oxoimidazo[5,1-d][1,2,3,5]tetrazine-8-carboxamide and 3-fluoromethyl-4-oxoimidazo [5,1-d][1,2,3,5]tetrazine-8-carboxamide.

EXPERIMENTAL

The molecular structures are optimized by *ab initio* method¹¹. The optimized geometries are solvated with solvent of various ranges of dielectric constants using HF/6-31G (d,p) basis set. The computer program Gaussian 03 W was used for this purpose¹².

RESULTS AND DISCUSSION

Electrostatic contributions in free energy: The solvation effects for the most stable conformers of each halogenated 4-oxoimidazo [5,1-d][1,2,3,5]tetrazine-8-carboxamide are investigated. For this purpose the free energy, electrostatic interaction, dispersion energy and repulsion energy of three halogenated 4-oxoimidazo[5,1-d][1,2,3,5]tetrazine-8-carboxamide in different solvents are evaluated by polarizable continuum model. The data tabulated in Tables 1-6. These quantities typically cover quickly during a simulation and thus can provide a good assessment of the computational approaches in describing solvent-solute interaction¹³. The induced dipole moments are cavitation enthalpies are also by the same model for different solvents in order to correlate the solvation effect with the properties of the solvents. The electrostatic contribution to the total solvation energy is maximum in CH₃OH. It is least in CCl₄ among the aprotic solvents. However in protic solvents, the electrostatic contribution does not correlate with the dielectric constant because the protic solvent is associated through intermolecular hydrogen bonds.

TABLE-1
FREE ENERGY OF SOLVATION OF HALOGENATED 4-OXOIMIDAZO [5,1-d] [1,2,3,5]
TETRAZINE-8-CARBOXAMIDE IN VARIOUS SOLVENTS (kJ/mol)

Solvent/solute	3-Chloromethyl-4-oxoimidazo[5,1-d] [1,2,3,5]tetrazine-8-carboxamide	3-Bromomethyl-4-oxoimidazo[5,1-d] [1,2,3,5]tetrazine-8-carboxamide	3-Fluoromethyl-4-oxoimidazo[5,1-d] [1,2,3,5]tetrazine-8-carboxamide
H ₂ O	-3060692.042	-8601560	-2115427
C ₂ H ₅ OH	-3060706.094	-8601574	-2115440
CH ₃ OH	-3060707.918	-8601576	-2115443
C ₆ H ₅ Cl	-3060674.493	-8601542	-2115409
C ₆ H ₆	-3060650.633	-8601519	-2115384
CHCl ₃	-3060675.002	-8601543	-2115409
CCl ₄	-3060646.497	-8601514	-2115380

TABLE-2
DISPERSION ENERGY OF SOLVATION OF HALOGENATED 4-OXOIMIDAZO [5,1-d]
[1,2,3,5]TETRAZINE-8-CARBOXAMIDE IN VARIOUS SOLVENTS (kJ/mol)

Solvent/solute	3-Chloromethyl-4-oxoimidazo[5,1-d] [1,2,3,5]tetrazine-8-carboxamide	3-Bromomethyl-4-oxoimidazo[5,1-d] [1,2,3,5]tetrazine-8-carboxamide	3-Fluoromethyl-4-oxoimidazo[5,1-d] [1,2,3,5]tetrazine-8-carboxamide
H ₂ O	-20.44	-21.08	-19.01
C ₂ H ₅ OH	-18.02	-18.59	-16.76
CH ₃ OH	-17.62	-18.18	-16.38
C ₆ H ₅ Cl	-19.68	-20.32	-18.30
C ₆ H ₆	-19.50	-20.12	-18.13
CHCl ₃	-15.56	-16.08	-14.45
CCl ₄	-15.77	-16.30	-14.64

TABLE-3
REPULSION ENERGY OF SOLVATION OF HALOGENATED 4-OXOIMIDAZO [5,1-d]
[1,2,3,5] TETRAZINE-8-CARBOXAMIDE IN VARIOUS SOLVENTS (kJ/mol)

Solvent/solute	3-Chloromethyl-4-oxoimidazo[5,1-d] [1,2,3,5]tetrazine-8-carboxamide	3-Bromomethyl-4-oxoimidazo[5,1-d] [1,2,3,5]tetrazine-8-carboxamide	3-Fluoromethyl-4-oxoimidazo[5,1-d] [1,2,3,5]tetrazine-8-carboxamide
H ₂ O	1.56	1.61	1.37
C ₂ H ₅ OH	1.31	1.36	1.14
CH ₃ OH	1.30	1.34	1.13
C ₆ H ₅ Cl	2.14	2.22	1.86
C ₆ H ₆	2.23	2.31	1.95
CHCl ₃	1.07	1.12	0.91
CCl ₄	1.09	1.15	0.93

TABLE-4
CAVITATION ENERGY OF SOLVATION OF HALOGENATED 4-OXOIMIDAZO [5,1-d]
[1,2,3,5]TETRAZINE-8-CARBOXAMIDE IN VARIOUS SOLVENTS (kJ/mol)

Solvent/solute	3-Chloromethyl-4-oxoimidazo[5,1-d] [1,2,3,5]tetrazine-8-carboxamide	3-Bromomethyl-4-oxoimidazo[5,1-d] [1,2,3,5]tetrazine-8-carboxamide	3-Fluoromethyl-4-oxoimidazo[5,1-d] [1,2,3,5]tetrazine-8-carboxamide
H ₂ O	25.92	26.34	25.10
C ₂ H ₅ OH	18.93	19.21	18.35
CH ₃ OH	18.61	18.89	18.03
C ₆ H ₅ Cl	22.28	22.62	21.61
C ₆ H ₆	20.78	21.09	20.14
CHCl ₃	18.41	18.68	17.85
CCl ₄	19.08	19.36	18.50

TABLE-5
INDUCED DIPOLE MOMENT OF HALOGENATED 4-OXOIMIDAZO [5,1-d] [1,2,3,5]
TETRAZINE-8-CARBOXAMIDE IN VARIOUS SOLVENTS (DEBYE)

Solvent/solute	3-Chloromethyl-4-oxoimidazo[5,1-d] [1,2,3,5]tetrazine-8-carboxamide	3-Bromomethyl-4-oxoimidazo[5,1-d] [1,2,3,5]tetrazine-8-carboxamide	3-Fluoromethyl-4-oxoimidazo[5,1-d] [1,2,3,5]tetrazine-8-carboxamide
H ₂ O	2.4540	2.7922	2.0459
C ₂ H ₅ OH	2.4155	2.7518	2.0102
CH ₃ OH	2.4224	2.7674	2.0188
C ₆ H ₅ Cl	2.2401	2.5672	1.8356
C ₆ H ₆	2.0085	2.3167	1.6006
CHCl ₃	2.2208	2.5400	1.8094
CCl ₄	2.0056	2.3135	1.5972

TABLE-6
SOLVENT DESCRIPTIONS

Solvent/ solute	Dielectric constant (ϵ)	Refractive index (n)	Macroscopic surface tension (γ)	Molar volume (v)
H ₂ O	78.36	1.33	71.81	18.07
C ₂ H ₅ OH	24.85	1.36	31.62	46.07
CH ₃ OH	32.63	1.33	22.12	40.70
C ₆ H ₅ Cl	5.62	1.52	32.69	101.79
C ₆ H ₆	2.24	1.50	28.18	88.91
CHCl ₃	8.93	1.37	27.33	64.50
CCl ₄	2.23	1.46	38.04	90.60

The trend in electrostatic energy can be explained as follows. Among the halogens, chlorine is the most electronegative atom and hence the electrostatic interaction is large. Bromine is less electronegative and the interaction is also less. However, iodine is a large atom and its polarizability is large. This follows from the large value of the dispersion energy in the case of 3-bromomethyl-4-oxoimidazo[5,1-d][1,2,3,5]-tetrazine-8-carboxamide. The same reason accounts for a large induced dipole moment.

Dispersion energy: The dispersion energies are due to polarization of the solvent molecules by the solute molecules. This polarization, in turn, may depend on the dipole moment of the solvent molecule. From the data in Table-2, it is found that the dispersion energy of halogenated 4-oxoimidazo[5,1-d][1,2,3,5]tetrazine-8-carboxamide is lower in CHCl₃, while it is larger in H₂O, which has higher dipole moment. Thus the dispersion energy of halogenated 4-oxoimidazo[5,1-d][1,2,3,5]tetrazine-8-carboxamide in different solvents may be correlated with the dipole moment of the solvent. However, there is not much change in the dispersion energies in protic solvents of varying dipole moment. Plots of the dielectric constant *versus* dispersion energy for the three compounds are given in Fig. 1.

Fig. 1. Dielectric constant vs. dispersion energy

Repulsion energy: The repulsion energies of halogenated 4-oxoimidazo[5,1-d][1,2,3,5]tetrazine-8-carboxamide in different solvents are given in Table-3. This value also indicated that the dielectric constant as well as the molecular size of the solvent molecules determine the repulsive energies. This is

supported by the higher values of the repulsion energies of the halogenated 4-oxoimidazo[5,1-d][1,2,3,5]tetrazine-8-carboxamide in C₆H₆ compared to protic solvents chosen in the present investigation. Plots of the dielectric constant *vs.* repulsion energy for the three compounds are given in Fig. 2.

Fig. 2. Dielectric constant vs. repulsion energy

Prediction of dipole moment: Dipole moments are more sensitive to details of the model, because the non-electrostatic effects are not treated self consistently¹⁴. The dipole moments are calculated based on the wave function. The changes in the dipole moments are based on the dielectric behaviour of the solvent. The value of the dipole moments increases with the increase in dielectric constant of both molecules. But in the case of protic solvent, there is zigzag trend in dipole moment with dielectric constant. This may be due to the hydrogen bonding nature of the solvents. However, the solvation effect leads to a systematic increase in the dipole moment similar to empirical and semi-empirical calculations of other similar types of organic compounds^{15,16} (Table-5).

Cavitation energies: Cavitation energies of halogenated 4-oxoimidazo[5,1-d][1,2,3,5]tetrazine-8-carboxamide in different solutions are the measure of enthalpy contribution to the free energy of solvation. The computed values in different solutions are presented in Table-4. Table-6 contains the properties of the solvent used in present study. The cavitation enthalpies calculated by two methods give two different results.

Conclusion

The quantum mechanical solvation analyses have been carried out for halo substituted alkanes. The computed physical properties such as free energy components, electrostatic interaction, dipole moments and induced dipole moments are discussed. The dipole moment values caused by solvent-solute interaction lead to a systematic increase in all molecules studied here. The interaction between the three halogenated 4-oxoimidazo[5,1-d][1,2,3,5]tetrazine-8-carboxamide and various solvents are investigated to explain the condensed phase simulation, which will be useful for the study of solvation of the titles compounds.

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