13. Thermodynamic Studies on Molecular Interactions in Aqueous Solutions of Barbituric Acid

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Abstract

The densities, ultrasonic velocities and refractive indices of barbituric acid, 1,3-dimethyl barbituric acid and thiobarbutric acid in aqueous solutions have been measured at 37 ^{o}C. The volumetric and acoustical properties were calculated from densities and ultrasonic velocities in order to understand the interactions between barbituric acid-water, 1,3-dimethyl barbituric acid-water and thiobarbituric acid-water. The quantum chemical calculations of barbituric acid, 1,3-dimethyl barbituric acid and thiobarbituric acid in gas phase and in water performed employing GAUSSIAN 16 programme. Energies, bond lengths, IR frequencies of selected interacting groups are reported for studying the solute-solvent interactions.

Keywords: Thermodynamic properties

- Molecular interaction
- Compressibility
- Barbituric acid
- Density functional theory

Introduction

Drug-macromolecular inter-actions are an important phenomenon in physiological media such as blood, membranes, intra and extracellular fluids. The processes of drug transport, protein-binding and anaesthesia are few examples where drug and bio macromolecules appear to interact in an important and vitally significant manner. Thermodynamic properties are generally convenient parameters for interpreting solute-solvent and solute-solute interactions in the solution phase [1-6]. Fundamental properties such as enthalpy, entropy and Gibbs energy represent the macroscopic state of the system and interpretation of these macroscopic properties in terms of molecular phenomena is generally difficult. Sometimes, higher derivatives of these properties can be interpreted more effectively in terms of molecular interactions.

However, some drug effects are non-receptor mediated and are caused by the particular physical or chemical properties of the drug molecule. To firmly grasp the concepts of how desired and deleterious effects are induced in the body by a drug molecule requires an understanding of where and how these molecules interact.

The study of volumetric, acoustical and optical properties of biomolecules in aqueous and aqueous-cosolute solutions provide significant information regarding molecular interactions and hydration behaviour of these molecules. The organic salt like disodium tartarate can change the binding trends and hydration behaviour of biomolecules in solution. The changes in molecular environment and molecular interactions involved are reflected in thermodynamic properties. Interactions between drug and macromolecule are important in biophysical chemistry [7-8]. Drug-electrolyte or drug-active organic molecule interactions are significant for pharmacokinetics and pharmacodynamics. The thermodynamic properties and molecular interactions in aqueous solutions of drug in presence of electrolytes and other cosolutes have been studied [9-13]. The systems involving different interactions including hydrogen bonding interactions has applications in different fields.

The densities, ultrasonic velocities and refractive indices of barbituric acid, 1, 3-dimethyl barbituric acid and thiobarbituric acid (0.02-010 $mol \cdot kg^{-1}$) in aqueous solutions have been measured at 37 ^{o}C. The volumetric and acoustical properties were calculated from densities and ultrasonic velocities in order to understand the interactions between barbituric acid-water, 1, 3-dimethyl barbituric acid-water and thiobarbituric acid-water. The quantum chemical calculations of barbituric acid (BA), 1, 3-dimethyl barbituric acid (1,3-DMBA) and thiobarbituric acid (TBA) in gas phase and in water performed employing GAUSSIAN 09 programme. Energies, bond lengths, IR wave numbers of selected interacting groups are reported for studying the solute-solvent interactions.

Experimental

Solutions of BA, 1, 3-DMBA and TBA in water were prepared in double distilled water using an analytical grade balance, Anamed (Model AA-2200, ±0.0001 g). Densities were measured using graduated pycnometer in triplicate for each solution. The ultrasonic velocities were measured using ultrasonic interferometer (M-F05, Mittal Enterprises) at frequency 2 ± 0.0001 MHz. Temperature of solutions was maintained by electronically controlled thermostatic water bath (±0.1 K). Refractive indices were measured using Cyber LAB-Cyber Abbe

Refractometer (*Amkette Analytics*, ±0.0002, 1.3000 to 1.7000). We have used the purified drug molecules directly from different source and detail is as given in Table **1**.

Theoretical

Isentropic compressibility κ_s is calculated from density and ultrasonic velocity [14,15] using Equation (1)

$$\kappa = \frac{1}{u\rho} \quad (1)$$

For solvent and solvent mixture, the isentropic compressibility is

$$\kappa_0 = \frac{1}{u_0^2 \rho_0} \quad (2)$$

Specific acoustic impedance (Z) is calculated using Equation (3).

$$Z = u\rho \quad (3)$$

Relative association (R_A) is calculated using Equation (4).

$$R_A = \frac{\rho}{\rho_0} \times \left(\frac{u_0}{u} \right)^{1/3} \quad (4)$$

Where, ρ_0 is density of solvent and ρ is density of solution (kg·m^{-3}), u_o is ultrasonic velocity of solvent and u is ultrasonic velocity of solution (m·s^{-1}), κ_s and κ_0 are isentropic compressibilities of solution and solvent respectively (Pa^{-1}).

Computational Study

The quantum chemical calculations are performed employing GAUSSIAN 16 programme [16]. The geometries of BA, 1,3-DMBA and TBA in gas phase and in water optimized using density functional calculations using PCM model at B3LYP/6-31G(d) basis set [17,18]. In order to understand the interactions between BA, 1,3-DMBA and TBA and Water, the calculations were performed for BA, 1,3-DMBA and TBA in water in presence of Density Functional Theory (DFT).

Results and Discussion

Measured densities, ultrasonic velocities and refractive indices and calculated isentropic compressibility, specific acoustic impedance and relative association of BA, 1, 3-DMBA and TBA at 37 ^{o}C are reported in Table **2**. The density, ultrasonic velocity and refractive index increases with increase in the concentration of BA, 1, 3-DMBA and TBA which is due to the increase in the solute-solvent interactions between BA, 1, 3-DMBA and TBA and water. Further,

the isentropic compressibility of solution decreases with increase in the concentration of BA, 1, 3-DMBA and TBA which indicates the solution becomes compressible with increase in the concentration of BA, 1, 3-DMBA and TBA. The molecular interactions between BA, 1,3-DMBA and TBA and water like hydrogen bonding interactions, dipole-dipole interactions in solution strengthens with BA, 1,3-DMBA and TBA concentration and solution becomes tight which leads to decrease in the compressibility of solution. The decrease in κ_s with concentration of BA, 1, 3-DMBA and TBA indicates that water molecule around polar groups in BA, 1, 3-DMBA and TBA are less compressible than bulk [19] due to hydrophilic-hydrophilic interactions [20]. The specific acoustic impedance and relative association support the solute-solvent interactions and strengthening of these interactions with BA, 1, 3-DMBA and TBA concentration.

The optimized geometrical structures of BA, 1,3-DMBA and TBA in gas phase and in water at B3LYP/6-31G(d) basis set are shown in Figure **1-3** and the geometrical parameters are reported in Table **S1-3**. Energies and dipole moments of BA, 1, 3-DMBA and TBA in gas phase and in water at B3LYP/6-31G (d) basis set are reported in Table **3**.

The energy of BA, 1, 3-DMBA and TBA decreased by -9.0434, -7.17 and -11.4712 from gas phase to water and these molecules are stabilized. This stabilization of these molecules in water is due to solvation through solute-solvent interaction. The solute-solvent interactions like hydrogen bonding interactions, dipole-dipole interactions between barbituric acid or 1,3-dimethyl barbituric acid or thiobarbituric acid and water molecule hence stabilize the drug molecules in water has been occur. The change in the dipole moment of the molecules from gas phase to water indicates the solute-solvent interactions have reported. The IR spectra of BA, 1, 3-DMBA and TBA (solid, Gas and in water) are recorded and shown in Figure **S1-12**.

The theoretical IR spectra of BA, 1,3-DMBA and TBA in gas phase and in water at B3LYP/6-31G(d) basis set are given in Figure **S1-12**. The shift in the wave number values (Table **4**) of important vibrations like >C=O, >N-H in BA, >C=O in 1,3-DMBA and –O-H, -S-H in TBA clearly indicates the interactions between water and BA.

Fig. 1. Optimized structure of barbituric acid in water using PCM model at DFT b3lyp/6-31g(d) basis set.

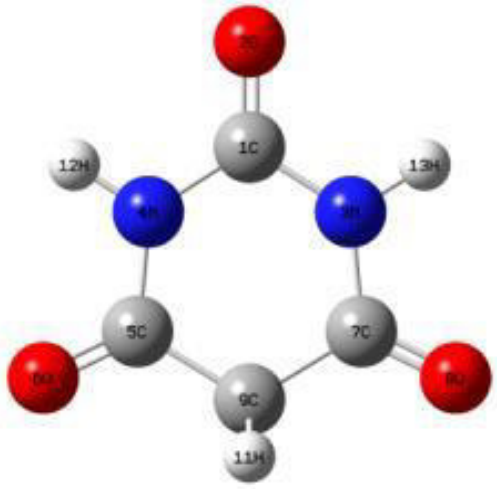


Fig. 2. Optimized structures of 1,3-dimethyl barbituric acid in water using PCM model at DFT b3lyp/6-31g (d) basis set.

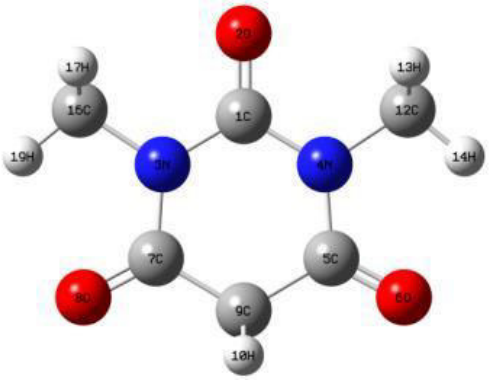


Fig. 3. Optimized structures of thiobarbituric acid in water using PCM model at DFT b3lyp/6-31g (d) basis set.

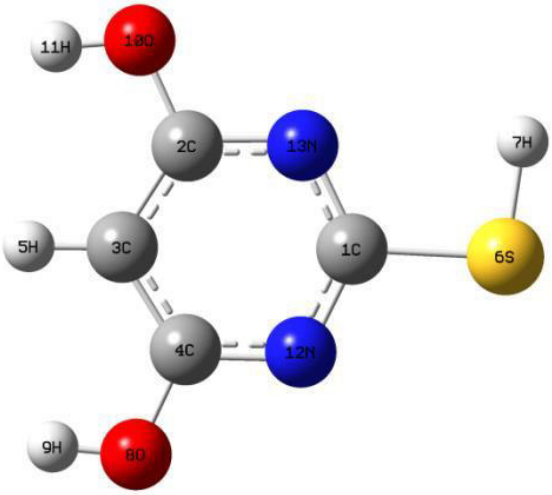


Table 1. Specification of chemicals

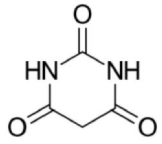
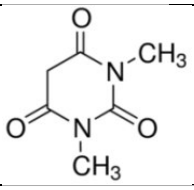
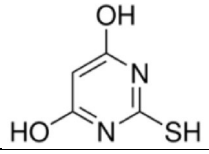
Name of Chemical	Molar mass, g·mol^{-1}	Source	Structure	Formula	Mass Fraction Purity
Barbituric acid (BA)	128.09	HiMedia		$C_4H_4N_2O_3$	≥98.00%
1,3-dimethyl barbituric acid (DMBA)	156.14	Sigma-Aldrich		$C_6H_8N_2O_3$	≥98.00%
Thiobarbituric acid (TBA)	144.15	Sigma-Aldrich		$C_4H_4N_2O_2S$	≥98.00%

Table 2. Measured densities, ultrasonic velocities and refractive indices and calculated isentropic compressibility, specific acoustic impedance and relative association of barbituric acid, 1,3-dimethyl barbituric acid and thiobarbituric acid at 37 °C.

m mol·kg^{-1}	ρ kg·m^{-3}	u m·s^{-1}	n	K_S ×10^{-10} m^{-2}·N^{-1}	Z ×10^6 kgm^{-2}s^{-1}	R_A
BA + Water						
0.0000	993.37	1528.90	1.3312	4.3066	1.519	1.0000
0.0202	994.42	1535.22	1.3315	4.2667	1.527	0.9997
0.0404	995.39	1537.41	1.3318	4.2504	1.530	1.0002
0.0607	996.34	1539.27	1.3322	4.2361	1.534	1.0007
0.0810	997.27	1540.46	1.3326	4.2256	1.536	1.0014
0.1015	998.15	1542.24	1.3330	4.2121	1.539	1.0019
1,3-DMBA + Water						
0.0000	993.37	1528.90	1.3312	4.2943	1.521	1.0000
0.0202	994.26	1561.39	1.3315	4.1255	1.552	0.9939
0.0405	995.08	1562.08	1.3318	4.1185	1.554	0.9946
0.0608	995.87	1563.13	1.3320	4.1097	1.557	0.9951
0.0813	996.56	1564.17	1.3323	4.1014	1.559	0.9956
0.1019	997.17	1566.43	1.3325	4.0870	1.562	0.9957
TBA + Water						
0.0000	993.37	1528.90	1.3312	4.3066	1.519	1.0000
0.0201	994.95	1545.04	1.3315	4.2104	1.537	0.9981
0.0403	996.49	1547.13	1.3320	4.1925	1.542	0.9992
0.0606	997.95	1548.17	1.3325	4.1807	1.545	1.0004
0.0809	999.37	1549.91	1.3330	4.1654	1.549	1.0015
0.1013	1000.79	1551.87	1.3335	4.1490	1.553	1.0025

Standard uncertainties, u are u(T)=0.1 K, u(p)=±2.0 kPa, u(ρ)=0.08 kg·m^{-3}and u(m)=0.0005 mol·kg^{-3}.

Table 3. Energies and dipole moments of BA, 1, 3 -DMBA and TBA in gas phase and in water at B3LYP/6-31G(d) basis set.

System	Energy, kcal/mol	Energy difference	Dipole Moment	Dipole Moment difference
BA-GP	-307517.5877	-9.0434	0.0410	-0.0348
BA-W	-307526.6311		0.0062	
1,3-DMBA-GP	-356854.2941	-7.1700	0.7542	0.0602
1,3- DMBA -W	-356861.4641		0.8144	
TBA-GP	-510143.9823	-11.4712	5.2408	1.8052
TBA-W	-510155.4535		7.0460	

Foot note- GP=gas phase, W=water, BA=barbituric acid, 1,3-DMBA=1,3-dimethyl barbituric acid, TBA-Thiobarbituric acid.

Table 4. Theoretically calculated wave number of BA, 1,3-DMBA and TBA in gas phase and in water at B3LYP/6-31G(d) basis set

Functional group	BA		1,3-DMBA		TBA	
	Gas	water	Gas	Water	Gas	water
>C=O	1839.51	1833.05	1834.21	1815.79	-	-
>N-H	3599.30	3590.29	-	-	-	-
-O-H	-	-	-	-	3749.54	3732.91
-S-H	-	-	-	-	2712.03	2720.23

Conclusion

The volumetric, ultrasonic, optical properties of barbituric acid, 1, 3-dimethyl barbituric Acid and thiobarbituric acid in water at 37 ^{o}C have been studied. The computational and IR spectroscopic study of these molecules have also carried out. The experimental and computational studies confirmed the existence of strong solute-solvent interactions like hydrogen bonding and dipole-dipole interaction between barbituric acid or 1,3-dimethyl barbituric acid or thiobarbituric acid and water. Further, these interactions strengthen with increase in the concentration of barbituric acid or 1,3-dimethyl barbituric acid or thiobarbituric acid. The stabilization of barbituric acid or 1,3-dimethyl barbituric acid or thiobarbituric acid in water is due to solvation through solute-solvent interaction. The change in the IR frequencies from gas phase to liquid water and from solid to liquid water from computational and experimental IR frequencies of barbituric acid or 1,3-dimethyl barbituric acid or thiobarbituric acid confirmed the hydrogen bonding and dipole-dipole interaction.

Conflict of Interest

The authors declared that this article content has no conflict of interest, financial or otherwise.

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