



Computational Molecular Characterization of Thiourea and Its Derivatives

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The polarizable continuum solvation model (PCSM) analysis has been carried out for thiourea and its derivatives in polar and non-polar solvents of wide range of dielectric constants. The effects of dispersion energy, repulsion energy, cavities and the dipole moments are examined. Thermodynamical quantities of cavitations are calculated and compare the results. The polarizable continuum solvation method provides the solvation analysis and explains the properties of the compounds satisfactorily.

Key Words: *Ab initio*, Polar and non-polar solvents, Thiourea and its derivatives.

INTRODUCTION

Thiourea is reasonably anticipated to be a human carcinogen based on sufficient evidence of carcinogenicity in experimental animals¹. When administered in the drinking water, thiourea induced thyroid adenomas and carcinomas in rats of both sexes and squamous cell carcinomas of the zymbal gland in male rats.

No adequate human studies of the relationship between exposure to thiourea and human cancer have been reported¹. Thiourea occurs as white, lustrous crystals or flaky solids. It is soluble in water, ammonium thiocyanate solution and ethanol and almost insoluble in ether. When heated to decomposition, it emits toxic fumes of nitrogen oxides and sulphur oxides. Thiourea is available in the United States as a 99 % pure reagent grade. It may react violently with acrolein and is incompatible with acryldehyde, hydrogen peroxide and nitric acid².

There is a small risk of consumer exposure to thiourea in silver tarnish removers or in liquid animal glues, which have been widely replaced by woodworking glues. Thiourea has been found to occur naturally in laburnum shrubs and as a metabolite of *Verticillium alboatrum* and *Bortrylio cinerea*¹. Theoretical investigations of the physical and chemical properties of thioureas and its derivatives are very important in order to disclose the relationship between the structure, properties and performance and to help in the design and synthesis of new derivatives with improved properties.

In this paper, we reported the results obtained in the computation of electrostatic contribution of free energy of

solvation of thiourea and its derivatives namely, *n*-acetyl thiourea, 1,3-ethylene thiourea, *n*-amino thiourea using polarizable continuum solvation model (PCSM). The effects of dispersion energy, repulsion energy, cavities and dipole moments are examined. The HOMO and LUMO orbital's and the chemical reactivity parameters that arise from conceptual DFT are reported.

COMPUTATIONAL METHOD

For all the calculations, solvation analysis is done using a wide range of polar and non polar solvents, which has been performed both in the gas phase and in the solvent medium of various dielectric constants using polarized continuum model (PCM) by STO-6-31 basis set to interpret the solvent effect of the molecules. The computer program GAMESS³ was used for this purpose.

The polarizable continuum model (PCM) by Tomasi and coworkers⁴ is one of the most frequently used continuum solvation methods and has seen numerous variations over the years. The polarizable continuum model model calculates the molecular free energy in solution as the sum over three terms:

$$G = G + G + G$$

These components represent the electrostatic (es) and the dispersion- repulsion (dr) contributions to the free energy and the cavitations energy (cav). All three terms are calculated using a cavity defined through interlocking van der Waals spheres centred at atomic positions⁵. The 6.3-21G(d,p) basis set was used for the geometry optimizations and evaluations

of harmonic frequencies both in the gas phase and in aqueous solution of the thiourea. It has been found that this basis set has a remarkable ability to predict the molecular structure and properties of large systems. The electronic properties were calculated with the 6.31G(d,p) basis set. Solvation energies were computed by the integral equation formalism-polarisable continuum model. All the calculations have been performed with Gaussian 03W series of program.

RESULTS AND DISCUSSION

Cavity formation energy: The idea of formally breaking the process of transfer of a molecule from the gas phase to a liquid in two steps, first the formation of a cavity in the bulk of the liquid and then the insertion of the molecule in the cavity.

With regard to the cavity formation energy, the attempts to arrive at reliable values for G have a probability of success relatively higher than for the other terms, because the interaction potentials are simpler in this case⁵. The way to get these reliable values is based on the use of computer simulations of liquids.

Free energy of solvation: Table-1 shows 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 solvent is always unfavourable⁵. By comparing the free energies of the molecules, it is more favoured in thiourea than other derivatives.

Electrostatic interaction: The physics of the electrostatic solute-solvent interaction is simple. The charge distribution ρ of the solute, inside the cavity, polarizes the dielectric continuum, which in turn polarizes the solute charge distribution. This definition of the interaction corresponds to a self-consistent process, which is numerically solved following potential is the one that can be put in the Hamiltonian of the model. As this potential depends on the final value of ρ reached at the end of this iterative procedure, the Hamiltonian thus turns out

to be non-linear⁵. This formal aspect has important consequences in the elaboration and use of the computational results. In this model, we considered a cavity with a dielectric constant equal to 1 and an external medium with ϵ (a finite value > 1). This condition leads to

$$[\partial V] = \left(\frac{\partial V}{\partial n} \right) = \epsilon \left(\frac{\partial V}{\partial n} \right) = 0$$

where \vec{n} the outward-pointing vector is perpendicular to the cavity surface. The above equations are the basic elements to use in the elaboration of salvation methods according to standard electrostatics.

The solvation effects of thiourea and its derivatives are investigated for the most stable conformers of each thiourea. For this purpose the free energy, electrostatic interaction, dispersion energy and repulsion energy of three thiourea and its derivatives in different solvents are evaluated by polarizable continuum model. The data are presented in Tables 1-5. These quantities typically converge quickly during a simulation and thus can provide a good assessment of the computational approaches in describing solvent-solute interaction. The induced dipole moments and cavitation enthalpies are also calculated 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 for the total solvation energy which is maximum for the three thiourea and its derivatives in CHCl_3 . This may be due to the dielectric constant of CHCl_3 . It is least in C_6H_6 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.

The trend in the electrostatic energy can be explained as follows. Among the thiourea 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

TABLE-1
FREE ENERGY (kcal/mol) OF THIOUREA AND ITS DERIVATIVES

Solvents	Thiourea	N-Acetyl thiourea	1,3-Ethylene thiourea	N-Amino thiourea
CH_2Cl_2	-342955.97	-437898.18	-391180.96	-377456.84
$\text{C}_6\text{H}_5\text{NH}_2$	-342955.48	-437899.62	-391182.31	-377456.25
THF	-342955.67	-437898.23	-391181.14	-377457.98
DMSO	-342957.36	-437900.08	-391182.69	-377456.49
$\text{C}_6\text{H}_5\text{Cl}$	-342954.99	-437897.48	-391180.52	-377455.68
CH_3NO_2	-342957.29	-437900	-391182.62	-377458.38
C_7H_{16}	-342950.31	-437892.29	-391176.26	-377450.12
C_6H_{12}	-342950.44	-437892.67	-391176.18	-377450.53

TABLE-2
ELECTROSTATIC INTERACTION OF THIOUREA AND ITS DERIVATIVES IN kcal/mol

Solvents	Thiourea	N-Acetyl thiourea	1,3-Ethylene thiourea	N-Amino thiourea
CH_2Cl_2	-13.38	-15.67	-12.26	-15.73
$\text{C}_6\text{H}_5\text{NH}_2$	-12.69	-16.07	-11.62	-14.95
THF	-12.96	-14.2	-11.87	-15.26
DMSO	-15.34	-16.7	-14.1	-17.96
$\text{C}_6\text{H}_5\text{Cl}$	-12.04	-8.55	-6.97	-9.16
CH_3NO_2	-15.24	-13.22	-11.01	-14.2
C_7H_{16}	-6.11	-16.59	-14	-16.59
C_6H_{12}	-11.53	-6.83	-5.5	-7.31

TABLE-3
 DISPERSION AND REPULSION ENERGY OF SOLVATION OF THIOUREA AND ITS DERIVATIVES

Parameter	Thiourea	N-Acetyl thiourea	1,3-Ethylene thiourea	N-Amino urea
Dispersion energy	-11.64	-17.19	-15.09	-3.51
Repulsion energy	1.87	2.60	2.25	2.10

 TABLE-4
 DIPOLE MOMENT OF THIOUREA AND ITS DERIVATIVES IN kcal/mol

Solvents	Thiourea	N-acetyl thiourea	1,3-Ethylene thiourea	N-Amino thiourea
CH ₂ Cl ₂	7.1614	5.9928	7.9588	7.8426
C ₆ H ₅ NH ₂	7.0949	5.9346	7.8800	7.7702
THF	7.1213	5.9576	7.9112	7.7989
DMSO	7.3489	6.1577	8.1810	8.0462
C ₆ H ₅ Cl	67.0302	5.8781	7.8035	7.6998
C ₇ H ₁₆	6.4114	5.3446	7.0749	7.0240
C ₆ H ₁₂	6.4557	5.3824	7.1269	7.0725

 TABLE-5
 THERMODYNAMIC QUANTITY OF CAVITATION ENTHALPIES CALCULATED AT 298 K (kcal/mol)

Solvents	Thiourea		N-Acetyl thiourea		1,3-Ethylene thiourea		N-Amino thiourea	
	Pierotti ¹⁰	Sinanoglu ¹¹	Pierotti ¹⁰	Sinanoglu ¹¹	Pierotti ¹⁰	Sinanoglu ¹¹	Pierotti ¹⁰	Sinanoglu ¹¹
CH ₂ Cl ₂	6.41928	0.85769	12.30879	12.21119	7.66734	1.78311	7.02119	1.22359
C ₆ H ₅ NH ₂	10.06499	8.84256	7.7741	1.37081	12.08414	11.94982	11.03819	10.07114
THF	70.28858	-0.32271	86.77822	0.70589	85.12445	1.30717	77.43263	0.05243
DMSO	708.61795	-21.63906	864.19906	-61.61779	848.63027	0.62608	776.12151	-36.21976
C ₆ H ₅ Cl	6.69284	-0.15821	8.14724	1.16815	8.00174	1.06524	7.324	0.32553
CH ₃ NO ₂	6.80255	9.35925	8.29074	13.2854	8.14184	12.98078	7.44831	10.79116
C ₇ H ₁₆	5.88712	3.61866	7.13145	5.87044	7.00707	5.69573	6.42741	4.43991
C ₆ H ₁₂	6.50066	4.45271	7.89592	7.19087	7.7564	6.97842	7.10631	5.45135

the large value of the dispersion energy in the case of thiourea. The same reason accounts for a large induced moment.

Repulsion energy: With polarizable continuum model it is possible to collect all the charging processes into a single process, performed at the QM level with the aid of an appropriate Schrodinger equation. This unique feature of polarizable continuum model, that is, the unification of different processes into a single step (or, in other words, to treat repulsion, dispersion and electrostatic contributions on the same footing), considerably reduces the problem of couplings. In fact, in a series of different charging processes performed in sequence, one has to use, for the second process, the solvent distribution function modified by the first. There are couplings among charge processes that are neglected in this sequence and the final result depends to some extent on the chosen sequence⁶.

The theory for the repulsion term derives from the theory of the exchange term as expressed in the perturbation theory treatment of no covalent interactions. Application of perturbation theories to the description of molecular interactions is quite complex problem and the main source of this complexity derives from the additional elements in the antisymmetry operator for the electronic wave function, which gives rise to the exchange terms. The difficulties quantum mechanics finds in describing a system M interacting with others. An exact expression for exchange contributions to the interaction energy is not available. There are excellent approximations that have given good results for molecular systems of small dimensions and there is a hierarchy of descriptions introducing more and more simplifications and ending with very simple expressions. An example of this last level of accuracy is the *r* term used.

Lennard-Jonnes site-site potential: The expression used in polarizable continuum model due to Amovilli and Mennucci is based on a dissection of the exchange energy for a dimer into terms, depending on the electronic densities of the partners. The elaboration of this expression, derived for the interactions energy of two molecules, to get G uses the replacement of the electron density of the second partner (the first is the solute) with a one-electron charge distribution averaged over the whole body of the solvent. When followed by proper mathematical manipulations, this elaboration reduces the double integral over the whole space to a simple integral of the solute charge distribution lying outside the cavity C multiplied by a constant factor⁶ namely

$$G = \alpha \int \rho(\vec{r}) dr$$

$$\alpha = k\rho \frac{n}{m}$$

where the subscript M refers to the solute (and ρ indicates its electronic density). S refers to the solvent. ρ is the density of the solvent relative to density of water at 298 K and *n* and *m* are the number of valence electrons and the molecular weight of the solvent respectively. The integral in the above equation which represents the portion of solute charge lying outside the cavity, is rewritten as the difference of total solute electronic charge inside the cavity. By applying the Gauss theorem, we obtain that the internal charge is

$$\frac{1}{4\pi} \int E(s)n(s)ds$$

where \mathbf{n} is the outward unit vector perpendicular to the cavity surface at point \mathbf{s} and \mathbf{E} the solute electric field due to the electrons only.

The repulsion energies of thiourea and its derivatives in different solvents are given in Table-4. This value also indicates that the dielectric constants 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 thiourea and its derivatives in CHCl_3 compared to protic solvents chosen in the present investigation. It may be noted that the repulsion energies of the thiourea and its derivatives in aqueous solution are much greater than those in methanol. This may be due to the slight attraction between methyl group and alkyl group of the thiourea and its derivatives.

Dispersion energy: The dispersion energy term is often collected with the repulsion term into a unique term defining the so-called van der Waals contribution to the interaction energy.

The method implemented in polarizable continuum model is based on the formulation theory⁷ and on the use of dynamic polarizabilities.

The final formula of the solute solvent dispersion free energy in the usual framework of a molecular orbital description of the wave function as follows:

$$G = -\frac{\beta}{2} \sum \left(\frac{rs}{tu} \right) P(S) + -\frac{\beta}{4} \sum \left(\frac{rs}{tu} \right) PP$$

where the subscripts refer to the elements of the selected basis set $\{X\}$. The term $[rs][tu]$ has the aspect of a two-electron integral, but simply involves combinations of one-electron integrals in the following way

$$\left(\frac{rs}{tu} \right) = \frac{1}{2} \int d(\vec{s}) [V(\vec{s})E(\vec{s}) + v(\vec{s})E(\vec{s})]$$

where the integration is done on the cavity surface and V and E represent the potential and the normal component of the electric field computed at the same point surface when expressed on the chosen basis set⁶.

The P coefficients in equation for G are elements of the first order solute density matrix P expressed in the same basis set. S is the overlap matrix in the same basis and has the expression

$$\beta = \frac{(n-1)}{4\pi n(n+)}$$

where n is the refractive index of the solvent, I its first ionization potential and ω the solute average transition energy. Expression G may be rewritten in a matrix form, making use, once again of the trace operator and introducing two new matrices with integrals performed over the basis set

$$G = \text{tr} P \left[\frac{h+}{X(P)} \right]$$

where the elements of the two matrices we have here introduced have the following form:

$$(h) = -\frac{\beta}{2} \sum \left(\frac{rs}{tu} \right) (S)$$

$$(X) = \frac{\beta}{2} \sum \left(\frac{rs}{tu} \right) P$$

The integrals defining these matrix elements can be computed in a discrete form, making use of the tessellation of the cavity surface used to compute the apparent charges in polarizable continuum model continuum methods. The nature of β indicates the approximations introduced in this elaboration of the dispersion energy operators among them one is specific for the solute, the average transition energy. Because the most important transitions in polarization of molecules occur between "frontier" orbital's-the average transition energy can be approximated by defining a proper window around the energy of the highest occupied orbital.

The computational demand is higher for dispersion than repulsion as the basic integrals are more complex in the dispersion than repulsion as the basic integrals are more complex in the dispersion term, which also includes a second term (X) not present in repulsion. In addition, G turns out to be quite sensitive to the quality of the basis set to have good values of this quantity we need to use basis sets decidedly larger than those necessary for geometry optimization and for the calculations of the solvation energy.

The dispersion and repulsion energies of thiourea and its derivatives are given in Table-3. Dispersion and repulsion energy of all solvents are same, but its values vary for derivatives. This value also indicates that the dielectric constant as well as the molecular size of the solvent molecules determine the repulsive energies. 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.

Prediction of dipole moment: In the case of binary solutions chosen for the present study, the solute-solvent interaction is mainly dipole-dipole attraction. In order to express the solute-solvent interaction, the dipole moment values are calculated and presented in Table-3. The dipole moments of thiourea and its derivatives in $\text{C}_6\text{H}_5\text{Cl}$ are higher than those of other solvents. This value indicates a strong solute-solvent interaction mainly in mixtures of thiourea and its derivatives in $\text{C}_6\text{H}_5\text{Cl}$. This is also supported by higher electrostatic interaction in this medium. The geometry and charge distributions of solute particles are changed in the presence of solvent by polarizability and hence solvation alters the electrostatic properties of the solute. The polarization effect by the solvent is reflected by the change in molecular dipole moment of the solute when going from the gas phase to the solution. Such change can be easily determined once the solute wave function in the solution is obtained. This can be done using either the HF potential or the GMIP perturbation approach⁸. The solvation effect leads to a systematic increase in the dipole moment by about 32 % which is similar to that reported in previous *ab initio* and semi-empirical SCRF calculations.

Contribution of cavitation enthalpies and microscopic cavity factor: The cavitation enthalpies obtained in the present calculations are expected to have reasonable accuracy based on the formula given by sinanoglu and pierotti. These formula obtained from experimental solubility have allowed to check the adequacy of the scaled particle theory to calculate free energy. Cavitation enthalpies of thiourea and its derivatives in different solutions are the measure of enthalpy contribution to the free energy of solvation⁹. The computed values of two

TABLE-6
THERMODYNAMIC QUANTITY OF MICROSCOPIC CAVITY FACTOR CALCULATED AT 298 K (kcal/mol)

Solvents	Thiourea	N-Acetyl thiourea	1,3-Ethylene thiourea	N-Amino thiourea
CH ₂ Cl ₂	0	0.972	0.972	0
C ₆ H ₅ NH ₂	0.972	0	0	0.972
THF	0	0	0	0
DMSO	0	0	0	0
C ₆ H ₅ Cl	0	0	0	0
CH ₃ NO ₂	0.808	0.808	0.808	0.808
C ₇ H ₁₆	0.687	0.687	0.687	0.687
C ₆ H ₁₂	0.621	0.621	0.621	0.621

different methods^{10,11} are presented in Table-5. The cavitation enthalpies calculated by two methods give two different results. However, the trend is similar. Among polar solvents, the cavitation enthalpy has the highest positive values for N-acetyl thiourea in DMSO. Thus the solvation of N-acetyl thiourea in DMSO is more endothermic than in the other polar solvents. In the case of non-polar solvents, this value is more positive in aqueous solution than in CH₃NO₂. Table-6 summarizes the microscopic cavity factor of the solvent calculated at 298 K.

Conclusion

The quantum mechanical solvation analyses have been carried out for thiourea and its derivatives. The computed physical properties such as free energy components, electrostatic interaction, 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 thiourea derivatives and various solvents are investigated to explain the condensed phase simulation, which will be useful for the study of solvation of the thiourea compounds.

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