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Molecular Modelling Analyses of the Dimerization of Acetic Acid in Non-polar Solvents

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Molecular modelling analyses using molecular mechanics and semi-empirical calculations were carried out to investigate the dimerization of acetic acid in a vacuum and in solution in non-polar solvents such as carbon tetrachloride through hydrogen bonding. The dielectric constant of solvent was varied from 1 to 80 to change its nature from non-polar to highly polar. The results of calculation using both molecular mechanics and semi-empirical routines show that as the polarity of the solvent increases, energetically the dimeric form becomes less favourable than the monomeric form so that the equilibrium: monomer ⇔ dimer is shifted to the left. Molecular mechanics calculations based on Amber force field show that the two forms may be equally stable when the dielectric constant of the solvent lies somewhere between 2 and 3.

Key Words: Acetic acid, Dimer, Molecular mechanics, Semi-empirical.

INTRODUCTION

Molecular association of acetic acid has been the subject of extensive investigation for many years[1–6]. Acetic acid vapour contains dimers in which two molecules of acetic acid are linked together through two O—H·····O=C C=O hydrogen bonds[7] as shown in Fig. 1. A hydrogen bond may be defined as a three centre bond in which a hydrogen atom bonded to one strong electronegative atom is attracted to another strong electronegative atom to which it is not bonded.

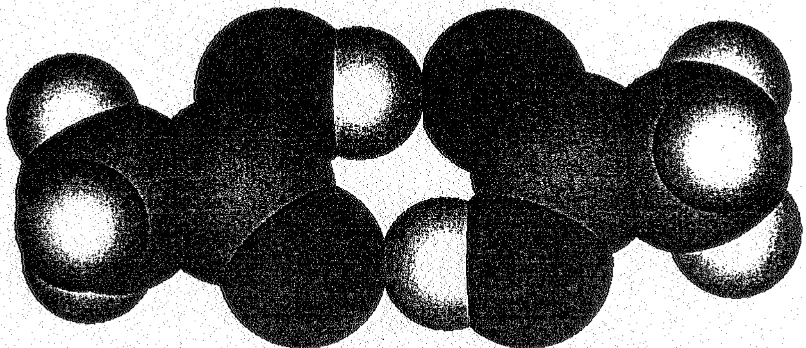

Fig. 1. Structure of acetic acid dimer formed by two hydrogen O—H·····O=C hydrogen bonds

Dimers of acetic acid are also formed when the compound is dissolved in a non-polar solvent such as benzene or carbon tetrachloride[8]. When the dimers are formed, polar groups of acetic acid are to some extent shielded from coming in contact with the non-polar solvent molecules. However, in a highly polar solvent such as water where there is a strong interaction between polar groups of acetic acid and polar solvent molecules, formation of dimers is less favourable[9]. Colominas *et al.*[9] carried out a number of theoretical calculations based on classical to high-level *ab initio* methods to study the dimerization of acetic acid in the gas phase. Their calculations show that dimerization free energies in the gas phase are of the order of –2 to –4 kcal mol^{-1}.

It is logical to think in solution, there may actually exist an equilibrium between monomeric and dimeric forms of acetic acid of the type: 2 monomers $\rightleftharpoons$ dimer with the equilibrium being shifted to the left in a polar solvent and to the right in a non-polar solvent. A natural question that follows is: "*What would be the dielectric constant of the solvent in which both the monomeric and dimeric forms of acetic acid would be equally stable?*" In the present study molecular mechanics and semi-empirical calculations have been carried out to investigate the relative stability of acetic acid monomer and acetic acid dimer as a function of the dielectric constant. Specifically, both the "molecules" have been optimized in a vacuum and a number of hypothetical solvents, based on molecular mechanics and semi-empirical calculations. At the end of calculations, total energy and heat of formation of the "molecules" have been calculated.

EXPERIMENTAL

The geometries of monomeric and dimeric forms of acetic acid in the gas phase, in solution in water and in a number of hypothetical solvents of dielectric constants ranging from 1 to 80, were optimized based on molecular mechanics and semi-empirical calculations, using the molecular modelling program HyperChem 7.0.[10] The actual values of dielectric constants used were 1, 2, 3, 5, 10, 20, 30, 40, 50, 60, 70 and 80 to simulate solvents from non-polar to highly polar. The dielectric constant of a substance may be defined as its relative permittivity. As applied to a solvent the dielectric constant defines the screening effect of the solvent molecules on nonbonded (electrostatic) interactions. A dielectric constant of 1 corresponds to a vacuum or the molecule in the gaseous state, *i.e.*, in solution in air. For structures optimized based on molecular mechanics calculations, the total energies were calculated and for structures optimized on semi-empirical calculations, single-point calculations were carried out to obtain the total energies and heats of formation. For molecular mechanics calculations, the O·····H hydrogen bond distance was fixed at 1.774 Å which was the value obtained from semi-empirical calculations using the routine PM3. Molecular mechanics calculations were carried out using both Amber and OPLS force fields. Semi-empirical calculations were carried out using the routine PM3. In molecular mechanics calculations, electrostatic and van der Waals scale factors were set at 0.833 and 0.5 for the Amber force field, 0.5 and 0.125 for the OPLS force field. The total energies of the dimer and two monomeric acetic acid molecules obtained from molecular mechanics calculations using Amber force field were plotted against dielectric constant values. The point at which the two curves intersected gave the dielectric constant of the solvent in which both the monomeric and dimeric forms are considered to be equally stable from energy considerations. For calculations in solution in particular solvent water, the solute was placed in a periodic box of dimensions 18.70 × 18.70 × 18.70 Å containing 216 TIP3P water molecules[11, 12] and minimum solvent to solute atom distance of 2.3 Å.

RESULTS AND DISCUSSION

Table-1 gives the total energy of the monomeric and dimeric forms of acetic acid in solution in solvents of dielectric constant ranging from 1 to 80, obtained from molecular mechanics calculations using the Amber force field. As noted earlier, dielectric constant 1 corresponds to molecules in a vacuum or in the gaseous state. Table-1 also gives the total energy and heat of formation of monomeric and dimeric forms of acetic acid in both gaseous state and in solution in water, obtained from semi-empirical calculations. It can be seen that the total energies of both the monomeric and dimeric forms of optimized acetic acid molecules, obtained from molecular mechanics calculations using the Amber force field increase (*i.e.*, become less negative or more positive) with the increase in the dielectric constant of the solvent. (A similar trend was observed with molecular mechanics calculations using OPLS force field (results not shown). For example, when the dielectric constant equals one, the total energies of monomeric and dimeric forms are –21.89 and –58.96 kcal mol^{-1} respectively and when the dielectric constant equals five, the corresponding values are –3.91 and 1.41 kcal mol^{-1} respectively.

It can however be noted that the increase is more pronounced for the dimeric form than for the monomeric form so that the decrease in "stability" is less marked for the monomeric form. Put in another way, the equilibrium between the monomeric and dimeric forms of acetic acid will be shifted to the monomeric form with the increase in the dielectric constant of the solvent. Fig. 2 gives the plot of total energy *vs.* solvent dielectric constant for both monomeric and dimeric forms of acetic acid obtained from molecular mechanics calculations using the Amber force field. As applied to the monomeric form, the total energy is that of two molecules of acetic acid (2CH_3COOH) (rather than one) to correspond to the dimeric form [$(CH_3COOH)_2$]. Fig. 3 gives the same plot on a logarithmic scale for the dielectric constant.

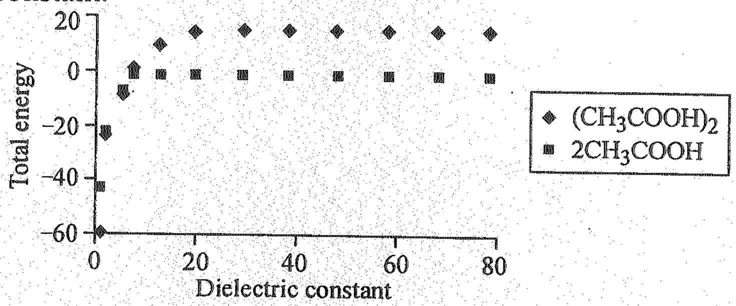

Fig. 2. Plot of total energy *vs.* solvent dielectric constant obtained from molecular mechanics calculations using the Amber force field.

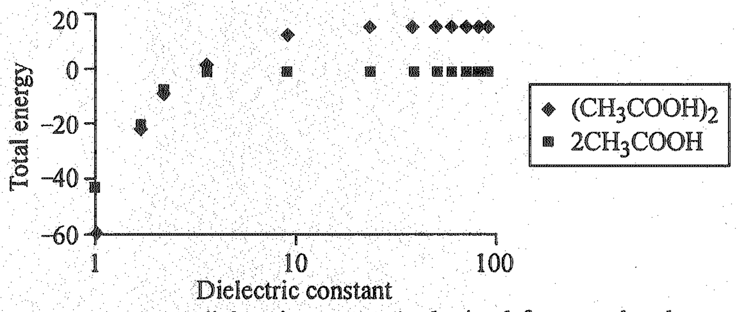

Fig. 3. Plot of total energy *vs.* log (dielectric constant) obtained from molecular mechanics calculations using the Amber force field.

TABLE-1
TOTAL ENERGY, HEAT OF FORMATION FOR OPTIMIZED STRUCTURES OF ACETIC ACID MONOMER AND DIMER

Molecule	Calculation type	Force field/ routine used	In vacuum or solution	Dielectric constant	Total energy (kcal mol^{-1})	ΔH_f (kcal mol^{-1})
Acetic acid monomer	Molecular mechanics	Amber	Vacuum	1	–21.89	
			Solution	2	–10.63	
				3	–6.90	
				5	–3.91	
				10	–1.68	
				20	–0.56	
				30	–0.19	
				40	–0.004	
				50	0.11	
				60	0.18	
				70	0.23	
				80	0.27	
	Semi-empirical	PM3	Vacuum	1	–20452.40	–102.0
			Solution	80	–20459.08	–108.69
Acetic acid dimer	Molecular mechanics	Amber	Vacuum	1	–58.96	
			Solution	2	–21.19	
				3	–8.63	
				5	1.41	
				10	8.94	
				20	12.70	
				30	13.95	
				40	14.58	
				50	14.95	
				60	15.20	
				70	15.38	
				80	15.52	
	Semi-empirical	PM3	Vacuum	N/A	–40913.86	–213.18
			Solution in water	80	–40910.42	–209.63

It can be seen from Figs. 2 and 3 that when the dielectric constant is very low, equilibrium favours the formation of dimeric form and conversely when the dielectric constant is very high, the equilibrium favours the formation of the monomeric form. When the dielectric constants of the solvent lies somewhere between 2 and 3, both the monomeric and dimeric forms of acetic acid are equally stable from energy consideration. It should however be noted that entropy would also play a role in determining the free energy change associated with the conversion of one form of acetic acid into another.

Semi-empirical calculations based on PM3 routine show that for the monomeric form of acetic acid both the total energy and heat of formation are more negative in solution in water than in a vacuum indicating that the monomeric molecule is more stable in solution in water than in a vacuum (the difference is -6.69 kcal mol^{-1}). Conversely, for the dimeric form of acetic acid, both the total energy and heat of formation are less negative in solution in water than in a vacuum, indicating that the dimeric form of acetic acid is more stable in a vacuum (and in the gaseous state) than in solution in water. The difference between the heats of formation of the dimer in solution in water and that in a vacuum is $+3.55$ kcal mol^{-1}. The other point to note from the results of semi-empirical calculations is that in the gaseous state the enthalpy of dimerization is -9.2 kcal mol^{-1} ($-213.18 - 2 \times -102.0 = -9.2$) and the corresponding value in solution in water is $+7.8$ kcal mol^{-1}, again highlighting the point that whereas dimeric form is more stable in the gaseous state, it is the monomeric form of acetic acid that is more stable in solution in water. It should be noted that the calculated value of heat of dimerization in the gaseous state is significantly higher than the experimentally reported value[9] of about -14.5 kcal mol^{-1}.

Fig. 4 gives the various bond lengths for the dimeric form of acetic acid optimized based on semi-empirical calculations using the routine PM3.

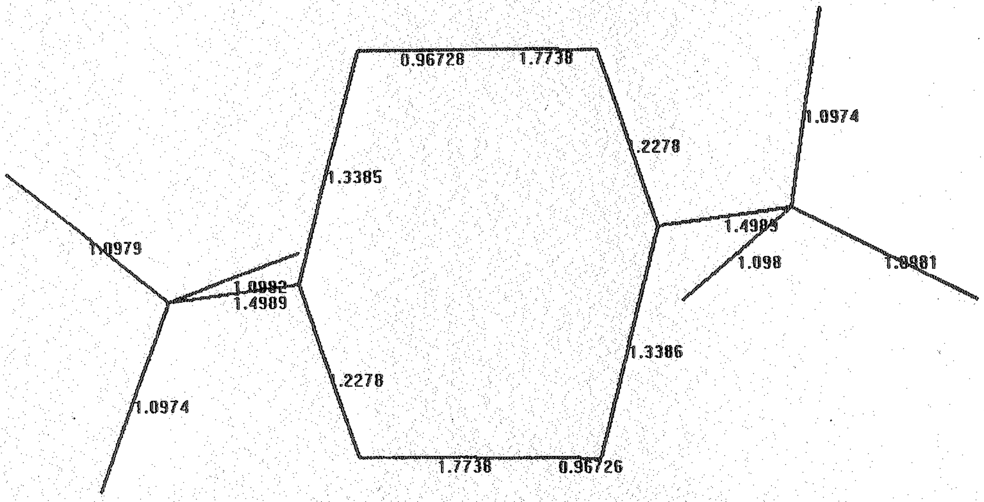

Fig. 4. Bond lengths of dimeric form of acetic acid optimized based on semi-empirical calculations using the routine PM3

The values are in reasonably good agreement with the reported values for the dimeric structure[13].

Why is the dimeric form of acetic acid more stable in a vacuum, in the gaseous state or a non-polar solvent?

It is appropriate to consider the charge centres and charge density in the molecules as these will have an effect on both the nature and magnitude of interaction between solute and solvent molecules. Fig. 5 gives the charge densities around atoms in both monomeric and dimeric forms of acetic acid, obtained from

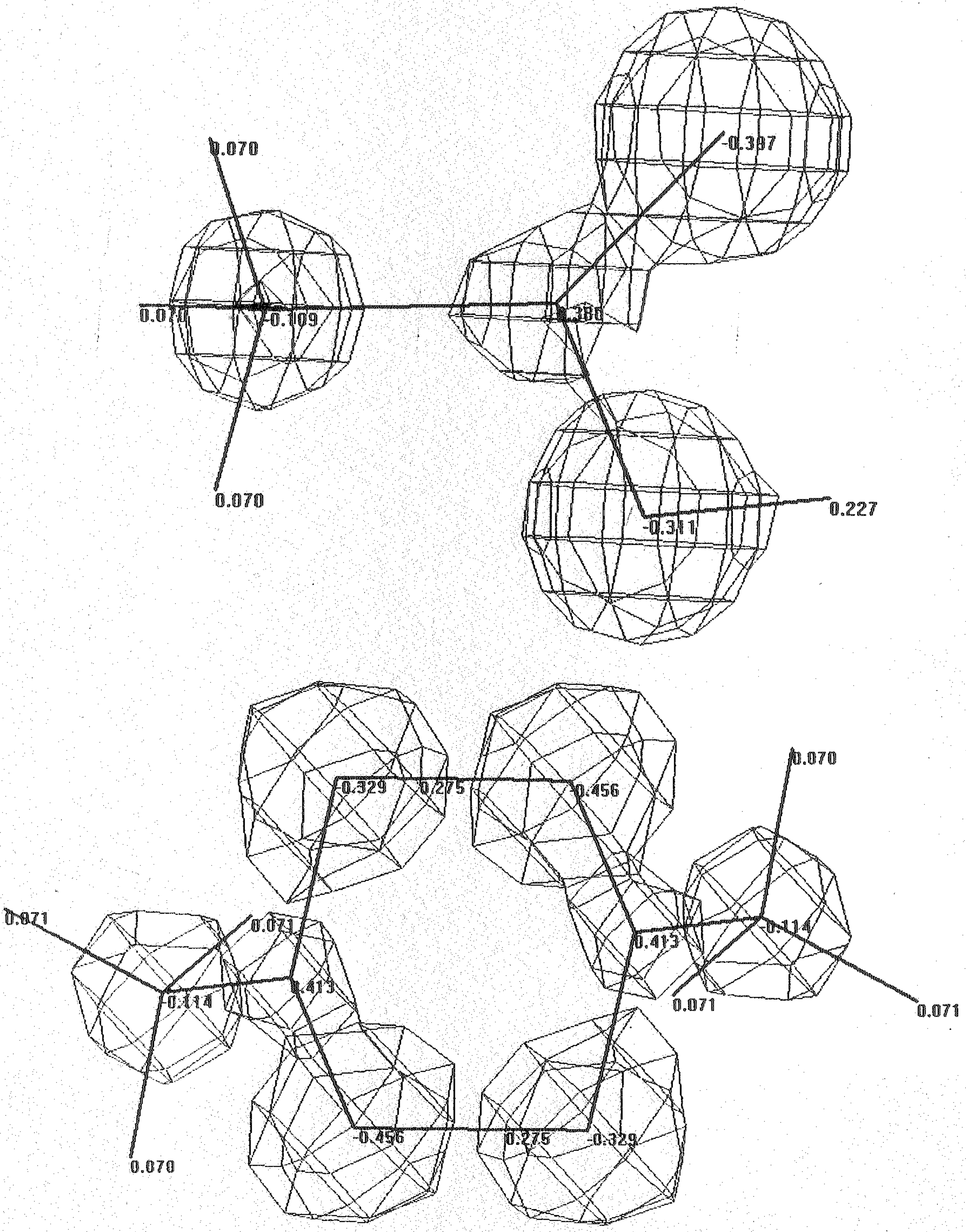

Fig. 5. Charge densities around atoms in acetic acid as applied to monomeric and dimeric forms

PM3 single point calculation. The calculated charge on each atom is given as its label. It can be seen that in the monomeric form of acetic acid, the positions of significant negative charge are the carbonyl and the hydroxyl oxygens and those of significant positive charge are the hydroxyl hydrogen and the carbonyl carbon. The carbonyl oxygen and the hydroxyl hydrogen are more exposed to solvent molecules than the carboxyl oxygen and the carbonyl carbon. By avoiding contact with polar part of a molecule, non-polar molecules avoid repulsive interaction that serves the purpose of increasing potential energy of the molecular system. One way of avoiding such repulsive contact between acetic acid and non-polar solvent molecules is for the acid to form dimer in which polar groups are involved in intermolecular hydrogen bonds and thus not available for interaction with the solvent.

Conclusion

Molecular mechanics and semi-empirical calculations show that as the dielectric constant of the solvent is increased, in terms of energy, the monomeric form of acetic acid becomes more favourable than the dimeric form so that the monomer $\rightleftharpoons$ dimer equilibrium is shifted towards the monomeric form in polar solvents.

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