

## Why the Lower-membered Alkanoic Acids are Infinitely Soluble in Water whereas the Higher-membered Ones have a Very Low Solubility in Water? A Molecular Modeling Analysis

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Molecular mechanics, semi-empirical and density function theory (DFT) calculations using HyperChem 7 and Spartan'02 were carried out to investigate whether the results obtained can explain the decrease in solubility in water of alkanolic acids with the increase in carbon chain length. Semi-empirical calculations using HyperChem 7 according to AM1 procedure show that for methanoic acid, ethanoic, propanoic acid and butanoic acid, the energy of hydration is indeed greater in magnitude than the heat of evaporation so that there is a net release of heat energy as the compounds go in solution in water. A decrease in enthalpy and an increase in entropy mean that the change in Gibb's free energy is negative so that solubility equilibrium cannot be established for the compounds. For the higher-membered alkanolic acids, the calculated energy of hydration is found to be less in magnitude than the heat of evaporation so that solubility equilibrium is established for the compounds. Although PM3 calculations provide a better estimate of heat of formation in the gaseous state, it is found that the calculations generally underestimate the energy of hydration.

**Key Words:** Alkanoic acids, Carbon chain length, Energy of hydration, Solubility in water, Change in polarity.

### INTRODUCTION

It is a common chemistry knowledge that polar compounds dissolve more easily in a polar solvent than in a non-polar one. A polar solvent is one that is composed of polar molecules and a polar molecule may be defined as a molecule that has a permanent non-zero dipole moment. The permanent dipole moment stems from the partial separation of charges that arise from the differences in electronegativity or other features of bonds<sup>1</sup>. As the polarity of a compound decreases, its solubility in water also decreases. Conversely, as the polarity of a molecule increases, the solubility in water also increases<sup>2</sup>. For alkanolic acids, as the carbon chain length increases, the polarity of the molecule decreases and

hence the solubility in water also decreases<sup>3</sup>. For example, whereas methanoic, ethanoic, propanoic and butanoic acids are miscible with water, the solubility of heptanoic acid is 0.242 g per 100 mL and that of octanoic acid is only 0.068 g per 100 mL (Table-1)<sup>4</sup>.

TABLE-1  
SOLUBILITY AND EXPERIMENTALLY MEASURED THERMAL PARAMETERS  
OF ALKANOIC ACIDS

Name	m.p. (°C)	b.p. (°C)	$\Delta H_f$ (g) (kcal mol <sup>-1</sup> )	$\Delta H_{vap}$ (kcal mol <sup>-1</sup> )	Solubility in water (g per 100 mL of water)
Methanoic acid	8.4	100.6	-90.6	11.0	infinite
Ethanoic acid	16.7	117.9	-103.5	11.7	infinite
Propanoic acid	-20.8	141.41	-108.3	13.6	infinite
Butanoic acid	-5.2	163.3	-112.4	15.3	infinite
Pentanoic acid	-34.0	185.5	-117.2	16.7	30
Hexanoic acid	-3.0	205.7	-122.7	17.0	1.08
Heptanoic acid	-7.5	223.0	-128.2	17.3	0.242
Octanoic acid	16.5	239.3	-132.5	19.4	0.068
Nonanoic acid	15.0	255.0	-137.8	19.7	negligible
Decanoic acid	31.5	270.0	-142.0	21.4	negligible
Undecanoic acid	28.6	280.0	(-147.3)*	22.3	negligible
Dodecanoic acid	44.0	131.0	(-152.6)	23.5	negligible
Tridecanoic acid	44.5	236.0	-157.6	24.7	negligible
Tetradecanoic acid	58.0	250.5	(-162.8)	26.0	negligible
Pentadecanoic acid	53.5	257.0	-166.8	27.3	negligible
Hexadecanoic acid	63.0	—	(-172.1)	24.2	negligible
Heptadecanoic acid	62.3	227.0	(-177.4)	24.2	negligible
Octadecanoic acid	71.2	360d	(-182.8)	24.9	negligible
Nonadecanoic acid	65.0	255.0	-187.4	31.4	negligible
Eicosanoic acid	77.0	328.0	(-192.8)	(33.5)	negligible

\*Figures given in parentheses are estimated values.

# 'd' = decomposes at the temperature.

For alkanolic acids having nine or more carbon atoms, solubility in water is so small that for all practical purposes the compounds may be considered to be insoluble in water. The aim of this paper is to investigate whether semi-empirical and density function theory (DFT) analyses provide a theoretical explanation as to why the solubility of alkanolic acids in water decreases with the increase in carbon chain length.

Although a number of theoretical studies on different aspects of carboxylic acids have been carried out, to our knowledge no such study has considered the change in solubility of alkanolic acids in water with the change in carbon chain length. Recently, Exner *et al.*<sup>5</sup> considered the acidity of carboxylic acids based on calculations at MP2/6-31++G(2d, p) level and concluded that the acidity of carboxylic acids lies in the electrostatic potential of the anion rather than that of the acid molecule.

A number of methods including group additivity<sup>6,7</sup>, molecular orbital calculations<sup>8,9</sup> and density functional theory<sup>10</sup> have been applied to calculate the heat of formation of organic compounds including carboxylic acids. Castro<sup>11</sup> applied a simplified scheme of atom equivalents to relate *ab initio* molecular energies to heats of formation of carboxylic acids and esters. Recently, Dolney *et al.*<sup>12</sup> described a universal solvation model based on SM5-type functional forms for atomic surface tensions combined with a quantum mechanical self-consistent reaction field (SCRf) electrostatic calculation based on conductor-like screening model (COSMO). It was shown that the model could be used to calculate the free energies of solvation in water and virtually any organic solvent. The model is parameterized using rigid (gas-phase) solute geometries, intended for use with semi-empirical molecular orbital methods AM1, PM3 and MINDO/d.

More recently, Xie and Liu<sup>13</sup> treated solvation by a generalized Born (GB) model and a self-consistent charge-density functional theory-based tight-binding (SCC-DFTB) method with the non-electrostatic contributions to the free energy of solvation being described in terms of solvent-accessible surface areas (SA). They combined the GB solvation model proposed by Still *et al.*<sup>14</sup> with SCC-DFTB method to come up with GB/SA model. They showed that the model could be extended to calculate free energy of solvation of large biomolecules with the use of divide-and-conquer linear-scaling algorithm<sup>15</sup>. However, in the calculations it is assumed that the solute molecule is introduced from gas phase into the solvent. Since alkanolic acids exist as liquids and solids (Table-1) at room temperature and pressure, we need to consider the enthalpy and entropy changes associated with the phase change (liquid to gas or solid to gas) along with the calculated free energy of solvation to obtain a clear understanding of the change in solubility of alkanolic acids in water. The situation is further complicated due to the dissociation of the molecules in solution in water (although the degree of dissociation remains quite small, *e.g.*, in 0.1 M ethanoic acid solution in water only 1.34% of the acid molecules in solution in water is dissociated into ions) and the resonance stabilization of the anion formed<sup>16</sup>.

In this study, molecular mechanics, semi-empirical and DFT calculations have been carried out using HyperChem 7<sup>17</sup> and Spartan'02<sup>18</sup> to investigate whether the change in solubility in water of 'straight-chain' (*i.e.*, no branching of the carbon chain) alkanolic acids can be explained in terms of energies of hydration and enthalpy and entropy changes associated with the phase change.

The results show that as per AM1 calculations using HyperChem 7.0, for methanoic, ethanoic, propanoic and butanoic acids, the energy of hydration is indeed greater in magnitude than the heat of evaporation so that both minimization of enthalpy and maximization of entropy would favour the dissolution process, thus providing an explanation as to why the compounds are infinitely soluble in water. For higher-membered alkanolic acids, the energy of hydration is found to be less in magnitude than the heat of evaporation (or heat of sublimation if the compound exists as a solid at room temperature) so that whereas the process of dissolution is favoured by increase in entropy, it is opposed by the increase in enthalpy. Hence, solubility equilibrium is established for the higher-membered alkanolic acids.

### EXPERIMENTAL

The structures of straight-chain alkanolic acids having one to twenty carbon atoms have been optimized based on molecular mechanics and semi-empirical calculations using the programs HyperChem 7 and Spartan'02. DFT calculations were also carried out for the first twelve alkanolic acids using the program Spartan'02. As applied to calculations using HyperChem 7, the molecules were optimized in a vacuum and in solution in water and the total energy values and heats of formation of optimized structures were then determined using single point calculations. The difference between the heat of formation of the molecule in solution in water and that in the gas phase was taken as the energy of hydration. It must, however, be noted that since alkanolic acids do not exist as gases (but as liquids and solids) at 298 K, enthalpy and entropy changes associated with the phase change (*i.e.*, change from liquid or solid to gas) must also be considered. Also, it is to be noted that since a number of conformations are likely to exist in solution, a better estimate of thermodynamic properties would have been obtained from the averages resulting from molecular dynamics calculations. This could not be done because of excessive amounts of time required to obtain meaningful results. As applied to Spartan'02 program, the structures were optimized using the routines AM1, PM3 and DFT and then single point calculations were carried out to give various thermodynamic parameters including total enthalpy; total entropy, free energy of solvation and log P. In Spartan'02 the energy of hydration is calculated using the SM5.4 procedure of Cramer *et al.*<sup>19</sup> log P (where P stands for the partition coefficient of the compound between 1-octanol and water) was calculated according to the method of Ghose *et al.*<sup>20</sup> For geometry optimization using both molecular mechanics and semi-empirical calculations using HyperChem 7, Polak-Ribiere routine with RMS gradient of 0.02 as the termination condition was used. To simulate the conditions in solution, the molecules were placed in a periodic box of TIP3P water molecules<sup>21, 22</sup> followed by further cycles of geometry optimization. The actual dimensions of the boxes used and the maximum number of water molecules present are given in Table-2. These are the default values suggested by HyperChem based on the sizes of the molecules.

TABLE-2  
 DIMENSIONS OF PERIODIC BOX AND MAXIMUM NUMBER OF TIP34 WATER  
 MOLECULES USED IN MOLECULAR DYNAMICS CALCULATIONS

Molecule	Box size			Number of water molecules
	X (Å)	Y (Å)	Z (Å)	
Methanoic acid	18.7	18.7	18.7	216
Ethanoic acid	18.7	18.7	18.7	216
Propanoic acid	18.7	18.7	18.7	216
Butanoic acid	18.7	18.7	18.7	216
Pentanoic acid	18.7	18.7	18.7	216
Hexanoic acid	18.7	18.7	18.7	216
Heptanoic acid	19.0	19.0	19.0	226
Octanoic acid	19.1	19.1	19.1	232
Nonanoic acid	24.2	24.2	24.2	468
Decanoic acid	28.2	28.2	28.2	739
Undecanoic acid	29.2	29.2	29.2	825
Dodecanoic acid	28.2	28.2	28.2	744
Tridecanoic acid	30.6	30.6	30.6	943
Tetradecanoic acid	31.2	31.2	31.2	1008
Pentadecanoic acid	37.3	37.3	37.3	1704
Hexadecanoic acid	37.3	37.3	37.3	1709
Heptadecanoic acid	37.9	37.9	37.9	1803
Octadecanoic acid	42.6	42.6	42.6	2561
Nonadecanoic acid	47.6	47.6	47.6	3557
Eicosanoic acid	53.3	53.3	53.3	4991

The minimum distance between solvent molecules and solute atoms was set at 2.3 Å. Molecular dynamics calculations were used to obtain a lower energy minimum by enabling molecules to cross potential barriers<sup>23</sup>. The parameters used in simulated annealing were: heat time = 1 ps, run time = 0.5 ps, cool time = 0 ps, step size = 0.0005 ps, bath relaxation time = 0.1 ps, starting temperature = 100 K, simulation temperature = 300 K, temperature step = 30 K and data collection period = 4 time steps. For the structures optimized based on semi-empirical calculations, single point calculations were carried out to determine the total energies and heats of formation. The numbers of occupied and unoccupied orbitals in the single point CI calculations were both set equal to five. For DFT calculations using the program Spartan'02, B3LYP exchange-correlation function<sup>24, 25</sup> together with the 6.31G\* basis set<sup>26</sup> was used.

## RESULTS AND DISCUSSION

Table-3 gives the calculated total energies and heats of formation of optimized alkanolic acid molecules in a vacuum and in solution in water as per the routine AM1 in HyperChem 7.

TABLE-3  
ESTIMATED TOTAL ENERGIES AND HEATS OF FORMATION OF ALKANOLIC ACIDS IN THE GASEOUS STATE AND IN SOLUTION IN WATER OBTAINED FROM AM1 CALCULATIONS USING HYPERCHEM 7.0

Molecule	Total energy (kcal mol <sup>-1</sup> )		Heat of formation (kcal mol <sup>-1</sup> )		Energy of hydration (kcal mol <sup>-1</sup> )
	Gaseous	Aqueous	Gaseous	Aqueous	
Methanoic acid	-1835.1	-18397.6	-90.0	-112.5	-22.5
Ethanoic acid	-21975.0	-21995.5	-103.1	-123.5	-20.4
Propanoic acid	-25568.0	-25587.0	-109.2	-128.2	-19.0
Butanoic acid	-29161.8	-29177.6	-116.1	-132.0	-15.9
Pentanoic acid	-32755.2	-32763.7	-122.7	-131.2	-8.5
Hexanoic acid	-36349.2	-36355.2	-129.9	-135.9	-6.0
Heptanoic acid	-39942.6	-39945.2	-136.5	-152.8	-16.3
Octanoic acid	-43536.4	-43557.1	-143.4	-164.1	-20.7
Nonanoic acid	-47130.4	-47137.1	-150.5	-157.3	-6.8
Decanoic acid	-50723.8	-50725.6	-157.1	-158.9	-1.8
Undecanoic acid	-54317.5	-54335.0	-164.0	-188.4	-24.4
Dodecanoic acid	-57911.2	-57923.6	-170.9	-183.2	-12.3
Tridecanoic acid	-61504.9	-61528.9	-177.7	-201.7	-24.0
Tetradecanoic acid	-65098.7	-65129.0	-184.7	-215.0	-30.3
Pentadecanoic acid	-68692.2	-68709.5	-191.3	-208.7	-17.4
Hexadecanoic acid	-72286.2	-72295.2	-198.5	-207.5	-9.0
Heptadecanoic acid	-75879.8	-75881.7	-205.3	-207.1	-1.8
Octadecanoic acid	-79473.8	-79516.4	-212.4	-255.0	-42.6
Nonadecanoic acid	-83067.3	-83095.7	-219.1	-239.5	-20.4
Eicosanoic acid	-8660.8	-8682.7	-225.8	-243.7	-17.9

Table-4 gives the calculated total energies and heats of formation of optimized alkanolic acid molecules in a vacuum and in solution in water as per the routine PM3 in HyperChem 7.

TABLE-4  
ESTIMATED TOTAL ENERGIES AND HEATS OF FORMATION OF ALKANOIC ACIDS IN THE GASEOUS STATE AND IN SOLUTION IN WATER OBTAINED FROM PM3 CALCULATIONS USING HYPERCHEM 7.0

Molecule	Total energy (kcal mol <sup>-1</sup> )		Heat of formation (kcal mol <sup>-1</sup> )		Energy of hydration (kcal mol <sup>-1</sup> )
	Gaseous	Aqueous	Gaseous	Aqueous	
Methanoic acid	-16997.5	-17012.2	-90.2	-104.9	-14.7
Ethanoic acid	-20452.5	-20457.8	-102.1	-107.4	-5.3
Propanoic acid	-23900.0	-23909.9	-106.5	-116.4	-9.9
Butanoic acid	-27348.6	-27355.8	-112.0	-119.2	-7.2
Pentanoic acid	-30795.0	-30795.0	-117.4	-113.3	4.1
Hexanoic acid	-34245.7	-34241.5	-122.8	-118.6	4.2
Heptanoic acid	-37694.3	-37691.5	-128.3	-125.5	2.8
Octanoic acid	-41142.9	-41139.7	-133.7	-130.6	3.1
Nonanoic acid	-44591.4	-44588.4	-139.2	-136.2	3.0
Decanoic acid	-48040.0	-48049.9	-144.6	-135.5	9.1
Undecanoic acid	-51488.6	-51480.7	-150.1	-142.2	7.9
Dodecanoic acid	-54936.8	-54930.6	-155.2	-148.6	6.6
Tridecanoic acid	-58385.7	-58384.9	-161.0	-159.0	0.9
Tetradecanoic acid	-61834.3	-61832.3	-166.5	-164.5	2.0
Pentadecanoic acid	-65282.9	-65281.8	-171.9	-170.9	1.0
Hexadecanoic acid	-68730.6	-68725.5	-176.5	-171.4	5.1
Heptadecanoic acid	-72180.0	-72175.9	-182.8	-178.0	4.8
Octadecanoic acid	-75628.7	-75622.9	-188.3	-183.1	5.2
Nonadecanoic acid	-79077.3	-79071.6	-193.8	-188.1	5.7
Eicosanoic acid	-82525.4	-82429.6	-198.8	-195.3	3.5

Table-5 gives log P values, the estimated heats of formation and solvation energies of alkanolic acids based on semi-empirical (as per AM1 and PM3 routines) and DFT calculations using the program Spartan'02.

When the calculated heats of formation are compared with the experimentally determined values, it is found that the values obtained from PM3 calculations rather than those obtained from AM1 calculations agree more closely with the experimental values (Fig. 1). The values obtained from AM1 calculations are generally larger in magnitude than those obtained from PM3 calculations, especially for the higher-membered alkanolic acids. However, for methanoic and ethanoic acids, the experimentally observed values and the calculated ones (based on both AM1 and PM3) are practically the same as are those obtained from *ab initio*<sup>10</sup> calculations.

TABLE-5  
THE log P VALUES, HEATS OF FORMATION AND SOLVATION ENERGIES  
( $\Delta H_{\text{solution}}$ ) OF ALKANOIC ACIDS BASED ON SEMI-EMPIRICAL AND DFT  
CALCULATIONS USING SPARTAN'02

Name	log P	Heat of formation ( $\Delta H_f$ ) (kcal mol <sup>-1</sup> )		Solvation energy ( $\Delta H_{\text{solution}}$ ) (kcal mol <sup>-1</sup> )		
		AM1	PM3	AM1	PM3	DFT#
Methanoic acid	-0.57	-97.4	-94.4	-6.07	-6.01	-5.02
Ethanoic acid	-0.31	-103.0	-102.0	-6.09	-6.03	-5.07
Propanoic acid	0.35	-109.1	-106.4	-5.53	-5.32	-4.70
Butanoic acid	0.76	-116.0	-111.8	-5.07	-4.92	-4.15
Pentanoic acid	1.18	-122.8	-117.1	-4.92	-4.88	-4.17
Hexanoic acid	1.60	-129.4	-122.6	-4.55	-4.59	-3.81
Heptanoic acid	2.02	-136.5	-128.0	-4.58	-4.56	-3.84
Octanoic acid	2.43	-143.3	-133.4	-4.40	-4.28	-3.49
Nonanoic acid	2.85	-150.2	-138.8	-4.25	-4.25	-3.34
Decanoic acid	3.27	-157.0	-144.2	-4.08	-4.08	-3.52
Undecanoic acid	3.69	-163.9	-149.7	-3.89	-3.80	-3.02
Dodecanoic acid	4.10	-170.4	-155.1	-3.55	-3.65	-3.03
Tridecanoic acid	4.52	-177.6	-160.5	-3.54	-3.48	
Tetradecanoic acid	4.94	-184.4	-165.9	-3.36	-3.43	
Pentadecanoic acid	5.35	-191.0	-171.3	-3.01	-3.14	
Hexadecanoic acid	5.77	-198.1	-176.3	-3.00	-2.88	
Heptadecanoic acid	6.19	-204.2	-182.1	-2.82	-2.86	
Octadecanoic acid	6.61	-211.1	-187.4	-2.67	-2.75	
Nonadecanoic acid	7.02	-217.9	-192.5	-2.42	-2.40	
Eicosanoic acid	7.44	-224.8	-197.4	-2.29	-1.88	

#DFT calculations were done only for the first twelve alkanolic acids

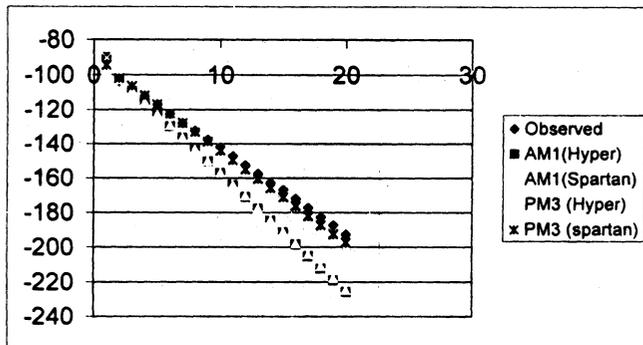


Fig. 1.  $\Delta H_f$  vs. number of carbons plot

For example, for methanoic acid, the experimental value of the heat of formation in the gaseous state is  $-90.6 \text{ kcal mol}^{-1}$ , the value obtained from PM3

calculations is  $-90.2 \text{ kcal mol}^{-1}$ , that from AM1 calculations is  $-90.0 \text{ kcal mol}^{-1}$ , from *ab initio* calculations it is  $-89.5 \text{ kcal mol}^{-1}$ . For ethanoic acid, the experimental value is  $-100.4 \text{ kcal mol}^{-1}$ , while the value obtained from PM3 calculations is  $-102.1 \text{ kcal mol}^{-1}$ , from AM1 calculations it is  $-103.1 \text{ kcal mol}^{-1}$  and from *ab initio* calculations it is  $-103.5 \text{ kcal mol}^{-1}$ .

**Why are methanoic acid, ethanoic acid, propanoic acid and butanoic acid are infinitely soluble in water whereas the higher-membered alkanolic acids have very low solubility in water?**

Although the dissolution process involves the transfer of solute molecules from their natural state at room temperature to the aqueous state, in attempting to answer the question, we may break down the dissolution process into the following two steps:

(1) Change in the state of aggregation of the compound from the natural state at 298 K to the gaseous state.

(2) Dissolution of gaseous molecule in solution in water.

The calculations carried out in the present study provide information directly or indirectly about the free energy change in the second step. Since the first step is thermodynamically feasible (as evident from the establishment of the phase change equilibrium under appropriate conditions), it can be deduced that it is the free energy change in the second step that will be critical in answering the question why the lower-membered alkanolic acids are infinitely soluble in water.

The thermodynamic requirement for a solute to be infinitely soluble in a solvent is that the overall change in Gibb's free energy ( $\Delta G$ ) in the dissolution process must be negative. Since entropy is increased in dissolution, a negative value for the energy of hydration ( $\Delta H_{\text{hydration}}$ ), which is taken as the difference in the heat of formation of aquated molecule and that of the molecule in the gaseous state, would mean that the change in Gibb's free energy ( $\Delta G$ ) in dissolution would also be negative.

For example, it is found that (as per AM1 calculations) the energy of hydration of the first four alkanolic acids (methanoic, ethanoic, propanoic and butanoic acids) is greater than the heat of vaporization, indicating that in all the four cases there will be a net decrease in the free energy when the molecules go in solution in water from their natural state (namely the liquid state) (Tables 3 and 4).

Thus when methanoic, ethanoic, propanoic and butanoic acids go in solution in water, enthalpy is decreased but entropy is increased meaning that both the natural tendencies applying to a system of a large number of bodies (*i.e.*, the minimization of enthalpy and maximization of entropy) favour the dissolution process. Hence, no solubility equilibrium can be established, *i.e.*, the compounds would be infinitely soluble in water. As stated earlier, although PM3 calculations provide a better estimate of heat of formation in the gaseous state, the calculations are found to underestimate the energy of hydration (Tables-3 and 4).

From pentanoic acid onward, the AM1 calculations using HyperChem 7 show that the energy of hydration is less than the heat of evaporation so that when the molecules go in solution in water there is a net increase in enthalpy. Since from decanoic acid onward, the compounds are solid at room temperature (Table-1),

it is the difference between the energy of hydration and the heat of sublimation (rather than heat of evaporation) that would give a more realistic estimate of the overall enthalpy change associated with the dissolution of the compounds.

Thus according to AM1 calculations, from pentanoic acid onward whereas maximization of entropy favour the process of dissolution in water, minimization of enthalpy opposes the process. Hence, according to Gibb's equation ( $\Delta G = \Delta H - T\Delta S$ ), a solubility equilibrium is established when  $\Delta G = 0$  (*i.e.*,  $\Delta H = T\Delta S$ ). As alkanolic acid molecules go in solution in water, it is reasonable to assume that the increase in entropy is likely to be similar irrespective of their size. However, the calculated results show that (beyond four carbons) as the molecular size increases, the magnitude of the increase in enthalpy associated with dissolution also gets larger. This means that solubility equilibrium would be shifted more and more towards the left, thus making the molecules practically insoluble in water when a certain size is reached ( $C_9$ ).

TABLE-6  
HEATS OF EVAPORATION AND CALCULATED ENERGIES OF HYDRATION  
( $\Delta H_{\text{hydration}}$ ) OF ALKANOIC ACIDS

Molecule	$\Delta H_{\text{vap}}$ (kcal mol <sup>-1</sup> )	$-\Delta H_{\text{solution}}$	
		AM1	PM3
Methanoic acid	11.0	22.5	14.7
Ethanoic acid	11.7	20.4	5.3
Propanoic acid	13.6	19.0	9.9
Butanoic acid	15.3	15.9	7.2
Pentanoic acid	16.7	8.5	-12.6
Hexanoic acid	17.0	6.0	-4.2
Heptanoic acid	17.3	16.3	-11.9
Octanoic acid	19.4	20.7	-27.5
Nonanoic acid	19.7	6.8	-20.0
Decanoic acid	21.4	1.8	-25.2
Undecanoic acid	22.3	24.4	-3.9
Dodecanoic acid	23.5	12.3	-0.9
Tridecanoic acid	24.7	24.0	-2.0
Tetradecanoic acid	26.0	30.3	-2.0
Pentadecanoic acid	27.3	17.4	-1.0
Hexadecanoic acid	24.2	9.0	-5.1
Heptadecanoic acid	24.2	1.8	-4.8
Octadecanoic acid	24.9	42.6	-6.1
Nonadecanoic acid	31.4	20.4	-5.7
Eicosanoic acid	(33.5)	17.9	-17.6

When the heats of formation calculated using the programs HyperChem 7 and Spartan'02 are compared, it is found that both the programs give almost identical values for the same procedure such as AM1 or PM3. However, as noted earlier, the values obtained using the procedure AM1 are consistently higher than those obtained using the procedure PM3. For example, for gaseous ethanoic acid, according to AM1 procedure the heat of formation values based on HyperChem 7 and Spartan'02 are respectively  $-103.1$  and  $-103.0$  kcal mol<sup>-1</sup> respectively. The corresponding values according to PM3 procedure are  $-102.1$  and  $-102.0$  kcal mol<sup>-1</sup> respectively.

When we consider the results obtained from semi-empirical and DFT calculations using the program Spartan'02 (Table-5), it can be seen that for all alkanolic acids the estimated solvation energies are negative with the values obtained from AM1 calculations (Table-6) being largest in magnitude and those obtained from DFT calculations being the smallest. However, according to all the procedures (AM1, PM3 and DFT), as the number of carbon atoms present in the molecule increases the solvation energy decreases. Conversely, as the solvation energy decreases, the log P value (which may be considered to be a measure of lipid solubility) increases (more linearly) with the increase in the number of carbon atoms (Fig. 2). The decrease in solvation energy with the increase in size of the alkanolic acid molecules is in line with the decrease in their solubility in water. However, it is not obvious whether these data alone can provide an answer as to why only the first four alkanolic acids are infinitely soluble in water.

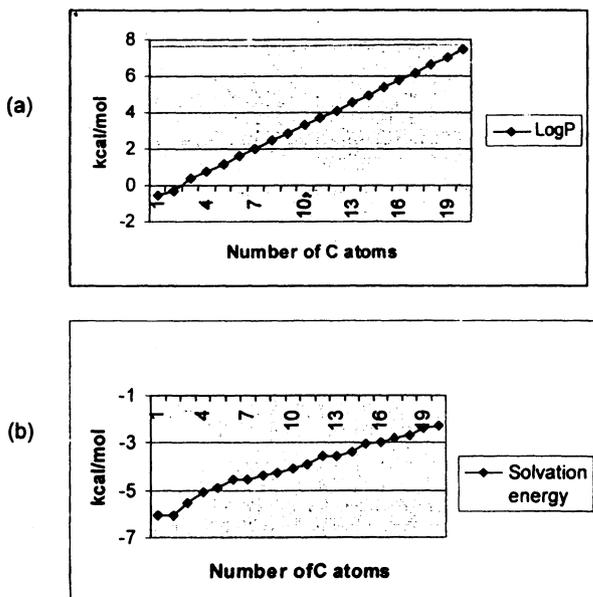


Fig. 2. (a) log P vs. number of carbons plot, (b)  $\Delta H_{\text{solvation}}$  vs. number of carbons plot

## Conclusion

Semi-empirical calculations using HyperChem 7 according to AM1 procedure show that for methanoic acid, ethanoic acid, propanoic acid and butanoic acid, the magnitude of energy of hydration is less than heat of evaporation so that there is a net decrease in enthalpy when the molecules go in solution in water. The decrease in enthalpy and increase in entropy mean that no solubility equilibrium can be established for the compounds, thus providing an explanation as to why the compounds are infinitely soluble in water. For the higher-membered alkanolic acids, as the molecules are allowed to go in solution in water, there is an increase in enthalpy as well as entropy so that a solubility equilibrium is established.

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