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Hydrophobicity of small alkane molecules (propane dimer) in solvents: a classical molecular dynamics study

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ABSTRACT

Molecular Dynamics (MD) simulations of propane dimer in different solvents (water, acetonitrile and methanol) were performed by using CHARMM platform for modeling the solute and solvents. A series of Umbrella sampling MD simulations were carried out in each solvent separately and potential of mean force (PMFs) were calculated by using Weighted Histogram Analysis Method. Results show that two minima (contact minima and solvent separated minima) characterize the PMF of propane dimer in all three solvent environments. The contact minima are deeper and less sensitive to solvent environment for its position. However, significant effect in the position of second minima, solvent separated minima, was observed. Our study reveals that the interaction between propane dimer is softer in methanol and acetonitrile than in water.

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1. Introduction

The organic compounds were once considered to be obtained from living organisms only. It was believed that only a special force, existing in living organisms, called vital force could produce the organic compounds. However, urea and many other compounds found in living organisms were later on synthesized in lab without vital force. This led to the synthesis of organic compounds as hydrocarbons: compounds with basic components hydrogen and carbon [1].

Propane is a saturated hydrocarbon with three carbon atoms bonded together with single covalent bonds along with eight hydrogen atoms. The

molecular formula of propane is C_3H_8 . The angle between two C-C bonds is 112° . The separation of carbon atoms is 153 pm and the bond length between carbon and hydrogen atoms is 111 pm [2].

Hydrophobicity

The exclusion of water molecules due to the aggregation of non-polar substances in aqueous solution is called hydrophobic effect [3]. Hydrophobic hydration and hydrophobic interactions are indicated by the term hydrophobic effect. Hydrophobic interactions refer to the solvent induced interactions between the apolar

solutes whereas hydrophobic hydration deals with the change in water structure in presence of non polar solute[4]. When the highly dynamic hydrogen bonds get disrupted, hydrophobic interactions are originated [5].

The hydrophobic effect is responsible for effects related to biology including cell membranes and vesicles formation, protein folding, insertion of membrane proteins into the non-polar lipid environment and protein [6]. For the proteins that have hydrophobic amino acids, hydrophobic effect is important to understand their structure. Proteins try to minimize the number of hydrophobic side chains exposed to water by forming a hydrophobic core covered by hydrophilic components. This tendency to reduce the number of side chains that are in contact with water provides a major contribution for folding process [7]. MD simulations of propane dimer in water have shown a deeper contact minima and a shallower solvent separated minima in the potential of mean force (PMF) curve [8].

Potential of mean force

Hydrophobic interactions are described in terms of potential of mean force (PMF). This potential is useful to get the average force acting over all the configurations of the given system [9]. Basically, PMF is the free energy profile along a reaction coordinate and is determined through the Boltzmann-weighted average over all degrees of freedom other than the reaction coordinate [10].

In other words PMF enables us to observe free energy changes with respect to some particular coordinates like solute-solute separation. The shape of PMF curve in the presence and absence of solvent environments is different. This difference in the PMF profile enables the use of PMF curve to analyze the solvent effect in solute-solute interactions. If distance between two particles r is taken as reaction coordinate then PMF $w(r)$ is related to the radial distribution function $g(r)$ as:

$$w(r) = -k_B T \ln g(r) + const. \quad (1)$$

The constant is chosen such that the most probable

distribution corresponds to a free energy of zero magnitude.

If $W(r)$ denotes the free energy change of the system then the relation between PMF and free energy is given by,

$$w(r) = W(r) + 2k_B T \ln r + const. \quad (2)$$

This equation shows that the free energy change of the system is not equal to the change in PMF. Distinction between them is very important while comparing with experiments and relating various approaches used for the study.

2. Computational details

Modeling of system

Molecular dynamics is computer simulation method for studying the physical movement of atoms and molecules. The inadequacy of the crystallographic images to provide information on dynamic features, lack of technique to provide high resolution in time and space, and the tedious experimental method require a new approach to follow the movement of individual molecules [11]. Method of computer simulation aims to fulfill this need. Molecular dynamics simulations are used to compute the equilibrium and transport properties by using process similar to the real experiments. We prepare the sample by selecting a model system with N particles and solve Newton's equation of motion for this system until we are assured that the properties of the system no longer change with time [12].

We have for the i^{th} particle with mass m_i , position r_i experiencing force F_i , Newton's equation of motion is:

$$m_i \frac{\partial^2 r_i}{\partial t^2} = -\nabla_i U(r) = F_i. \quad (3)$$

Equation (3) provides us with the relation between potential energy and the rate of change in position. Thus with the model of potential energy $U(r)$ of the system under study, integration of this equation yields trajectory of the system describing the positions, velocities and accelerations of particles with time.

The total potential energy of a system is sum of

all interaction potential energy:

$$U_{total} = U_{bond} + U_{angle} + U_{proper} + U_{LJ} + U_{Coulomb} \quad (4)$$

where the terms in right hand side represent potentials due to bond, angle, proper dihedral, Lennard-Jones and Coulomb interaction respectively.

Simulation set up

Molecular dynamics simulations were performed for three different systems (water-propane, acetonitrile-propane and methanol-propane). Propane has three carbon atoms covalently bonded with each other. The carbon atoms complete their valence shell by sharing electrons with hydrogen atoms. There are two methyl groups (CH_3) and one methylene group (CH_2) in propane. All bonded and non-bonded interactions were taken into account to make our system as real as possible. We also use LJ parameters to consider the van der Waals interaction. All the interactions were parameterized by using CHARMM force field parameters. Detail information about the solvents used for the simulations is presented in Table 1.

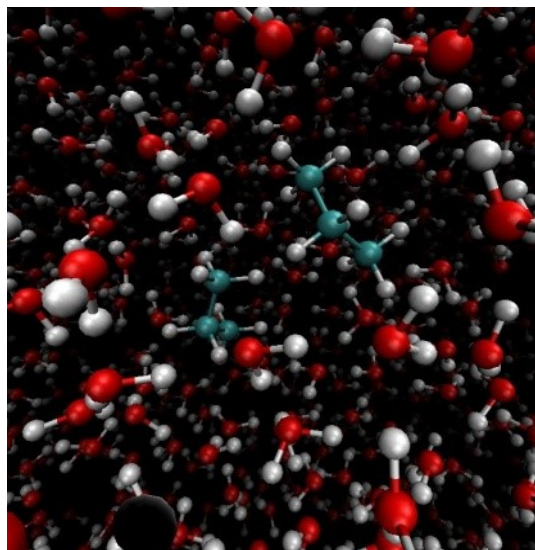


Fig.1: Sample of system under study (water-propane).

Table I: Partial charge and mass of each atom in solvents.

| Solvents | Atoms | Partial charge | Mass |
|--------------|-------|----------------|---------|
| Water | OW | -0.8476 | 15.9994 |
| | HW | 0.4328 | 1.008 |
| | HW | 0.4328 | 1.008 |
| Acetonitrile | C1 | -0.17 | 12.011 |
| | H11 | 0.09 | 1.008 |
| | H12 | 0.09 | 1.008 |
| | H13 | 0.09 | 1.008 |
| | C2 | 0.36 | 12.011 |
| | N3 | -0.46 | 14.007 |
| Methanol | CB | -0.04 | 12.011 |
| | HB1 | 0.09 | 1.008 |
| | HB2 | 0.09 | 1.008 |
| | HB3 | 0.09 | 1.008 |
| | OG | -0.65 | 15.9994 |
| | HG1 | -0.42 | 1.008 |

A cubic box of size 4 nm was taken in each of the three cases and was filled with the system (propane and solvent). Our system for simulation is ready after adding the solute and solvent in the box. Figure 1 is the sample of our system after adding the solute and solvent in the box.

However, the forces acting on molecules might be large and may result failure in MD simulation. To avoid this, we bring the system into equilibrium by performing energy minimization. After achieving energy minimization for the system, we bring the system to the state of thermo dynamical equilibrium. This is done because the dynamical variables that we intend to study change along with parameters like pressure, density, temperature and so on. Suitable thermostats are used to obtain thermal equilibrium. A process called temperature coupling is used to do so. Similarly, pressure coupling is done by using suitable barostat in order to obtain constant pressure [13].

We did equilibration in two steps. At first equilibration was done in NVT ensemble to attain thermal equilibrium and was followed by equilibration in NPT ensemble to maintain

constant pressure (density). This equilibration was done by using MD integrator. The simulation was done for 200 ps by taking step size of 0.001 for 200000 steps. The output control parameters specify when to write the position, velocity, energy and force in trajectory file. For coulomb interaction we used Particle Mesh Ewald (PME) with 0.12 fourier spacing along with cut-off distance of 1 nm. The simulations were intended for 298 K so the reference temperature is specified as 298 K for all simulations. To perform temperature coupling we use ν -scale thermostat. In NVT equilibration pressure coupling was kept off. LINCS was used as constraint algorithm.

NVT equilibration was followed by equilibration in NPT ensemble. This equilibration was done for 1 ns. The parameters were specified as in NVT equilibration however pressure coupling was done in addition using Berendsen barostat.

After equilibration of the system, a series of configuration were generated along the reaction coordinates. These configurations were then run in independent simulations. For generating configuration, we performed a pulling simulation for different windows. We then selected the frames based on their spacing and prepared for umbrella sampling. A short equilibration was then performed on the configuration of sampling windows. Umbrella sampling and production run for every window were performed by following the procedure of molecular dynamics simulation. The data collected from umbrella sampling was subjected to analysis by extracting potential of mean force using WHAM (weighted histogram analysis method).

3. Results and Discussion

The propane dimer modeled by specifying the parameters was kept inside a cubic box along with solvents water, acetonitrile and methanol respectively. The simulations were carried out for time period of 10 ns. In this section we discuss the structural properties of the system by analyzing the radial distribution function and the hydrophobic interactions in terms of potential of mean force.

Propane dimer in water

The simulation has been carried out with 2160 water molecules and 2 propane molecules in the box size of 4 nm.

After performing umbrella sampling, potential of mean effective force (PMEF) was determined by using WHAM. We then applied volume entropy correction to obtain potential of mean force (PMF). The system is shown in Figure 2 and the potential of mean effective force between the solutes in water is shown in Figure3.

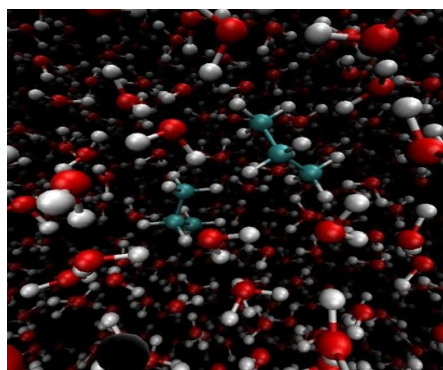


Fig. 2: Propane-Water system.

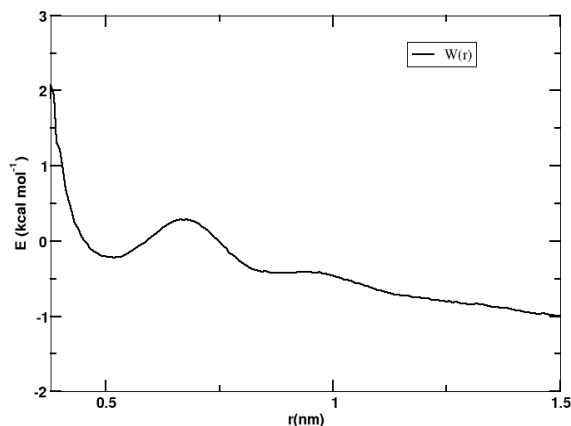


Fig 3: The potential of mean effective force calculated by means of umbrella sampling for water-propane system.

The first minima seen at 0.49 nm represents the minimum energy distance. This distance is the equilibrium distance between the molecules in the absence of solvent environment. This minima

resembles the LJ potential minima and is also regarded as contact minima. The contact minima is the position of minimum energy where the solute (propane) molecules come in contact with each other. Similarly the position of desolvation barrier represents the position when the solvent molecules are just about to penetrate the solute. Likewise, the position of solvent separated minimum resembles a layer of solvent in between the solutes.

The contact minima is followed by a hump representing the desolvation barrier which ends at 0.84 nm, i.e the position of second minima. The decreasing nature of PMEF has caused the second minima to be indistinct in absence of volume entropy contributions. For larger separations, the system becomes unstable as shown by the decreasing slope of PMEF curve.

We apply volume entropy correction in PMEF to obtain PMF. The volume entropy correction is given by $2k_B T \ln(r)$ and is shown in Figure 4. The Boltzmann's constant is taken to be $0.002 \text{ kcal mol}^{-1} \text{ K}^{-1}$ and temperature (T) is 298 K.

When the volume-entropy correction was done for the same system, we obtained the graph for potential of mean force with correction as in Figure 5.

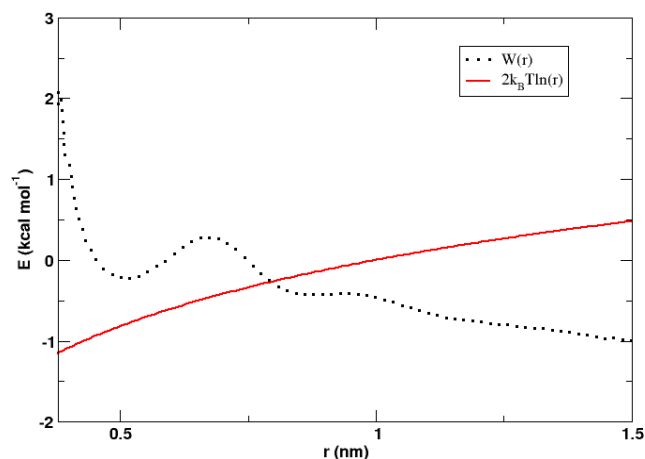


Fig. 4: The volume entropy correction term and PMEF shown together.

As discussed before, the observed contact minima at position 0.49 nm is followed by the hump. Further, second minima is seen at 0.84 nm just at the end of

hump. The addition of volume entropy correction term $2k_B T \ln(r)$ with the PMEF (Figure 3) line gives the potential of mean force. The PMF line has distinct second minima at 0.83 nm.

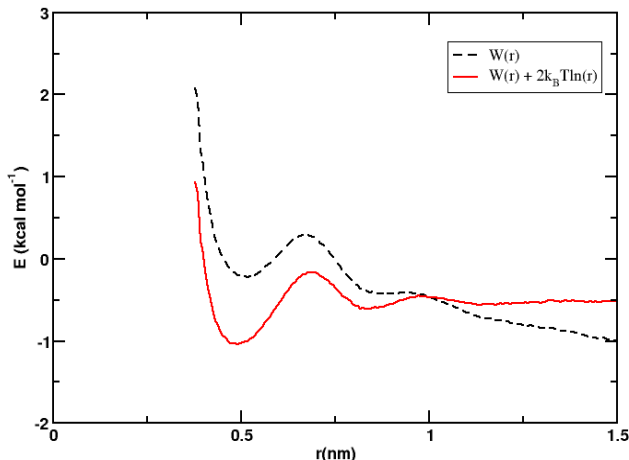


Fig. 5: The potential of mean effective force calculated by means of umbrella sampling for propane dimer in water.

This minima is also called solvent separated minima as it is the distance between the propane molecules separated by a layer of water between them. In other words, the second minima is the effect of solvent environment. The depth of contact minima is -0.58 kcal/mol and the solvent separated minima is -0.14 kcal/mol .

Structure of system

Radial distribution function is used to analyze the structure of solvent. The RDF of solvent describes the equilibrium structure of the water molecules in simulation box. Since, we have used SPC/E model for water in our simulation, the hydrogen atoms in water do not take part in LJ interaction with any other atoms.

RDF of central carbon of propane and oxygen of water (C2-OW)

Figure 6 shows the RDF $g_{C2-OW}(r)$ at 298 K temperature. Oxygen atom of water is taken as reference and is allotted a position at origin. The position of carbon atom with reference to this oxygen atom is studied with the help of Figure 6.

RDF shows first peak at 0.48 nm which is the most probable position of the closest carbon atom with respect to the reference propane molecule. Similarly, the second peak at 0.758 nm represents the position for second solvation shell. Beyond the second peak the RDF is a straight line with unit

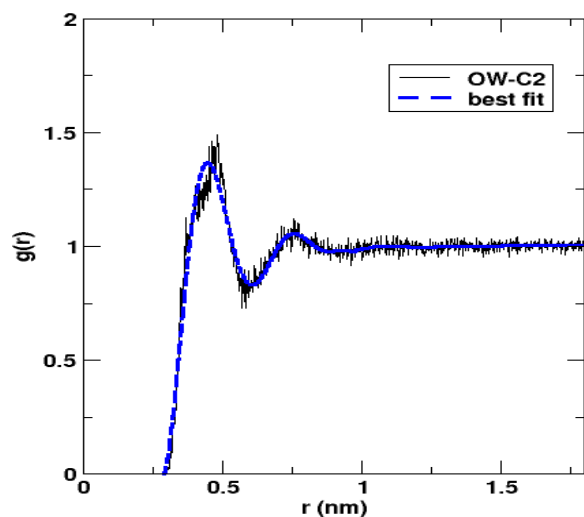


Fig. 6: RDF $g_{C2-OW}(r)$ for central carbon atom of propane with oxygen of water as reference.

value. The region up-to the distance of 0.294 nm is the exclusion region. This is the region around the reference atom without the possibility of presence of another atom.

The value of sigma (σ) for the atoms (OW-C2) is 0.327 nm and the van der Waals radius corresponding to this value of σ is 0.367 nm. The value of excluded region is less than the van der Waals radius, which is in agreement with the theory that no particle can be found in the excluded region. The dashed line in the graph is the line fitted for tenth order polynomial.

RDF of oxygen of water and oxygen of water (OW-OW)

Figure 7 depicts the RDF $g_{OW-OW}(r)$ at 298 K. This RDF represents the probability of finding the oxygen atoms at a distance (r) around the reference oxygen atom. In figure the reference oxygen atom is at zero (origin) and first peak represents the oxygen

atoms closest to the reference oxygen atom. The radial distribution function is essentially zero between origin (zero) and the molecular separation. The second peak is the position of the second closest atom and so on.

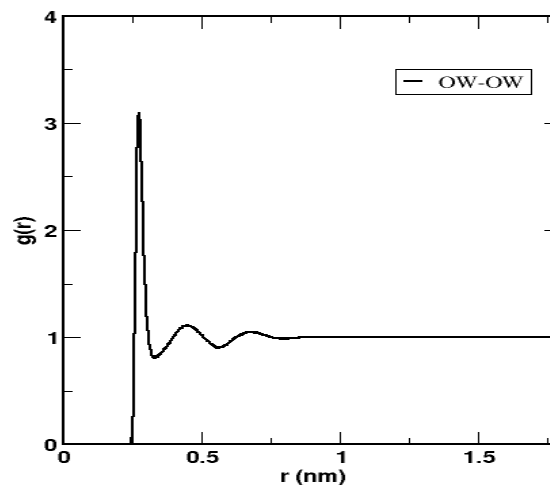


Fig 7: The RDF g_{OW-OW} , oxygen atom of water with another oxygen atom from reference water molecule.

As seen in Figure 7, three distinct peaks of height 3.088, 1.110, and 1.051 are obtained at distances 0.274 nm, 0.446 nm, and 0.684 nm respectively at 298 K.

This implies that the oxygen atom is at a distance 0.274 nm from the reference atom. Beyond the third peak the RDF is straight line with average value 1. The zero value of RDF from origin to the distance of 0.240 nm is the exclusion region. This is the minimum distance between the oxygen atoms and represents the intermolecular separation. The value of sigma (σ) for the atoms (OW-OW) is 0.315 nm and the van der Waals radius corresponding to this value of σ is 0.353 nm. Here, the value of excluded region is less than the van der Waals radius.

RDF of oxygen of water and terminal Carbon of propane (OW-C1)

To study the arrangement of terminal carbon atoms of propane around the oxygen atoms of water, we analyze the RDF g_{OW-C1} . Figure 8 shows g_{OW-C1} .

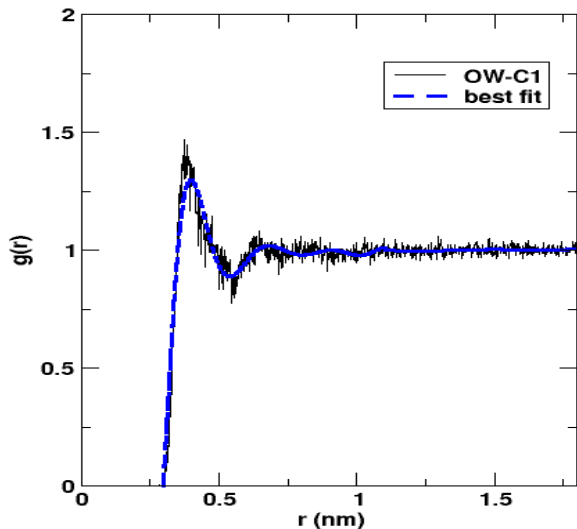


Fig. 8: The RDF g_{OW-C1} , terminal carbon of propane with oxygen atom of water as reference.

Two distinct peaks are seen at 0.374 nm and 0.646 nm with height of 1.471 and 1.084 respectively. The first peak represents the position of terminal carbon closest to the reference oxygen. Likewise, second peak represents the second closest atom. After, the second peak we can see a straight line with value 1. In this case, the exclusion region is seen up-to the distance of 0.290 nm. This implies that the terminal carbon of propane maintains at least this distance with the oxygen atom of water. The value of sigma (σ) for the atoms (OW-C1) is 0.327 nm and the van der Waals radius corresponding to this value of σ is 0.367 nm.

Propane dimer in acetonitrile

We took acetonitrile as solvent medium and performed similar simulations and procedures just like in water. The following Figure 9 shows our system and Figure (10) shows the PMEF and PMF of the system.

The system was prepared by adding propane dimer in solvent environment of 676 acetonitrile molecules. Whole process of simulation was repeated for this

system just like in water to obtain the PMEF and PMF curve depicting the contact minima along with solvent separated minima.

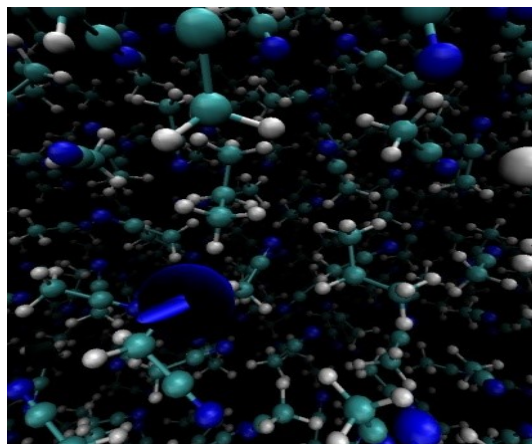


Fig. 9: Propane-acetonitrile system.

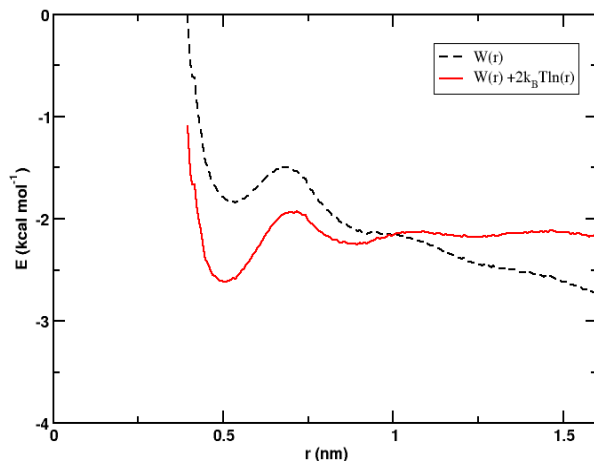


Fig 10: The potential of mean effective force calculated by means of umbrella sampling for propane dimer in acetonitrile.

In this case, the contact minima was seen at 0.50 nm followed by dissolution barrier and solvent separated minima at 0.90 nm. These minima are seen to have shifted to a larger distance than water. The depth of contact minima and solvent separated minima are -0.47 kcal/mol and -0.10 kcal/mol respectively.

Structure of system

As in water the structure of system was analyzed with the help of RDF. RDFs were used to

understand the radial distribution of molecules around a reference molecule.

RDF of carbon (of -CN group) of acetonitrile with reference carbon atom (of -CN group)

The Figure 11 shows the radial distribution function of carbon atom (C2) of cyanide group of acetonitrile molecule with respect to the similar carbon atom (C2) taken as reference. The RDF represents the probability of finding the carbon atom at certain distance from the reference atom.

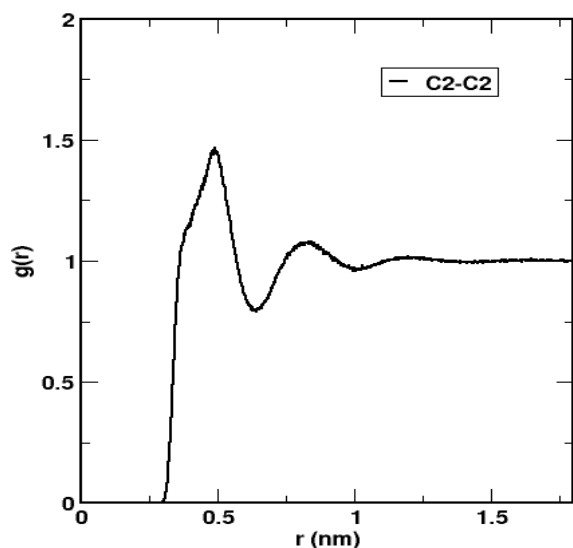


Fig. 11: The RDF g_{C2-C2} , Carbon of cyanide group with carbon of another cyanide group as reference molecule.

In Figure 11 first, second and third peaks are seen at the distance of 0.492 nm, 0.834 nm and 1.196 nm respectively. The first peak represents the most probable position for the closest cyanide carbon with respect to the reference carbon atom. We thus can expect the first solvation shell at 0.492 nm, second at 0.834 nm and so on. After the third peak, the RDF is seen to be a straight line with unit value. The exclusion region is observed up-to 0.294 nm from the reference atom. From this RDF, it can be assumed that the atoms maintain a minimum distance of 0.294 nm between them. Further, the value of sigma (σ) for the atoms (C2-C2) is 0.336 nm and the van der Waals radius corresponding to

this value of σ is 0.377 nm. The value of excluded region is less than the van der Waals radius, which agrees with the theory that no particle can be found in the excluded region.

RDF of Carbon atom (of methyl group) of Acetonitrile and Terminal Carbon of Propane (C1-C1)

The Figure 12 shows the radial distribution function of terminal carbon of propane with reference to carbon atom of acetonitrile. The peaks represent the most probable positions for carbon of solute with another carbon of solvent as reference.

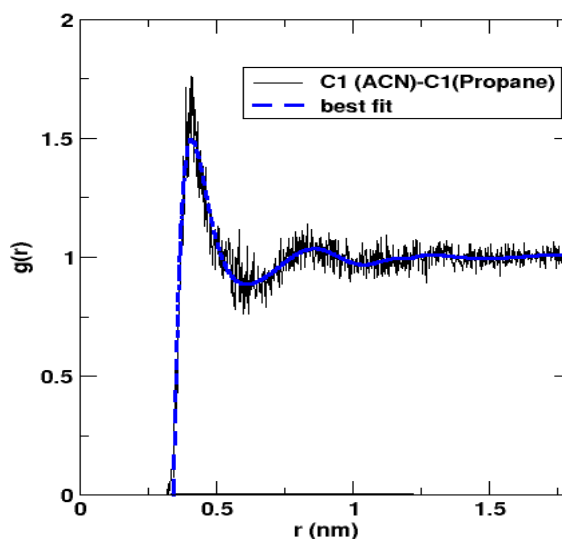


Fig. 12: The RDF g_{C1-C1} , terminal carbon of propane with methyl carbon of acetonitrile as reference molecule.

The RDF Figure 12 shows the first and second peak positions at distances 0.406 nm and 0.834 nm with corresponding heights 1.761 and 1.140. After the second peak position RDF is a straight line with value unity. It means that the most probable position of terminal carbon of propane is at distance 0.406 nm from the reference atom. Similarly, the second most probable position is at 0.834 nm. Since there are only two propane molecules, it is logical to get two peaks only. As in other RDFs, exclusion region up-to 0.322 nm represents the region without any possibility of

finding carbon atom of propane around the methyl carbon of reference molecule. The value of sigma (σ) for the atoms (C1-C1) is 0.339 nm and the van der Waals radius corresponding to this value of σ is 0.380 nm.

RDF of central carbon of propane and nitrogen of acetonitrile (C2-N3)

Following graph 13 depicts the position of nitrogen atom of cyanide group of acetonitrile with reference to the central carbon atom of propane. The reference carbon atom is considered to be at the origin and the corresponding probable positions of nitrogen are shown in graph.

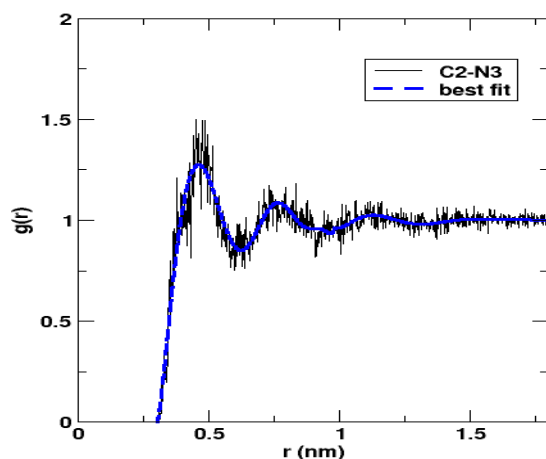


Fig. 13: The RDF g_{C2-N3} , nitrogen of acetonitrile with central carbon of propane as reference molecule.

The first peak position at 0.454 nm is the most probable position of finding propane molecule with the peak height of 1.501 followed by second peak at distance 0.834 nm with height 1.180. The third peak is observed at position 1.064 nm and the RDF curve gains value of unity thereafter. The exclusion region shows that the atoms are maintaining a distance of at least 0.3 nm between them. The value of sigma (σ) for the atoms (C2-N3) is 0.334 nm and the van der Waals radius corresponding to this value of σ is 0.375 nm. The dashed line in the graph is the line fitted for tenth order polynomial.

Propane Dimer in Methanol

Methanol was also considered as a solvent media

for the same solute dimer of propane. Figure 14 shows our system of methanol and propane dimer.

This system was prepared by adding propane dimer in 943 methanol molecules. The calculations were performed as in case of water and acetonitrile to obtain the graph for PMF. The resulting graph for PMEF and PMF after volume

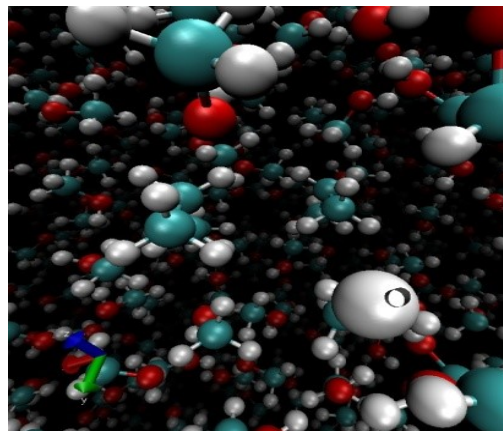


Fig. 14: Propane-methanol system.

entropy correction is demonstrated in Figure (15).

The PMF curve shows the first minima at 0.53 nm and second minima at 0.96 nm. These minima have shifted towards larger distances than in water and acetonitrile. Similarly, the depth of contact minima and solvent separated minima are

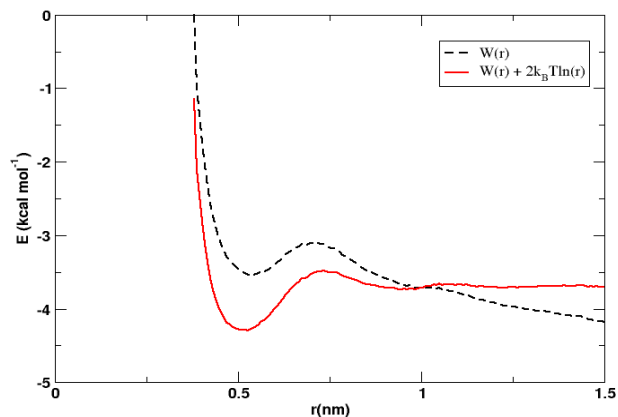


Fig. 15: The potential of mean effective force (PMEF) and potential of mean force (PMF) calculated by means of umbrella sampling for propane dimer in methanol.

-0.55 kcal/mol and -0.01 kcal/mol respectively.

Structure of system

The structure for this system was also analyzed with the help of RDF curve. The positions of the peaks were used to estimate the position of molecules around each other.

RDF of carbon and carbon of methanol (CB-CB)

The RDF of carbon atom present in methyl group of methanol with carbon from another methanol molecule, represented by Figure 16 has the peak positions at 0.404 nm, 0.786 nm and 1.160 nm representing the position of first, second and third solvation shell respectively. The distance of 0.306 nm is the distance between the atoms as represented by exclusion region of RDF. The RDF in this region has a zero value because it is the distance around the reference atom that has no possibility of finding another atom under observation. The value of sigma (σ) for the atoms (CB-CB) is 0.339 nm and the van der Waals radius corresponding to this value of σ is 0.380 nm. The value of excluded region is less than the van der Waals radius, which agrees with the theory that no particle can be found in the excluded region.

The peak positions are seen at distances 0.508 nm, 0.87 nm and 1.314 nm representing the first shell, second shell and so on. The exclusion region with zero value of RDF is observed up-to 0.322 nm, representing the minimum distance that the atoms maintain between them. The value of sigma (σ) for the atoms (CB-C2) is 0.339 nm and the van der Waals radius corresponding to this value of σ is 0.380 nm. The value of excluded region is less than the van der Waals radius. The dashed line in the graph is the line fitted for tenth order polynomial.

The obtained results for all the solvent environment are tabulated in Table II. E_1 and E_2 are in kcal/mol and represent the depth of contact minima and solvent separated minima respectively.

Comparison of pmf in water, acetonitrile and methanol

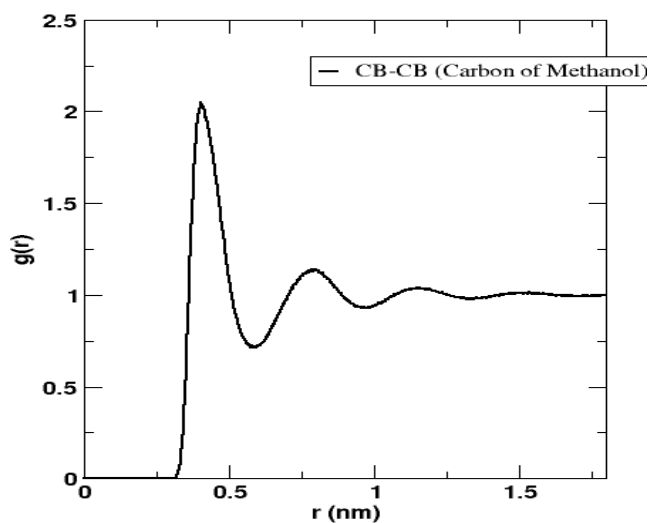


Fig. 16: The RDF g_{CB-CB} , carbon of methanol with carbon of reference methanol molecule.

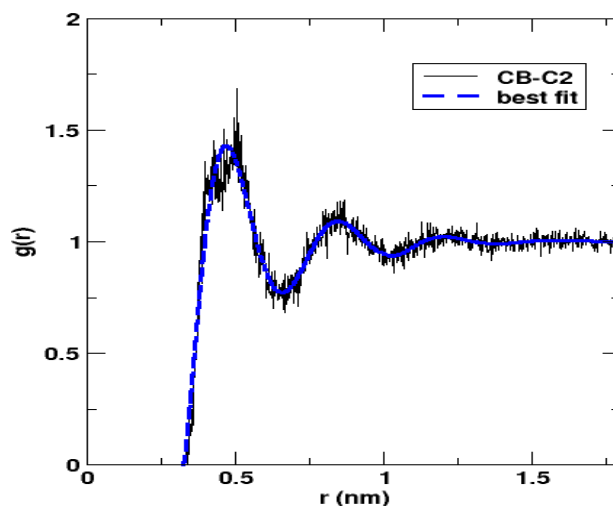


Fig. 17: The RDF g_{CB-C2} , central carbon atom of propane with carbon of methanol as reference atom.

Comparing structures of PMFs and their contact minimum, it is seen that contact minimum is stiffer in water rather than that in methanol and acetonitrile. The presence of methyl group in both solute and solvent (in case of methanol and acetonitrile) might have caused competitive interaction between similar groups.

This results wider (shallower) contact minima in such cases. Further investigations are to be done to have better understanding of this result.

Table II: Details of PMF curve for propane dimer in different solvents.

| Solvents | Contact minima (nm) | E1 kcal/mol | Solvent separated minima (nm) | E2 kcal/mol |
|--------------|---------------------|-------------|-------------------------------|-------------|
| Water | 0.49 | -0.58 | 0.84 | -0.14 |
| Acetonitrile | 0.50 | -0.47 | 0.90 | -0.10 |
| Methanol | 0.53 | -0.55 | 0.96 | -0.01 |

Figure 18 shows that the addition of solvent does not have greater effect on position of contact minima but it shows distinct effect on the solvent separated minima. The PMF curve shows a characteristic shape with deep minima at about 0.49 nm, 0.50 nm and 0.53 nm for water, acetonitrile and methanol respectively.

The comparison of the obtained results for propane dimer in water with the previous works shows good agreement. In the reference [5] the position of contact minima and solvent separated minima are 0.49 nm and 0.82 nm respectively. Our result for position of contact minima (0.49 nm) corresponds with the reference and the result for position of second minima (0.84 nm) shows a discrepancy of 2.4% [8].

This discrepancy might be due to the difference in the model of solvent used in the reference and in our work. In contrast to the TIP3P model of water and AMBER force field used in reference we used SPCE model of water in CHARMM force field.

Conclusions and concluding remarks

Molecular Dynamics simulations of systems containing a propane dimer and different solvents (water, acetonitrile and methanol) were carried out. Classical MD simulations were done using GROMACS and CHARMM force fields. Umbrella sampling was done for biased sampling and WHAM was used for unbiasing the potential.

We obtained the PMF curve for each system and observed its characteristic shape. The PMF curve possessed its characteristic shape with two distinct minima along with dissolution barrier. The results for propane-water system were compared with previous works. Comparison shows a good agreement in the position of contact minima (at 0.49 nm) and a small

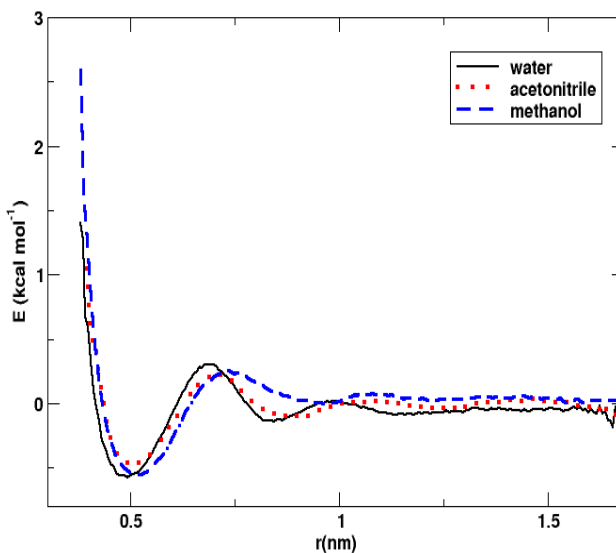


Fig. 18: The potential of mean effective force calculated by means of umbrella sampling for propane dimer in water (solid line), acetonitrile (dotted dash line) methanol (dotted line).

discrepancy (of 2.4%) in the position of solvent separated minima (at 0.82 nm in reference and 0.84 nm in our work). With satisfactory results in water medium we conclude that the results for other two mediums are also reliable. Further, we observed the shifting of solvent separated minima towards larger distance for acetonitrile and methanol than in water, as in the reference works.

In this study, we observed the solvent perturbation on non-polar solute-solute interactions and the results were compared with previous works to study the size effect of hydrophobic interactions. In future, this work can be further extended to study the effect of temperature, shape of solvent environment or

solvents other than water, acetonitrile and methanol. Similar studies can also be done in alkanes like butane, pentane.

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