

MOLECULAR DYNAMICS SIMULATION OF ADENINE AND ITS DERIVATIVE IN DIMETHYL SULFOXIDE-WATER MIXTURE

ROBIN JAIN AND SHYAM KISHOR

Computational Chemistry Research Laboratory, Deptt. of Chemistry, Janta Vedic College, Baraut-250611, (U.P.)

RECEIVED : 13, April 2017

The interaction between the nucleic acid base (NABs) such as adenine and the solvent molecules plays a crucial role in understanding the chemistry of several molecular processes. We present results of constant volume constant temperature classical molecular dynamics (MD) simulation of solvation dynamics of adenine and methyadenine in dimethylsulfoxide (DMSO)-water binary mixture. Various structural and dynamical properties have been calculated and results are compared with the available experimental results.

KEYWORDS : MD simulation, Nucleobases, binary solution.

INTRODUCTION

Solvation dynamics in liquid phases of wide variety of chemical systems have been extensively studied [1, 2] employing experiment, theory and molecular dynamics (MD) simulations. In contrast to one-component solvents, studies of the solvation dynamics in mixed solvents are still relatively scarce. Amongst the binary solvents, DMSO-water system are of special interest because of their unique physio-chemical properties [1] and biological importance [2, 3, 4, 5, 6, 7]. To understand the molecular mechanism responsible for these properties require accurate description of the solvation dynamics of the DMSO-water systems in absence and presence of solute molecules including simple bio-molecules in addition to several other crucial information. Computer simulation techniques are well suited for investigating structure and dynamics of such solutions.

Systematic studies of the microscopic structure and dynamics of bioorganic molecule such as nucleobases in presence of binary mixture are however yet to appear. In the work described in the present paper, the structural aspects of the solvation shell and dynamics of adenine and its derivative (methyladenine) in water – DMSO mixture with 0.2 X_{DMSO} (mole fraction of DMSO) have been investigated. The work is organized as follows. In Section II, the computational method and details are briefly outlined. The results of our calculations are presented and discussed in Section III. The conclusions are summarized in the Section IV.

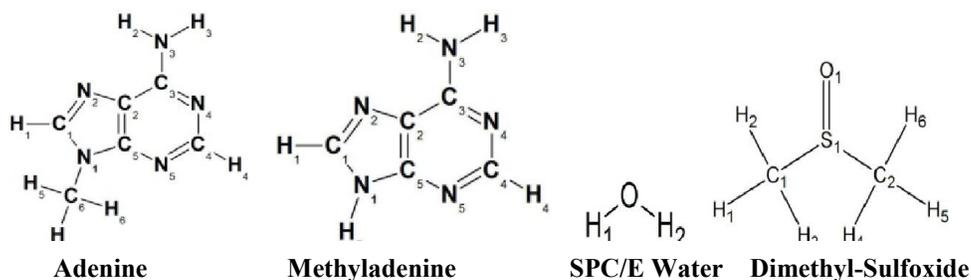


Fig. 1. Molecular structure and atomic numbering in adenine, methyladenine, SPC/E water and di-methyl sulfoxide (DMSO).

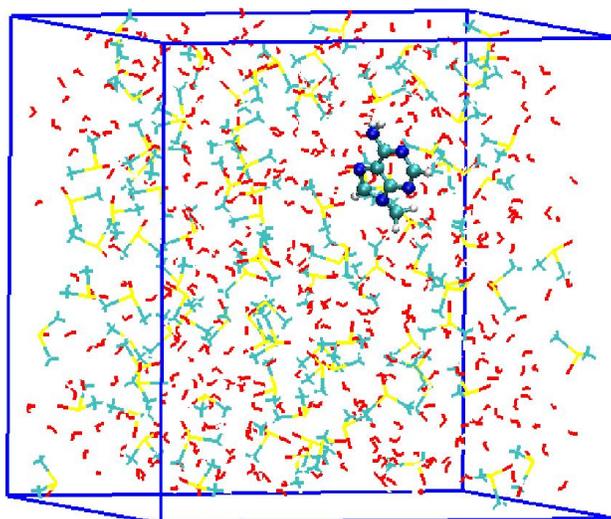


Fig. 2. Representative snapshot of the solute-solvent system as used in the present molecular dynamics simulations. The solvent molecules are depicted by line representation and the solute molecule by ball-and-stick model.

COMPUTATIONAL DETAILS

The calculations were carried out using classical molecular dynamics as implemented in AMBER-12 code [2]. In the present work, a single solute molecule (adenine or methyladenine) is immersed in a DMSO-water binary solvent. Both solvent and solute molecules are treated as rigid and nonpolarizable bodies and are characterized by multisite interaction models. The water molecules are described by three site extended simple point charge (SPC/E) potentials [22] in built in Amber-12 code. To parameterize generalized Amber force field (GAFF) for the other solvent (DMSO) and solutes (adenine and methyladenine), the respective molecules were optimized at HF/6-31G+(d) level by GAUSSIAN program [2] and the atomic point charges were calculated using restrained electrostatic potentials (RESP) [3]. The interaction between the atomic sites, i and j , at \mathbf{r}_i and \mathbf{r}_j positions are expressed as

$$u(\mathbf{r}_i, \mathbf{r}_j) = 4\epsilon_{ij} \left[\left(\frac{\sigma_{ij}}{r_{ij}} \right)^{12} - \left(\frac{\sigma_{ij}}{r_{ij}} \right)^6 \right] + \frac{q_i q_j}{r_{ij}}$$

where q_i is the charge of the i^{th} atom. The expression is a combination of both short range and long range interaction components. The Lennard-Jones (LJ) parameters σ_{ij} and ϵ_{ij} are obtained using the Lorentz-Berthelot rules $\sigma_{ij} = (\sigma_i + \sigma_j)/2$ and $\epsilon_{ij} = \sqrt{\epsilon_i \epsilon_j}$ where σ_i and ϵ_i are the LJ diameter and well-depth parameter for i^{th} atom or ion. The values of the potential parameters q_i , σ_i and ϵ_i for solvent molecules (water and DMSO) and solute molecules (adenine and methyladenine) that have been considered in this study are summarized in Table I and II respectively.

Table 1. Lennard-Jones parameters and partial charges for water and DMSO.

Atom	σ (Å)	ϵ (kJ/mol)	Charge (e)
S (DMSO)	3.564	0.250	0.360
O (DMSO)	2.960	0.210	-0.510
C (DMSO)	3.400	0.110	-0.424
H (DMSO)	2.471	0.016	0.166
O (Water)	3.151	0.152	-0.834
H (Water)	0.000	0.000	0.417

Table 2. Lennard-Jones parameters and partial charges for various atoms of solute.

Adenine				Methyladenine			
Atom	σ (Å)	ϵ (kJ/mol)	Charge (e)	Atom	σ (Å)	ϵ (kJ/mol)	Charge (e)
C2	3.400	0.086	-0.043	C2	3.400	0.086	-0.110
N2	3.250	0.170	-0.590	N2	3.250	0.170	-0.561
C1	3.400	0.086	0.318	C1	3.400	0.086	0.168
H1	2.650	0.016	0.127	H1	2.650	0.016	0.151
N1	3.250	0.170	-0.626	N1	3.250	0.170	-0.063
H5	1.070	0.016	0.413	C6	3.400	0.110	-0.326
C5	3.400	0.086	0.692	H5	2.650	0.016	0.143
N5	3.250	0.170	-0.790	C5	3.400	0.086	0.545
C4	3.400	0.086	0.565	N5	3.250	0.170	-0.783
H4	2.650	0.016	0.073	C4	3.400	0.086	0.616
N4	3.250	0.170	-0.784	H4	2.650	0.016	0.055
C3	3.400	0.086	0.739	N4	3.250	0.170	-0.817
N3	3.250	0.170	-0.922	C3	3.400	0.086	0.811
H2	1.070	0.016	0.414	N3	3.250	0.170	-0.947
				H2	1.070	0.016	0.416

The MD simulations were carried out in cubic cell of length 28.76 Å with a single solute molecule immersed in 512 solvent molecules (410 water + 102 DMSO) at 300 K. During the simulation, all intra-molecular bonds were constrained using the SHAKE algorithm [2, 3]. For the coulomb interaction a cut-off of 8.0 Å has been set to limit the direct space sum. The long range electrostatic interactions were treated using the Ewald method [2]. Periodic boundary condition [5] were utilized to avoid the hindrance of a large fraction of molecules lying on the containing wall [8]. The time step of the simulation was set to 0.5 fs. The NVT simulation was carried out in five steps, viz. minimization, heating, relaxation, equilibration and production. During minimization both the system was minimized up to an energy gradient 1×10^{-3} Kcal mol⁻¹ Å. During heating, the system was heated gradually for 100 ps up to 300 K

with a restrain on solute molecule. The temperature was regulated using Langevin dynamics [2] with a collision frequency of 1 ps^{-1} . In the relaxation step, the solute molecule was relaxed by applying a series of restraints and the force constant decreased progressively. In equilibration run, the system was equilibrated for 2500 ps without any restraint and constraint. Subsequently the production run was continued for 25 ns and snapshots were saved at an interval of 0.05 ps for calculation of structural and dynamical properties.

RESULTS

A. Radial distribution functions: The simplest quantity which describes the local structure at the molecular level is the site-site radial distribution functions $[g(r)]$ of different pairs as shown in Figs. 3-5. The corresponding radial integration number or coordination number $[n(r)]$ are also shown.

(a) Solvent-Solvent interaction:

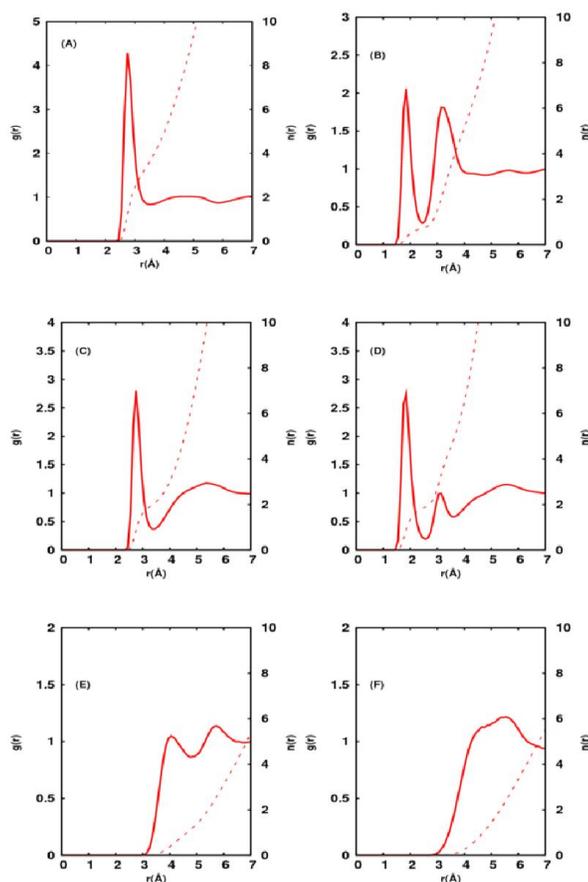


Fig. 3. The intermolecular radial distribution functions (RDF) for water-DMSO mixture. The different panels are: (A) oxygen (water) – oxygen (water), (B) oxygen (water) – hydrogen (water), (C) oxygen (DMSO) – oxygen (water), (D) oxygen(DMSO)-hydrogen(water), (E) Carbon(DMSO)-Carbon(DMSO) and (F) oxygen(DMSO)-oxygen(DMSO). The dashed line in each panel represents the corresponding running coordination number $n(r)$.

The pair correlation function obtained from our classical MD simulation for the water-water, DMSO-DMSO and Water-DMSO from methyladenine-water-DMSO solutions are given in Fig. 3. The system names are meaningful. The two capital letters specifies which two solvent molecules are present (W-water and D-DMSO) and the atom type and atom number are represented by the subscript. Table 3 gives the location of first maximum (r_{M1}), first minimum (r_{m1}), second maximum (r_{M2}) and second minimum (r_{m2}). Table 3 also contains for comparison the pair correlation function of pure water-DMSO binary solution obtained from experimental [2] and earlier classical and *ab initio* simulations. The sharp first peak in the $W_O W_H$ and $W_H W_H$ RDF corresponding the first solvation shell and the position of the peak indicates strong hydrogen bond between water molecules. The position of the first maximum is located at 1.85 Å for the $W_O W_H$ RDF and at 2.75 Å for the $W_O W_O$ RDF. The second hump at $r = 4.5$ Å in $W_O W_H$ RDF is a signature of the tetrahedral nature of hydrogen bonding [3]. On comparing the results with the experimental and previous simulation investigation [21, 3, 4] confirm that the most probable local structure of water is unaffected in presence of DMSO and solute molecule.

In fig. 3(E), the RDF's of the methyl group of distinct DMSO molecules is presented. The plot is consistent with the previous studies [23, 2]. The lack of sharp peak in the Fig. 3 (F) indicates the lack of first solvation shell and association of DMSO molecule and justifies the theory of two DMSO molecule bridged by one water molecule [2, 3, 4] [Fig. 4(b)]. As shown in Fig. 3(D) and 3(C), the position of the first peaks for $D_O W_H$ and $D_O W_O$ are observed at 1.85 Å and 2.75 Å suggests a linear hydrogen bonding between water acting as donor and the DMSO molecule as an acceptor [Fig. 4(a)]. The result is consistent with the earlier simulation investigation [23].

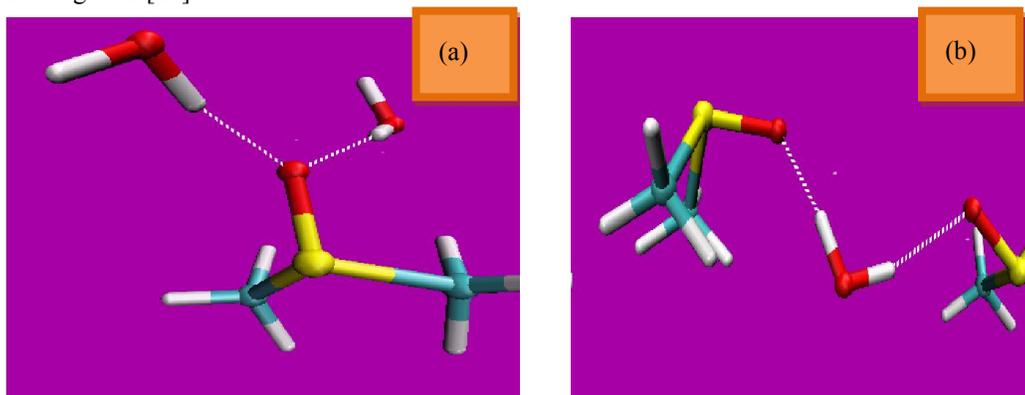


Fig. 4. Snapshots presenting DMSO-2H₂O aggregate (a) and 2DMSO-H₂O aggregate (b).

Table 3. Maxima r_M and minima r_m in Å obtained from RDFs plots. The system names are meaningful. The two capital letters specifies which two species are present (W-water, D-DMSO) while the subscript indicates atom type and atom number. Also given for comparison are the theoretical values obtained from the literature (*).

Pair	r_{M1}	r_{m1}	r_{M2}	r_{m2}	$N(r)$	Figure No.
$W_O W_O$	2.75	3.55 (3.4)	4.85(4.5) [1]	5.85	3.72	3(A)
$W_O W_H$	1.85	2.45(2.5) ²⁰	3.15	4.75	3.44	3(B)
$D_O W_O$	2.75 (2.7) ²⁰	3.35 (3.4) ²⁰	5.35	7.45	0.49	3(C)
$D_O W_H$	1.85(1.7) ²⁰	2.55	3.15	3.65	1.89	3(D)

D _c D _c	4.05	4.75	5.75	6.75	3.43	3(E)
D _o D _o	-	-	5.55	7.35	-	3(F)

(b) Solute-Solvent interaction:

In order to gain microscopic insights about the solvation dynamics of adenine and methyladenine in the binary solvent, the solvent density in the close vicinity of sites: N2, N3, N4, N5, H2 and H5 are investigated. The solvation structures are described in terms of correlation between the solute sites and hydrogen and oxygen atoms in water and oxygen atom of DMSO. The RDFs of hydrogen of water around N2, N3, N4 and N5 atoms of adenine and methyladenine are given in Figure 5 and the positions (maxima & minima) of the peaks are summarized in Table 4. The solvation structure of methyladenine is similar to that of adenine and the presence of sharp peak at 1.95 Å or 1.85 Å suggests presence of well defined first solvation shell of water around N2, N4 and N5. The corresponding $n(r)$ values suggest the presence of one water molecule in the vicinity of N2, N4 and N5.

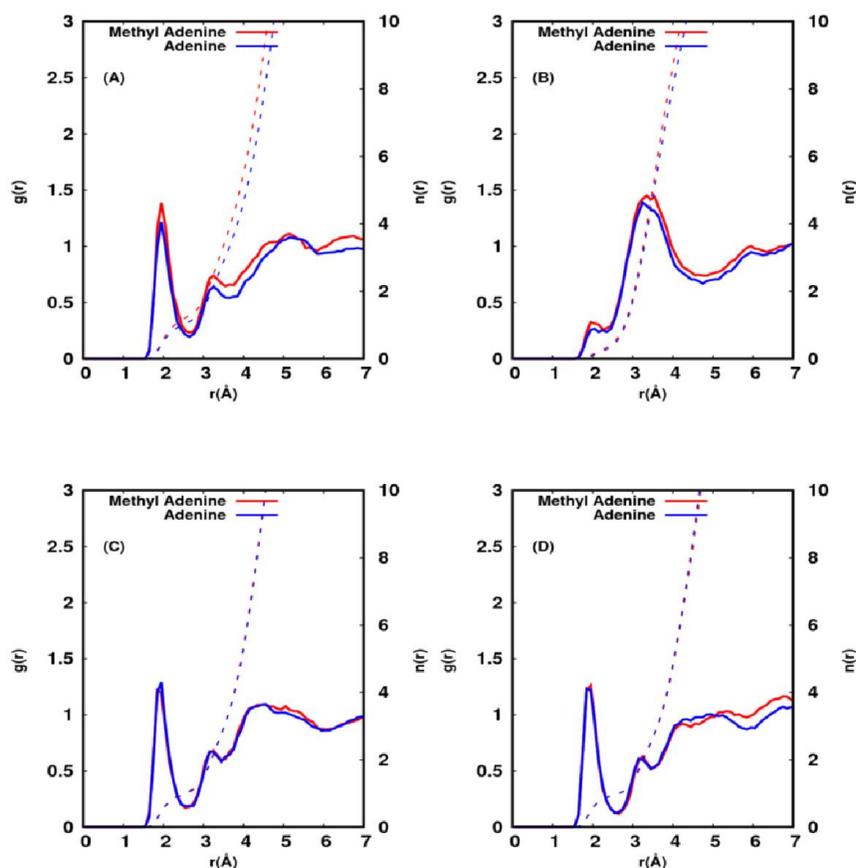


Fig. 5. The intermolecular radial distribution functions (RDF) for adenine and methyl adenine in water-DMSO mixture. The different panels are: (A) N2 – hydrogen (water), (B) N3 – hydrogen (water), (C) N4 – hydrogen (water), (D) N5 – hydrogen (water). The dashed line in each panel represents the corresponding running coordination number $n(r)$.

The Fig. 6 RDFs provide interesting information about the solvation structure around the hydrogen atoms attached to the nitrogens of adenine and methyladenine. The intensity of the first peak corresponding to the DMSO oxygen in the immediate vicinity of H2 (1.95 Å) in adenine and methyladenine and H5 (1.85 Å) in adenine are almost double to that of water oxygen suggesting a higher affinity for DMSO oxygen in comparison to water oxygen. The pair correlation around H5 in adenine is found to be in good agreement with other MD study in pure water [11].

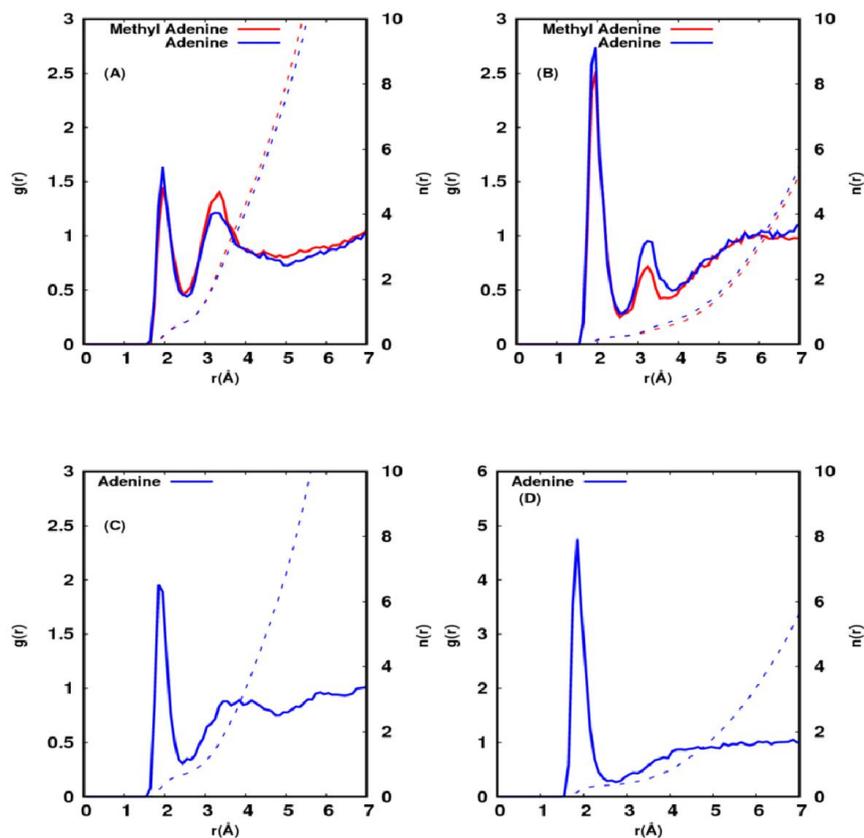


Fig. 6. The intermolecular radial distribution functions (RDF) for adenine and methyl adenine in water-DMSO mixture. The different panels are: (A) H2 – oxygen (water), (B) H2 – oxygen (DMSO), (C) H5 – oxygen (water) and (D) H5 – oxygen (DMSO).. The dashed line in each panel represents the corresponding running coordination number $n(r)$.

Table 4. Maxima r_M and minima r_m in Å obtained from RDFs plots. The system names are meaningful. The two capital letters specifies which two species are present (A-adenine, M-methyladenine, W-water, D-DMSO) while the subscript indicates atom type and atom number.

Pair	r_{M1}	r_{m1}	r_{M2}	r_{m2}	$N(r)$	Figure No.
$M_{N-2}W_H$	1.95	2.65	3.25	3.55	1.28	5(A)
$A_{N-2}W_H$	1.95	2.65	3.25	3.65	1.10	
$M_{N-3}W_H$	1.95	2.25	3.35	4.85	0.27	5(B)

$A_{N-3}W_H$	2.05	2.35	3.25	4.75	0.28	
$M_{N-4}W_H$	1.85	2.55	3.25	3.45	0.99	5(C)
$A_{N-4}W_H$	1.95	2.55	3.15	3.45	1.01	
$M_{N-5}W_H$	1.95	2.65	3.25	3.45	1.00	5(D)
$A_{N-5}W_H$	1.85	2.55	3.15	3.45	0.96	
$M_{H-2}W_O$	1.95	2.45	3.35	4.95	0.64	6(A)
$A_{H-2}W_O$	1.95	2.55	3.25	4.35	0.71	
$M_{H-2}D_O$	1.95	2.55	3.25	3.55	0.24	6(B)
$A_{H-2}D_O$	1.95	2.55	3.25	3.85	0.25	
$A_{H-5}W_O$	1.85	2.45	3.85	4.75	0.68	6(C)
$A_{H-5}D_O$	1.85	2.75	5.25	5.35	0.38	6(D)

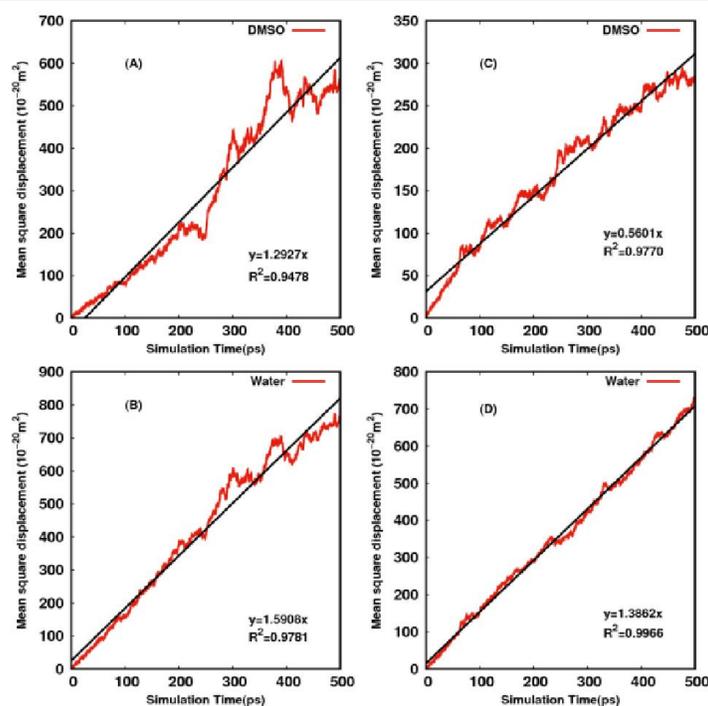


Fig. 7. The Mean square displacements of water and DMSO in the mixture. The different panels are: (A) DMSO (methyladenine in mixture) (B) water (methyladenine in mixture), (C) DMSO (adenine in mixture), (D) water (adenine in mixture).

B. Self-Diffusion coefficient analysis of Solvent molecules

The self diffusion coefficient water and DMSO is calculated using the Einstein equation [11]

$$D_s = \lim_{t \rightarrow \infty} \left[\frac{\langle |r(t) - r(0)|^2 \rangle}{6t} \right]$$

where $r(t)$ is the position vector of the centre of mass at time t . The results (self diffusion coefficient) obtained from the mean square displacement (MSD) of water and DMSO for systems containing adenine and methyladenine (Fig. 7) are summarized in Table 5. The self diffusion coefficient of DMSO and water is found to be higher for solution containing

methyladenine in comparison to the solution containing adenine. This notable change in the diffusion coefficient due to the stronger hydrogen bond interaction between the adenine molecule with water and DMSO molecules in comparison to that of methyladenine. This is verified from the Fig. 6(A) and 6(B) where the first peak around adenine is observed to be more pronounced than in methyladenine.

Table 5. Diffusion coefficients (in 10^{-9} m²/sec) of water and DMSO in different regions around the solute molecule.

System	Particle	D _{Theory} (10 ⁻⁹ m ² /sec)
Methyladenine (Water-DMSO)	DMSO	2.1545
	Water	2.6514
Adenine (Water-DMSO)	DMSO	0.9334
	Water	2.3104

CONCLUSION

In this work we have presented classical MD simulation study of the solvation of adenine and Methyladenine in water-DMSO mixture. Site-site intermolecular pair correlation function was studied at a concentration of 0.2 mole fraction of DMSO. Adenine and methyladenine have stronger hydrogen bond interaction with DMSO in comparison to water. In between the two solutes, adenine interaction with the two solvents is found to be higher in comparison to methyladenine.

ACKNOWLEDGEMENTS

We are thankful to the Inter-University Accelerator Centre (IUAC) – New Delhi for providing high performance computing lab facilities.

REFERENCES

1. For a general overview of the subject see for instance, Maroncelli, M., *J. Mol. Liq.*, **57**, 1 (1993); Rossky, P. J. and Simon, J. D., *Nature (London)*, **370**, 263 (1994); Fleming, G. R. and Cho, M. H., *Annu. Rev. Phys. Chem.*, **47**, 109 (1996); Barbara, P. F. and Jarzeba, W., *Adv. Photochem.*, **15**, 1 (1990).
2. For recent reviews emphasizing theoretical aspects, see Stratt, R. M. and Maroncelli, M., *J. Phys. Chem.*, **100**, 12981 (1996); Ladanyi, B. M. and Stratt, R.M., *ibid.*, **99**, 2502 (1995); **100**, 1266 (1996); Friedman, H. L., Raineri, F. O., Hirata, F. and Perng, B. C., *J. Stat. Phys.*, **78**, 239 (1995); Raineri, F. O. and Friedman, H. L., *Adv. Chem. Phys.*, **107**, 81 (1999); Bagchi, B. and Biswas, R., *ibid.*, **109**, 207 (1999).
3. Mancera, R.L., Chalaris, M., Refson, K. and Samios, J., *Phys. Chem. Chem. Phys.*, **6**, 94 (2004).
4. Ahkong, Q. F., Fischer, D., Tampion, W. and Lucy, J. A., *Nature*, **253**, 194 (1975).
5. Anchordoguy, T. J., Carpenter, J. F., Crowe, J. H. and Crowe, L. M., *Biochim. Biophys. Acta*, **117**, 1104 (1992).
6. Lovelock, J. E. and Bishop, M. W. H., *Nature*, **183**, 1394 (1959).
7. Anchordoguy, T. J., Ceccini, C. A., Crowe, J. N. and Crowe, L. M., *Cryobiology*, **28**, 467 (1991).
8. Jacob, S. W. and Herschler, R., *Cryobiology*, **23**, 14 (1986).
9. Willigan, J. R. and Ward, J. F., *Radiat. Res.*, **137**, 295 (1994).
10. Case, D.A., Darden, T.A., Cheatham, T.E., III, Simmerling, C.L., Wang, J., Duke, R.E., Luo, R., Walker, R.C., Zhang, W., Merz, K.M., Roberts, B., Hayik, S., Roitberg, A., Seabra, G., Swails, J., Götz, A.W., Kolossváry, I., Wong, K.F., Paesani, F., Vanicek, J., Wolf, R.M., Liu, J., Wu, X., Brozell, S.R., Steinbrecher, T., Gohlke, H., Cai, Q., Ye, X., Wang, J., Hsieh, M.-J., Cui, G., Roe,

- D.R., Mathews, D.H., Seetin, M.G., Salomon-Ferrer, R., Sagui, C., Babin, V., Luchko, T., Gusarov, S., Kovalenko, A. and Kollman, P.A., *AMBER*, 12 (2012), University of California, San Francisco.
11. Berendsen, H. J. C., Grigera, J. R. and Straatsma, T.P., *J. Phys. Chem.*, **91**, 6269 (1987).
 12. Frisch, M. J., Trucks, G. W., Schlegel, H. B., Scuseria, G. E., Robb, M. A., Cheeseman, J. R., Scalmani, G., Barone, V., Petersson, G. A., Nakatsuji, H., Li, X., Caricato, M., Marenich, A., Bloino, J., Janesko, B. G., Gomperts, R., Mennucci, B., Hratchian, H. P., Ortiz, J. V., Izmaylov, A. F., Sonnenberg, J. L., Williams-Young, D., Ding, F., Lipparini, F., Egidi, F., Goings, J., Peng, B., Petrone, A., Henderson, T., Ranasinghe, D., Zakrzewski, V. G., Gao, J., Rega, N., Zheng, G., Liang, W., Hada, M., Ehara, M., Toyota, K., Fukuda, R., Hasegawa, J., Ishida, M., Nakajima, T., Honda, Y., Kitao, O., Nakai, H., Vreven, T., Throssell, K., Montgomery, J. A., Jr., Peralta, J. E., Ogliaro, F., Bearpark, M., Heyd, J. J., Brothers, E., Kudin, K. N., Staroverov, V. N., Keith, T., Kobayashi, R., Normand, J., Raghavachari, K., Rendell, A., Burant, J. C., Iyengar, S. S., Tomasi, J., Cossi, M., Millam, J. M., Klene, M., Adamo, C., Cammi, R., Ochterski, J. W., Martin, R. L., Morokuma, K., Farkas, O., Foresman, J. B. and Fox, D. J., *Gaussian, Inc.*, Wallingford CT (2010).
 13. Bayly, C. I., Cieplak, P., Cornell, W. D. and Kollman, P. A., *J. Phys. Chem.*, **97**, 10269 (1993).
 14. Ryckaert, J. P., Ciccotti, G., Berendsen, H. J. C., *J. Comput. Phys.*, **23**, 327 (1977).
 15. Miyamoto, S., Kollman, P. A., *J. Comput. Chem.*, **13**, 952 (1992).
 16. Darden, T., York, D., Pedersen, L., *J. Chem. Phys.*, **98**, 10089 (1993).
 17. Alder, B. J. and Wainwright, T. E., *J. Chem. Phys.*, **31**, 459 (1959).
 18. Born, M., Karman, T. V., *Z. Physik*, **13**, 297 (1912).
 19. Pastor, R.W., Brooks, B. R., Szabo, A., *Mol. Phys.*, **65**, 1409 (1988).
 20. Soper, A. K. and Luzar, A., *J. Chem. Phys.*, **97**, 1320 (1992).
 21. Soper, A. K. and Luzar, A., *J. Phys. Chem.*, **100**, 1357 (1996).
 22. Vaisman, I.I., Berkowitz, M.L., *J. Am. Chem. Soc.*, **114**, 7889 (1992).
 23. Zhang, N., Li, W., Chen, C. and Zuo, J., *Computational and Theoretical Chemistry*, **1017**, 126 (2013).
 24. Banerjee, S., Roy, S., Baghchi, B., *J. Phys. Chem. B*, **114**, 12875 (2010).
 25. Borin, I.A., Skaf, M.S., *J. Chem. Phys.*, **110**, 6412 (1999).
 26. Wong, D.B., Sokolowsky, K.P., El-Barghouthi, M.I., Fenn, E.E., Giammanco, C.H., Sturlaugson, A.L., Fayer, M.D., *J. Phys. Chem. B*, **116**, 5479 (2012).
 27. Zhang, Q., Zhang, X., Zhao, D.-X., *J. Mol. Liq.*, **145**, 67–81 (2009).
 28. Chand, A. and Chowdhuri, S., *J. Chem. Sci.*, **128**, 1991 (2016).
 29. Furmanchuk, A., Isayev, O., Shishkin, O. V., Gorb, L. and Leszczynski, J., *Phys. Chem. Chem. Phys.*, **12**, 3363 (2010).
 30. Allen, M. P., Tildesley, D. J., *Computer Simulations of Liquids*, Oxford Science, Oxford (1987).

