J. Indian Inst. Sci.
A Multidisciplinary Reviews Journal
ISSN: 0970-4140 Coden-JIISAD

REVIEW ARTICLE

Hydration of Fluorobenzenes: A Molecular Dynamics Simulation Investigation

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Abstract | Molecular dynamics simulations of benzene and 12 fluorobenzenes with various degrees of fluorine substitution in water reveal that the accumulation of water in the first solvent shell decreases with increase in number of fluorine atoms relative to benzene, with an exception of hexafluorobenzene. Further, the solute–solute radial density function indicates that partially substituted fluorobenzenes sample π-stacked and T-shaped geometries. In contrast benzene and hexafluorobenzene sample only the T-shaped geometries. Comparison of solute–solute and solute–solvent radial density functions suggests that solute–solute interactions is preferred over solute–solvent interaction, which suggests the hydrophobic nature of fluorobenzenes, which increases with increase in number of fluorine atoms on the phenyl ring. The spatial distribution of water around the fluorobenzenes suggests that water avoids the C–F bond group, which indicates increase in hydrophobicity of fluorobenzenes with number of fluorine atoms.

1 Introduction

The C–H···F interactions in crystal structures of fluorinated organic compounds have structure directing ability similar to C–H···O and C–H···N hydrogen bonds[1–3]. However, the ability of the organic fluorine (C–F bond) to participate in hydrogen bonding has been a subject of debate [4, 5], and it has been concluded that C–F group is an extremely poor hydrogen bond acceptor. However, in recent times, it has been shown that organic fluorine does form weak hydrogen bonds[6–9]. Based on this unique property of C–F group, several experimental groups have investigated the ability of C–F group to impact the structures of biomolecular assemblies by substituting CH_3 group with CF_3 group [10, 11]. While these experimental investigations could bring out the differences in the properties of biomolecular assemblies with the substitution of C–F group vis-à-vis the C–H group, there has been very sparse attempt to rationalize these experimental results in terms of interaction potentials. In a recent report, it was pointed out that replacement of C–H group with C–F group in the side chain of amino acids involving methyl groups leads to changes in hydration free energy[12]; however, it was observed that the number of fluorine atoms is a poor predictor of hydrophobicity trends. In general, fluorine substitution is known to enhance the hydrophobic behavior of parent molecule; this capability of organic fluorine finds application in medicinal chemistry[13–15].

The most stable structure benzene–water dimer incorporates O–H···π interaction[16, 17], while interaction between oxygen lone-pair (lp) and π electron density (lp···π interaction) stabilizes the hexafluorobenzene–water dimer[18]. These dimer structures retain their significance in aqueous solvation of benzene and hexafluorobenzene. First principle molecular dynamics simulations of benzene and hexafluorobenzene in water reveal that hydration structure is distinct in these two cases with orientation of water molecules in accordance with the benzene–water and hexafluorobenzene–water dimer structures. Further, it was shown that the equatorial region of benzene and hexafluorobenzene behaves like typical hydrophobic solute; the solvation properties of the axial region depend strongly on the nature of water–π interactions[19]. Contrary

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to benzene and hexafluorobenzene, fluorobenzene and difluorobenzene complexes with water are stabilized by interaction in equatorial region with the formation of cyclic C–F⋯H–O⋯H–C structures, wherein water molecule simultaneous acts as hydrogen bond donor and acceptor[20]. The molecular dynamics simulations on partially substituted fluorobenzenes are almost non-existent in the literature, with an exception of molecular dynamics simulations of fluorobenzene with ten different solvents are reported, to understand the shielding of fluorine atom[21]. Importantly, the reversal of quadrupole moment from benzene to hexafluorobenzene makes the investigation of partially substituted fluorobenzenes more interesting[22]. Incorporation of explicit and large number of water molecules should provide sufficient insight on the hydrophobic interactions in benzene and fluorobenzenes. However, computation of large number of water molecules along with benzene and fluorobenzenes using first principle techniques is intractable. Thus, to overcome this limitation, classical molecular dynamics simulations based on Newtonian mechanics were carried out and the results are reported in this article.

2 Methodology

All-atom MD simulations were performed using GROMACS 2018.1 engine[23] using OPLS-AA[24] force field parameters for the fluorobenzenes which were taken from literature[25], along with TIP4P[26] water model. Initially, any bad contacts and steric clashes between atoms in the simulation box were removed by energy minimization which was carried out using steepest descent algorithm[27], with tolerance of 100 kJ mol^{-1}. Following energy minimization, each particle in the system was assigned velocity in accordance with Maxwell distribution of velocities. Maxwell distribution of velocities was generated at 298 K. This immediately follows the equilibration of simulation box in NVT ensemble. The temperature of system was relaxed for 100 ps using velocity-rescaling thermostat[28] with a relaxation time of 0.1 ps and a reference temperature of 298 K. Temperature relaxation was followed by pressure relaxation of the simulation box in NPT ensemble for 10 ns. Pressure equilibration was achieved using Berendsen barostat[29]. A relaxation time of 2 ps and reference pressure of 1 atm was used in pressure relaxation of simulation box. Leapfrog algorithm was used during simulation to integrate the equation of motion[30]. Periodic boundary condition was used during each step of simulation to account for any boundary effects in finite simulation box[31]. Long-range electrostatic interactions were accounted during simulation by Particle mesh Ewald method[32]. During simulation, a spherical cut-off of 1.2 nm was used for both electrostatic and van der Waals forces. To correct rotational lengthening of bonds during simulations, LINCS corrections were used[33]. During trajectory collection for analysis, temperature and pressure of system were maintained at 298 K and 1 atm using velocity-rescaling thermostat and Parrinello-Rahman barostat[34], respectively. Velocities, coordinates and energies of particles in simulation box were saved for every 10 ps over a period of 100 ns during production run simulations. To obtain radial distribution function of solute–water interactions, i.e., probability density of water around a given solute, one solute molecule (benzene/fluorobenzenes) was placed at the center of a 3.0-nm cubic simulation box along with ~ 900 TIP4P water molecules. To obtain solute–solute radial distribution function ten solute molecules along with ~ 1400 TIP4P water molecules were placed in a cubic simulation box of length 3.5 nm. A total of 2600 ns of MD simulations were carried out for 13 solute molecules considered in the present study. Fluorination of benzene results in 12 distinct fluorobenzenes (shown Fig. 1) which can be categorized into three sets based on their dipole moments. The OPLS-AA force field parameters were validated against the experimental densities of benzene and symmetrically substituted fluorobenzenes[35].

3 Results and Discussion

The radial distribution function (RDF), $g(r)$ as a function of distance between center-of-masses of solute and water is shown in Fig. 2d. For clarity, solute–water $g(r)$ is also shown in three more plots corresponding to solute molecules having dipole moment value of 0 D, ~ 5 D and ~ 10 D in Fig. 2. The RDF of benzene–water (black solid line in Fig. 2) shows three distinct maxima at 0.3, 0.5 and 0.75 nm. The maxima at 0.5 and 0.75 nm correspond to first and second solvation shells of benzene in water. The maxima at 0.3 nm is a distinct feature of where water molecule penetrates the first solvation shell of benzene to form O–H⋯π interaction[19]. Similarly, a shoulder can be observed in the case of RDF of hexafluorobenzene–water system, which is indicative of lp⋯π interaction. On the other hand, the RDFs of all the 11 partially fluorinated benzenes clearly show only two maxima corresponding to first (around 0.5 nm) and second (around

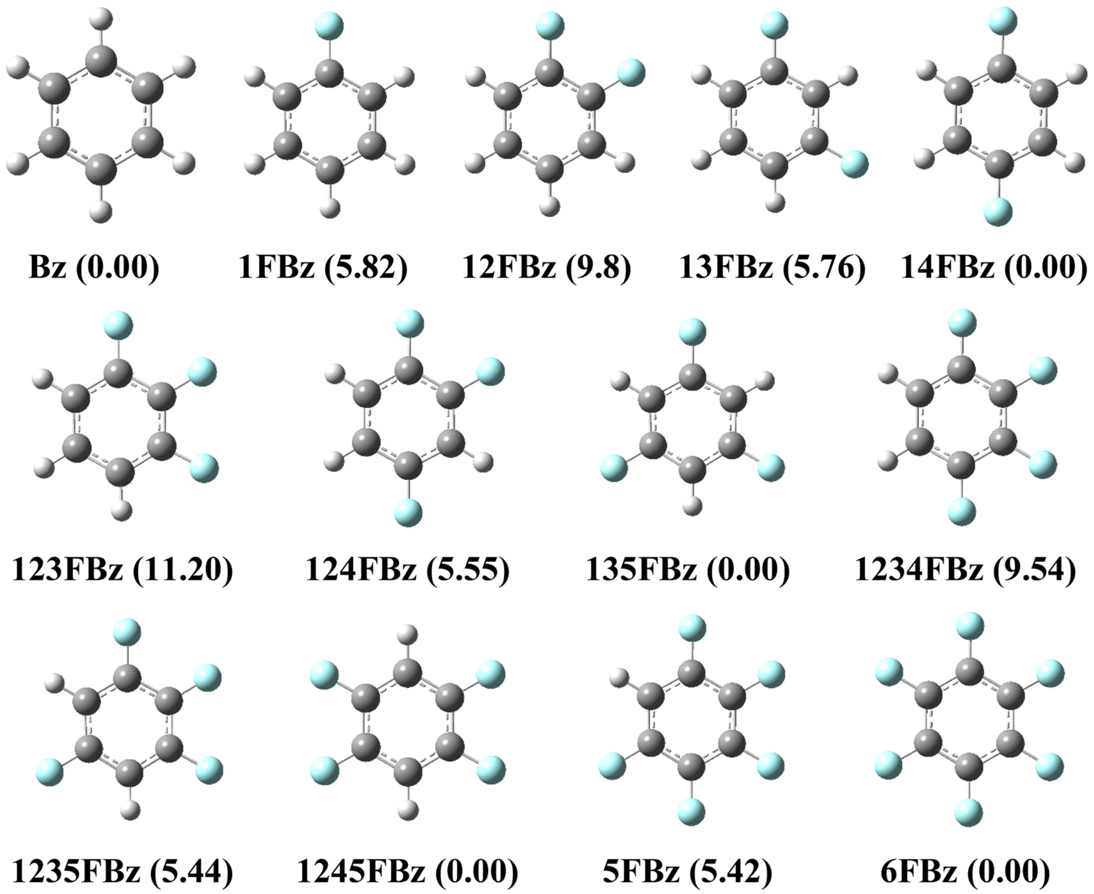


Figure 1: Molecular structures of benzene and fluorobenzenes along with their dipole moments in parenthesis.

0.8 nm) solvation shells. For fluorobenzenes, the first solvation shifts marginally to a larger distance with the increase in number of fluorine atom substituents, which can be attributed to slightly larger size of fluorine atom compared to hydrogen atom. Concurrently, the probability density of water in the first solvation shell is highest for benzene and decreases with the increase in number of fluorine atom substituents, with an exception of hexafluorobenzene. Interestingly, the probability density of water in the first solvation shell decreases with increase in number of fluorine atoms on the ring, irrespective of the position of the substitution, even in the case of fluorobenzenes having very high dipole moment (12FBz, 123FBz, 1234FBz) of about 10 D. This suggests that the hydrophobicity of fluorobenzenes increases with number of fluorine atoms. The second solvation shell corresponding to maxima in the range of 0.75–0.80 nm has a smaller probability density and has much less dependence on the number of fluorine atoms, which can be attributed to the fact that hydrophobicity does not affect the water structure at longer distances[36]. The absence of maxima around 0.3 nm for partially fluorinated fluorobenzenes suggests that the nature of interaction of water with benzene and hexafluorobenzene is fundamentally different than the interaction of water with partially fluorinated benzenes. This observation can be justified on the basis of structures of water complexes of benzene, fluorobenzene, difluorobenzene and hexafluorobenzene in the gas phase. Benzene and hexafluorobenzene interact with water via their π-electron density along the direction perpendicular to molecular plane. On the other hand, partially fluorinated fluorobenzenes prefer to interact with water in molecular plane leading to the formation of a six-membered cyclic C–F⋯H–O⋯H–C structure[37], wherein water simultaneously acts as proton donor and acceptor. Moreover, there have been no reports of linear in-plane C–F⋯H bonded interaction between fluorobenzenes and water in the literature, which

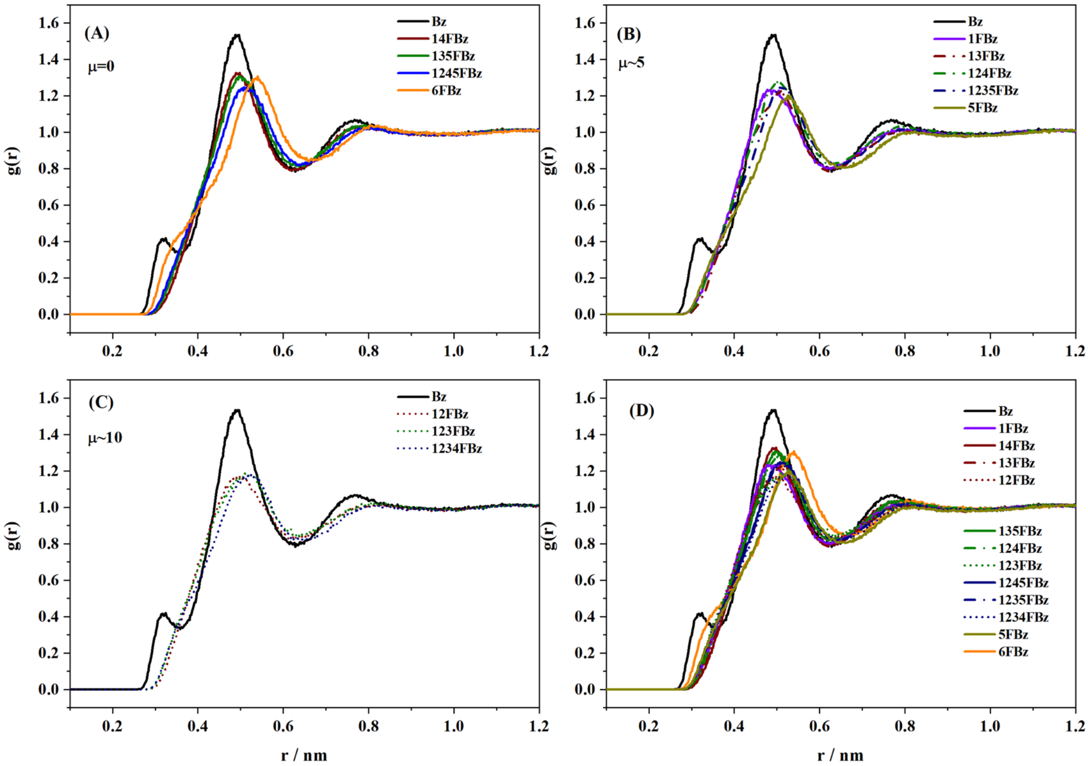


Figure 2: Fluorobenzene–water RDFs compared against benzene–water RDF (black solid line). RDFs of fluorobenzene–water system with fluorobenzenes having dipole moment **a** 0 D, **b** ~ 5 D, **c** ~ 10 D and **d** combined. For multiple isomers solid line ($\mu = 0$ D), dash–dot line ($\mu \sim 5$ D), and dotted line ($\mu \sim 10$ D).

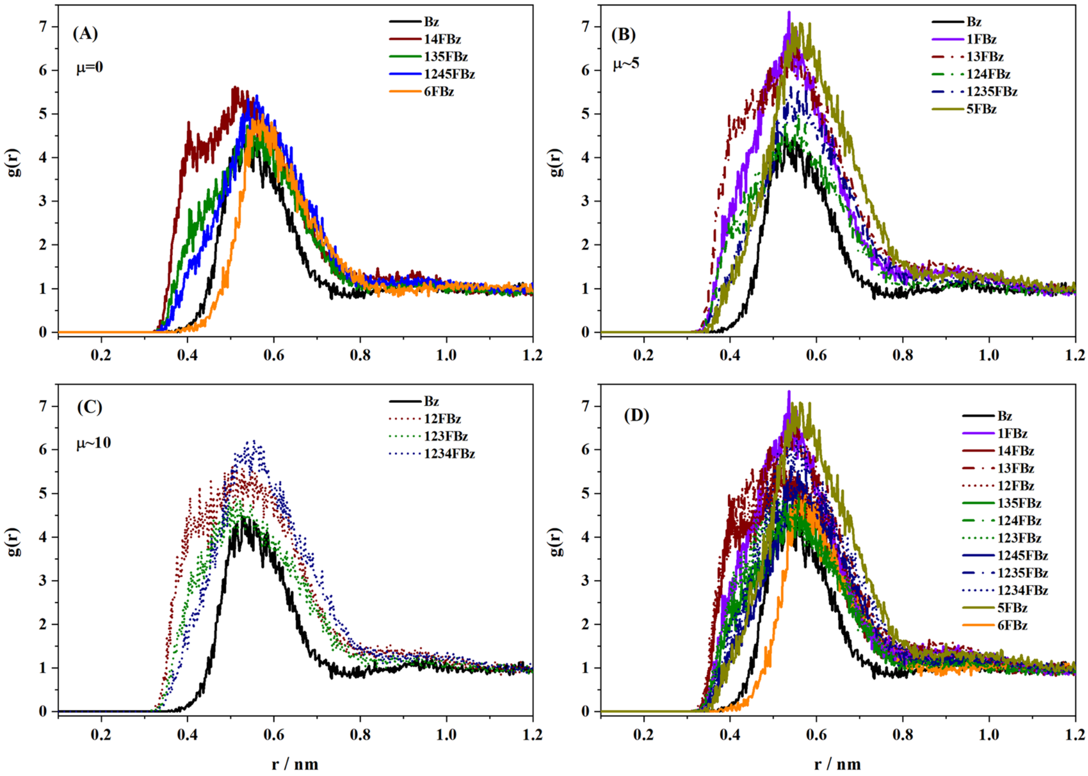


Figure 3: Solute–solute RDFs of benzene and fluorobenzenes. RDFs of fluorobenzenes having dipole moment **a** 0 D, **b** ~ 5 D, **c** ~ 10 D and **d** combined. For multiple isomers solid line ($\mu = 0$ D), dash–dot line ($\mu \sim 5$ D), and dotted line ($\mu \sim 10$ D).

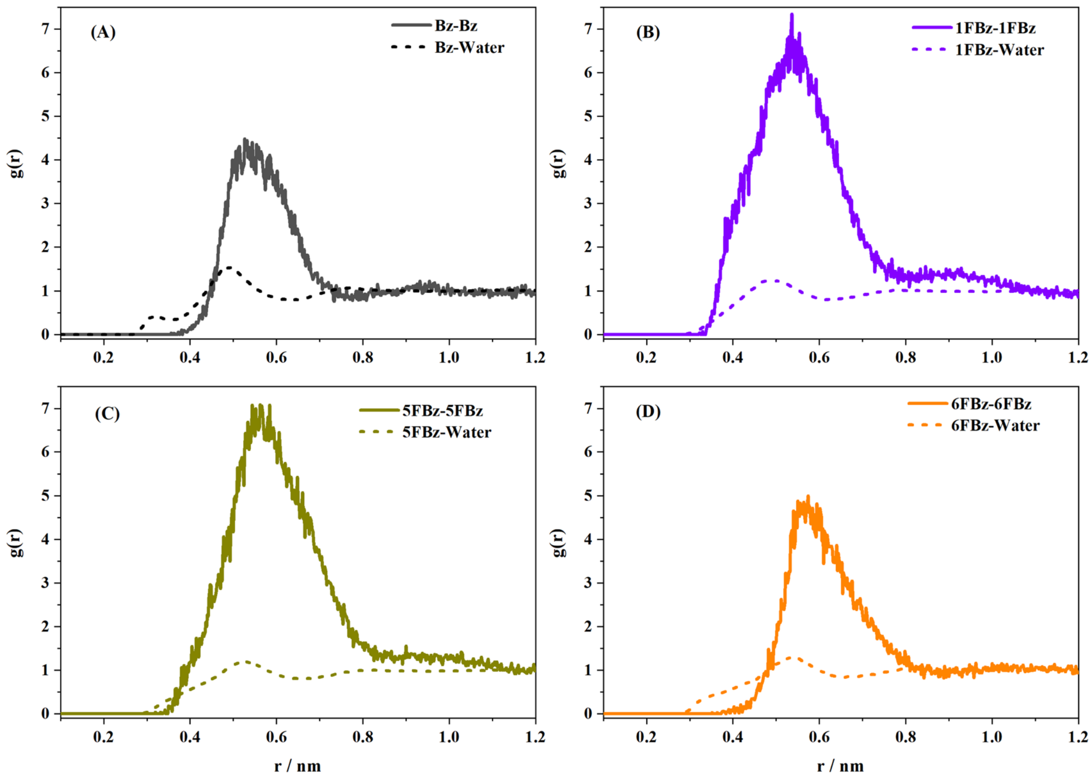


Figure 4: Comparison of solute–solute and solute–water RDFs of **a** benzene, **b** fluorobenzene and **c** pentafluorobenzene and **d** hexafluorobenzene.

once again suggests the hydrophobic nature of organic fluorine.

Solute–solute radial distribution functions were calculated from MD simulations of 10 solute molecules in 1400 TIP4P water molecules and Fig. 3 depicts the radial distribution function of all 13 solute molecules (Fig. 3d), while Fig. 3a–c represents solute–solute RDFs for solutes having dipole moment value around 0, 5, and 10 Debye, respectively. All 13 solute molecules considered in present study show characteristic solute–solute dimer formation in the presence of water in the range of 0.5–0.6 nm, which corresponds to T-shaped configuration. All fluorobenzenes show larger probability density compared to benzene, suggesting higher affinity of fluorobenzenes to aggregate and exclude water molecules. This in turn reiterates the larger hydrophobic behavior of fluorobenzenes relative to benzene. In the case of partially fluorinated fluorobenzenes, the solute–solute RDFs also show an additional peak/shoulder around 0.4 nm, which corresponds to sampling of π···π stacked configuration. However, in the case of benzene and hexafluorobenzene, RDF shows sampling of only T-shaped structure[35]. Figure 4 shows the comparison of solute–solute and solute–solvent RDFs for four representative systems viz., benzene, fluorobenzene, pentafluorobenzene and hexafluorobenzene. It is evident from Fig. 4 that the probability densities for the solute to interact with itself are much higher compared to its interaction with water. Similar results were observed for the remaining nine partially fluorinated benzene derivatives (figure not shown). These results suggest the hydrophobic nature of the fluorobenzenes. Further, the excess coordination number (ECN) was also analyzed and the results are depicted in Fig. 5. The ECN represents preferential solvation, a positive value indicates that a given solute molecule prefers to be surrounded by solvent molecules, while the negative value shows no preference for solvation by solute molecules. The negative value of water ECN around benzene and fluorobenzenes shows there is no preferential solvation of benzene and fluorobenzenes by water molecules. It can be seen from Fig. 5 that ECN decreases with increase in number of fluorine atoms on the phenyl ring, thus making fluorobenzenes more hydrophobic than benzene.

Distribution of water molecules around solute molecules was analyzed using spatial distribution function (SDF). SDF represents the average water density around the solute

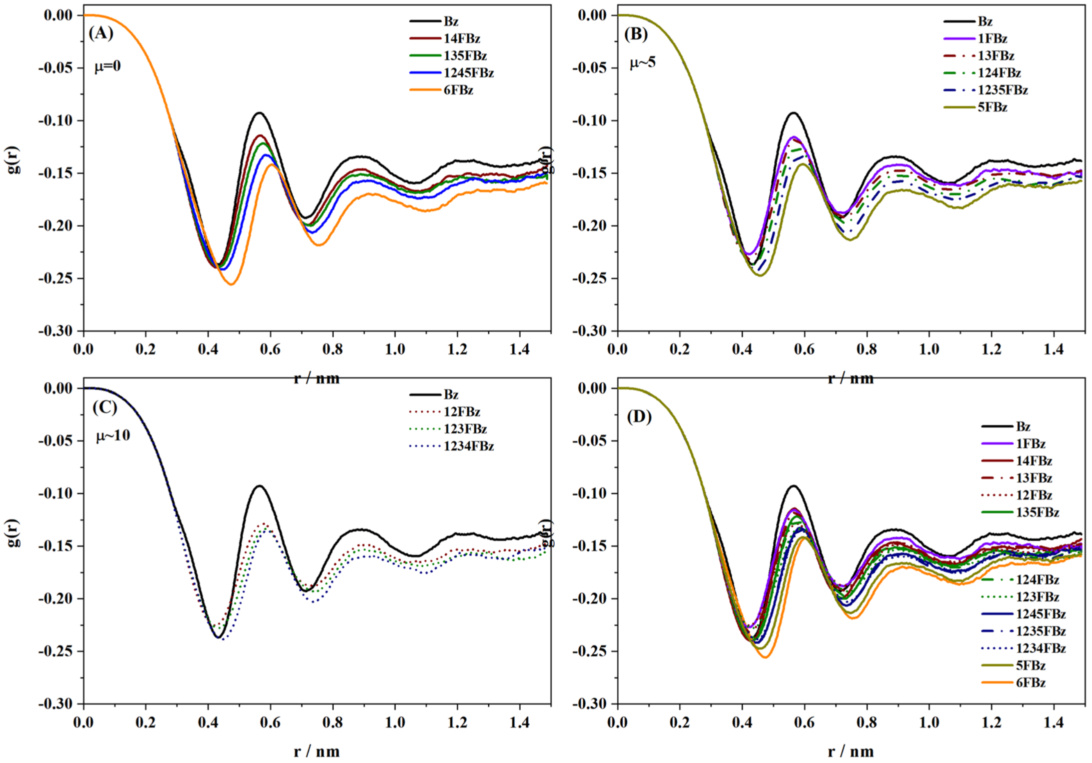


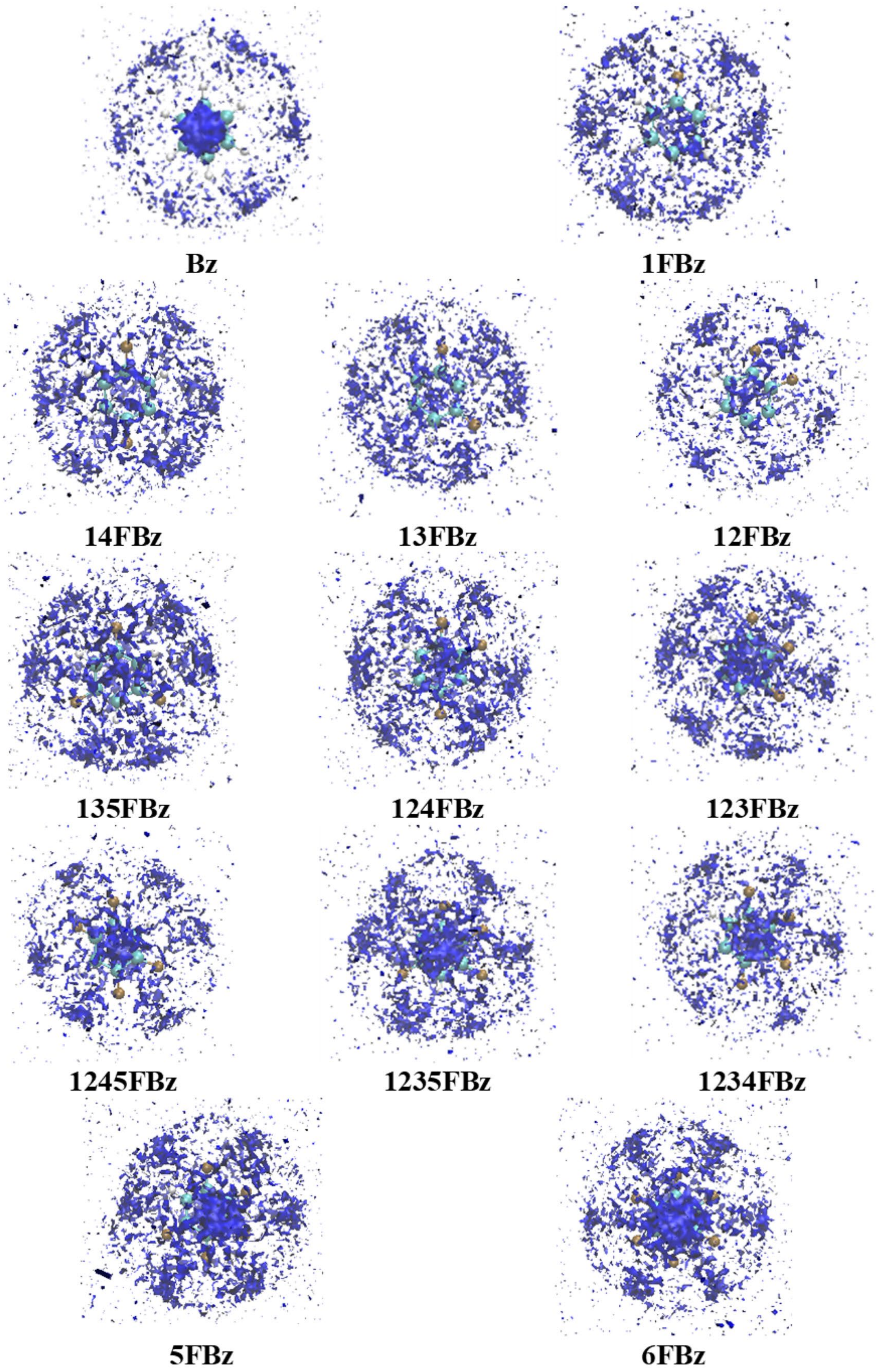
Figure 5: Excess coordination number of water around benzene and fluorobenzenes. ECN of fluorobenzenes having dipole moment **a** 0 D, **b** ~ 5 D, **c** ~ 10 D and **d** combined. For multiple isomers solid line (μ = 0 D), dash–dot line (μ ~ 5 D), and dotted line (μ ~ 10 D).

molecule. Figure 6 depicts the SDFs of benzene and fluorobenzenes for the last 50 ns of one-solute MD simulations. Average water density in first solvation shell of benzene is maximum in the direction perpendicular to molecular plane which commensurates with O–H···π interaction between water and benzene. In the case of hexafluorobenzene, the maximum average water density is also perpendicular to molecular plane which in accord with lp···π interaction. On the other hand, for the partially substituted fluorobenzenes, the maximum average water density is in the plane of the molecule with marginal amounts perpendicular to molecular plane. In the case of fluorobenzenes, it is interesting to note depleted water density along the C–F group, which suggests that organic fluorine preferentially avoids interacting with water molecules, which is in accordance with the fact that organic fluorine hardly accepts hydrogen bonds[4, 5].

In an effort to rationalize the observed results from MD simulations, molecular electrostatic potentials (MESP) of benzene and fluorobenzenes were calculated at MP2/aug-cc-pVDZ level of theory using Gaussian-16 suit of programs[38], and are depicted in Fig. 7. A negative electrostatic potential is seen on the fluorine atom, magnitude of which decreases with increase in number of fluorine atoms. Interestingly, the negative ESP on the fluorine atom does not favor interaction with water, which indicates the molecular origin of organic fluorine's inability to hydrogen bond. Increase in number of fluorine atoms lowers the negative ESP on the fluorine atoms which further diminishes its ability to hydrogen bond with water molecules, thereby increasing the hydrophobicity.

4 Conclusions

In summary, all-atom MD simulations of benzene and 12 fluorobenzenes were carried out using OPLS force field along with TIP4P water model. An important aspect of this work is the consideration of partially substituted fluorobenzenes to bridge the gap between the known hydrophobic behavior of benzene and hexafluorobenzene. Position of first solvation shell in benzene–water radial distribution function gradually shifts towards longer distance



Bz

1FBz

14FBz

13FBz

12FBz

135FBz

124FBz

123FBz

1245FBz

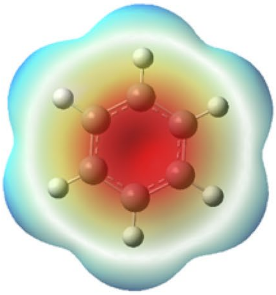
1235FBz

1234FBz

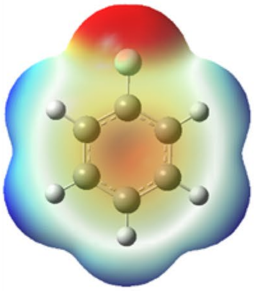
5FBz

6FBz

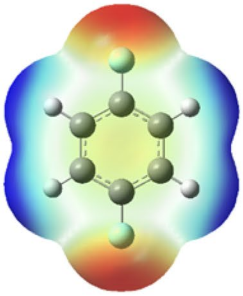
Figure 6: Spatial distribution function (SDF) of benzene and fluorobenzenes depicting the average water density around solute with isovalue of 13.5. Blue color represents water. Solute molecules are in CPK representation, wherein carbon, hydrogen and fluorine atoms are represented by cyan, white and brown colors, respectively.



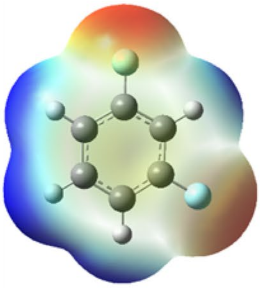
Bz



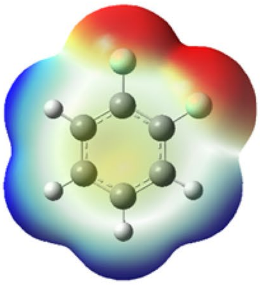
1FBz



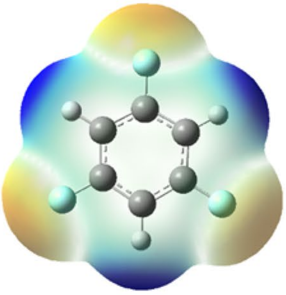
14FBz



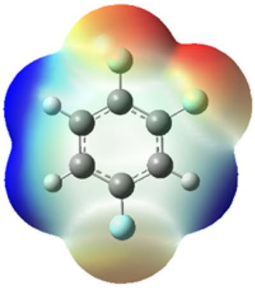
13FBz



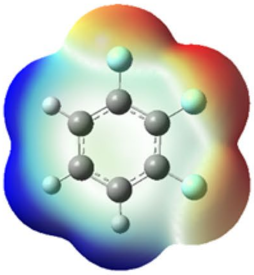
12FBz



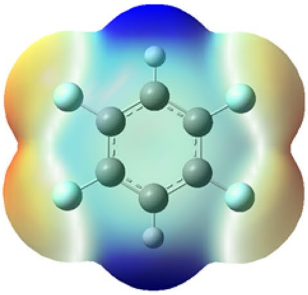
135FBz



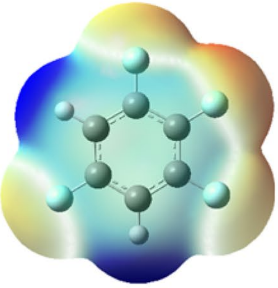
124FBz



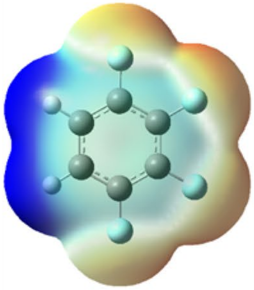
123FBz



1245FBz



1235FBz



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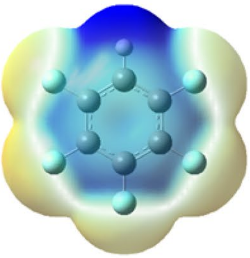
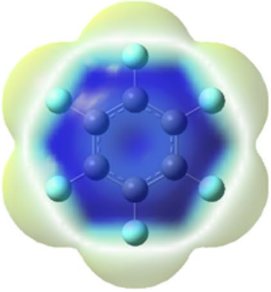


5FBz



6FBz

◀ ***Figure 7:*** Electrostatic potential (ESP) map of benzene and fluorobenzenes calculated at MP2/aug-cc-pVDZ level of theory using Gaussian09 software. In ESP map, red and blue colors represent negative and positive electrostatic potential. In solute molecules, carbon, hydrogen and fluorine atoms are represented by gray, white and cyan colors, respectively.

with the increase in number of fluorine atom substituents, while the probability density of partially substituted fluorobenzenes is closely spaced within thermal fluctuation but distinct from benzene and hexafluorobenzene. The distinct behavior of partially substituted fluorobenzene from those of benzene and hexafluorobenzene was rationalized from the different nature of interactions in the two cases, in the former water interacts along molecular plane, while in later along the direction perpendicular to molecular plane. Benzene–water interactions are preferred over fluorobenzenes–water interactions. Comparison of solute–solute and solute–water radial distribution show that fluorobenzene(s) prefer to interact with itself than with water suggesting the higher hydrophobic nature of fluorobenzenes compared to benzene. An interesting observation is that irrespective of molecular dipole moment of fluorobenzenes, the spatial distribution of water indicates that water avoids the C–F bond group, thereby increasing the hydrophobicity of fluorobenzenes with number of fluorine atoms.

Publisher's Note

Acknowledgements

Authors gratefully acknowledge SpaceTime-2 supercomputing facility at IIT Bombay for the computing time.

Received: 13 November 2019 Accepted: 16 December 2019
Published online: 30 December 2019

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