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Interaction between Bovine Serum Albumin and Gemini Surfactants Molecular Docking Characterization

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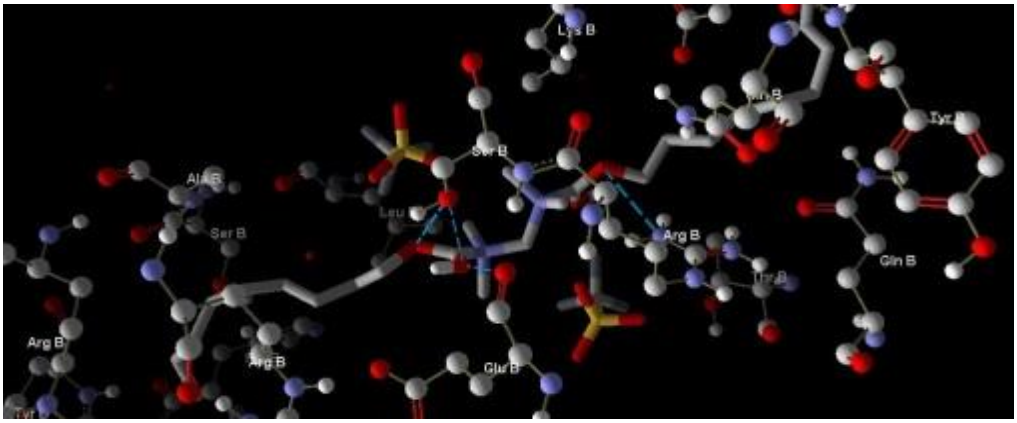
Abstract: In the present work, interactions between bovine serum albumin (BSA) with gemini surfactants were studied for their stabilization. A library of gemini surfactants has been designed on varying the cation and anion of parent surfactant. Geometry optimization of the surfactants has been performed by applying MOPAC approach to minimize energy of formation, where the RMS Gradient is set to 0.100. Further, molecular docking studies using iGEMDOCK software, was done to study the interaction between four hundred designed gemini surfactants molecyles and bouvine serum albumin (BSA). The binding between the BSA and surfactant was occurred due Vander Waals interaction, electrostatic interactions and hydrogen bonding, where the minimum binding energy approach were used to select the most potent compound. The molecular docking results successfully showed that, surfactant molecule are inserted into the cavity of BSA.



Keywords: Gemini surfactant, BSA, stabilization.

1 Introduction

A new class of surfactants referred as the second generation surfactants appeared recently in the scientific literature.(Sayre, Lee et al. 2011; Pabbathi, Ghosh et al. 2013) They bear two polar head groups or in other words hydrophillic in nature and two non-polar aliphatic tails or hydrophobic in nature are covalently bonded towards the head groups by another moiety known as spacer, as schematically represented in **Figure 1**. Such types of surfactants are known as Gemini surfactants. Due to this peculiar architecture they have properties better than those possessed by their single chain counterparts like low critical micelle concentration (cmc), low kraft temperature, strong hydrophobic micro-domain. The low cmc values of gemini surfactants is significant and decreases the concentration of free non-micellized gemini surfactant molecules, Further, it decreases the toxicity of the BSA-surfactant system and significantly increases the ability to dissolve the non-polar moieties. Due to this, their behaviour towards proteins is quite different than conventional surfactants. These properties of Gemini surfactant can be tuned easily by altering spacer, polar group and anions. Apart from better properties, they have better applications as well they are used as additives in daily used materials like hair conditioners, antiseptics, skin and eye irritation-free cosmetics.

Literature reported that albumin of serum is the significant

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carrier protein present in the plasma of blood and it has very high affinity for plenty of drugs and metabolites. It also plays important physiological roles like in transportation, distribution and metabolism of various endogenous and exogenous ligands.(Du, Yu et al. 2007; Bharmoria, Rao et al. 2013) Bovine serum albumin (BSA) is a popular protein due to high similarity with human serum albumin (HAS) and it has 582 amino-acids. BSA has two tryptophan amino-acids at 159 and 237 positions and also having intrinsic fluorescence. A study has reported that the weak interaction of drug with serum albumin shown a short lifetime as well poor distribution of drug. While strong binding between the drug and serum albumin may decrease the concentration of free drug in plasma.(Page, Kraut et al. 2009; Das, Kumar Das et al. 2011; Sasmal, Mondal et al. 2011; Weingartner, Cabrele et al. 2011; Naushad, Alothman et al. 2012) That's why, the study to see the interaction between drug with serum albumin has attracted the researchers, academicians in life sciences, chemistry and medicine. Currently, (Page, Kraut et al. 2009; Das, Kumar Das et al. 2011; Sasmal, Mondal et al. 2011; Weingartner, Cabrele et al. 2011; Naushad, Alothman et al. 2012)

Many researchers are working on BSA to increase the drug loading capacity, some of them were successfully characterize by molecular docking like the binding of an antimalarial drug chloroquine bonded to conjugated gold nanoparticles with bovine serum albumin. Further, the research group has investigated their spectroscopic and docking studies. Researchers also reported the interaction of bovine serum albumin with a psychotropic drug alprazolam and characterization by means of various physicochemical, spectroscopic and computational studies.

In this work, authors investigated the interaction between BSA and four hundred derivatives of Gemini surfactants to find the most prominent one. It is based on the molecular docking approach, where two synonymous works were done with taking BSA as a core and with a docked ligand, encoded by two PDB ID viz. 4F5S and 3V03 respectively.

2 Experimental

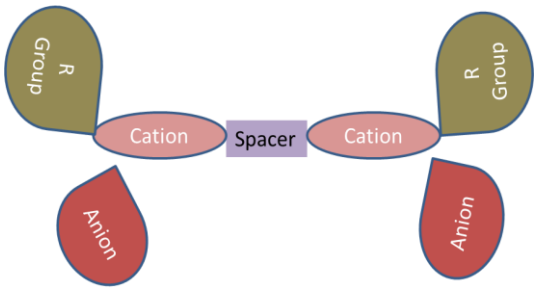


Figure 1a Schematic representation of Gemini Surfactant.

This work can be divided into two parts i.e. ligand preparation and molecular docking, where ligand preparation involves creation of 3D sketches of ligand and their geometry optimization while the molecular docking includes the docking of ligands and their modeling.

2.1 Ligand preparation

2.1.1 Designing of ligand

Gemini surfactant is chosen from database of research. It contains the spacer, cation bearing non-polar aliphatic chain and anions (**Figure 1a and 1b**). All derivatives are prepared by altering these components of surfactants. Herein, in present work, we altered non-polar aliphatic chain and anions. Spacers were taken in study are total four in number i.e. having chain length of maximum four carbon means one carbon, two, three and four carbon. Non-polar aliphatic side chain is of maximum twenty carbon i.e. one carbon, two, three carbon and upto twenty carbon. Anions were totally five in number viz. Cl^-, Br^-, I^-, BF_4^- and OTF^-. So that the total Surfactant derivatives will began to four hundred in number which are given in **Table 1**.

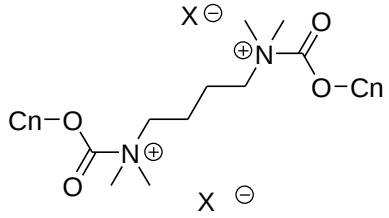


Figure 1b Structure of the gemini surfactant

Table 1: Frameworks of gemini surfactants

Anions	Alkyl chain	Spacer			
		One Carbon	Two Carbon	Three Carbon	Four Carbon
		Compound No.			
BF_4^-	C_1-C_{20}	1-20	101-120	201-220	301-320
Br^-	C_1-C_{20}	21-40	121-140	221-240	321-340
Cl^-	C_1-C_{20}	41-60	141-160	241-260	341-360
I^-	C_1-C_{20}	61-80	161-180	261-280	361-380
OTF^-	C_1-C_{20}	81-100	181-200	281-300	381-400

2.1.2 3D Sketching and Geometry Optimization

Sketches of all four hundred derivatives of Gemini surfactants were prepared with CS Chemdraw 7, firstly in 2D and later on it is converted into 3D with the help of Chem 3D of Cambridge Soft package. 3D geometry of the molecule were optimized also with the help of Chem 3D by the MOPAC simulation via minimizing the energy of formation where the RMS Gradient is set to 0.100. The optimized compound were further saved in suitable format and used in docking.

2.1.3 Protein Preparation

Protein preparation were done with the help of Molegro Molecular Viewer (MMV) where, the assigning of missing bonds, assigning of missing bond order and hybridization, assigning of missing explicit hydrogen, assigning of missing

charges always, assigning of flexible torsion in ligands always and assigning of tripos type atoms if missing were performed. Finely the prepared protein is used for molecular docking.

2.2 Molecular Docking

The docking of all derivatives of gemini surfactants into the binding pocket of the BSA protein (PDB ID- 4F5S and 3V03) was discovered using iGEMDOCK (Generic Evolutionary Method for molecular Docking) software. This computational tool has a program for computing the conformation of the Gemini surfactants and also its orientation towards the active site of the BSA. The binding pockets of the 4F5S and 3V03 was defined to include the amino acid residues in the region of 8˚A radius on the binding site of BSA.

In the present work, the parameters of this computational tools are the population size (n = 200), generations (g = 70) and number of solutions (s = 2). Finally, interaction profile of all docked poses was generated for the interaction analysis of ligand with proteins. Interaction data was short out by applying the default parameters energy and z-score and the top ten compound were selected on the basis of energy and z-score so that lead out will be most potent one.

3 Result and discussion

iGEMDOCKm a computational tools uses an empirical scoring function as well an evolutionary approach. The results were based on the total energy and it consists of energy contributed due to electrostatic, steric, and hydrogen-bonding potentials. Steric and hydrogen bonding use a linear model and it simple in working. It recognizes potential complexes rapidly. The idea behind this evolutionary approach is to design plenty of operators that cooperate using a family competition paradigm that is similar to a local search procedure.

Interaction or attractive forces between the Gemini surfactants and BSA may involve mainly hydrophobic forces, electrostatic interactions, van der Waals interactions, and hydrogen bonds. Literature reported that on varying the size of organic molecules, different types of interactions toward proteins has been observed. It is also reported that the negative value of binding energy change (ΔG) showed that the binding process between the Gemini surfactant and BSA is spontaneous. The hydrophobic interaction basically prevents the aggregation and the agitation including inactivation of the proteins during several practices. However, only hydrophobic interactions are not sufficient enough to stabilize the albumin protein by the Gemini surfactants.

Therefore, in this novel theoretical model based on atomic interactions we proposed that the ionic surfactants like Gemini bind to the BSA 3D structure effectively. The criteria that association between proteins and ionic surfactants is preferentially guided by hydrogen bond interaction. Nevertheless, it should be kept in mind that these computational simulations are limited to the role of the major component in the commercial products, where they approach to stabilize the macromolecule. Thus, experimental results using commercial Gemini surfactant in formulations containing globular proteins might include other effects due to heterogeneity in the samples.

The z-score value is a parameter to measure the interaction between the BSA and Gemini surfactants. The pharmacological scoring function is given as

$$E_{pharma} = E_{GEMDOCK} + E(E)_{pharma} + 2E(H)_{pharma} + 0.5E(V)_{pharma}$$

Where $E_{iGEMDOCK}$ is the docked energy of iGEMDOCK and $E(E)_{pharma}$, $E(H)_{pharma}$, and $E(V)_{pharma}$ are the pharmacological scores of electrostatics, hydrogen-bonding, and vdW interactions, respectively.

A docked result has been considered as an achievement if the root-mean-square derivation (RMSD) is found to be $\leq$2.0 Å between the docked solutions and X-ray crystal structures. Moreover, we calculated the number of molecules that are interacting directly with the BSA (at a distance of 4 Å), from the analysis of the data of 400 Gemini molecules, but only top 10 out of 400 derivatives are given in **Table 1**, where the highest negative value of binding energy is taken under consideration. This is a quite interesting finding which suggests that there are a maximum number of Gemini molecules able to interact directly at the protein surface, regardless of the surfactant type. In turn, it is a supporting argument toward the hypothesis that predominant interactions occur by polar heads, which are structurally the same in Gemini surfactant.

Herein, in the molecular docking simulation, we find that out of two chain of Gemini surfactant, the chain B show effective binding with Gemini surfactant. This may be also a new binding surface for the effective binding in BSA protein. This new binding domain may serve as valuable pocket in BSA, which leads to the search of new leads. This binding domain of BSA composed of arginine 427, serine 428 and glutamine 424, which can be clearly seen in **Figure 2**. This binding domain is acquired by derivative named S1OTfC9, means compound containing spacer of one carbon, anion as OTf and side chain length is of nine carbons. It also shows highest negative binding energy among the all 400 molecules having value -139.4. The pharma score or Z-score value for this is also found highest for it.

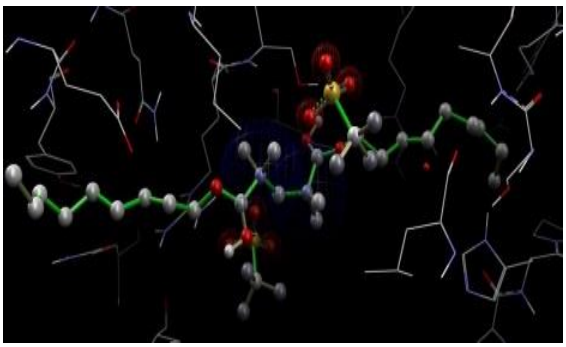
The second top score in 400 derivatives are S4OTFC3, means compound having spacer of four carbons, again OTf as anion and side chain length of three carbons. The binding pocket occupied by second top score is composed of serine 192, arginine 458 and histamine 145 of chain B. The binding energy value for this is -131.6.

Table 2: List of top 10 derivatives of Gemini surfactant with effective hydrogen bonding value with PDB ID 3V03.

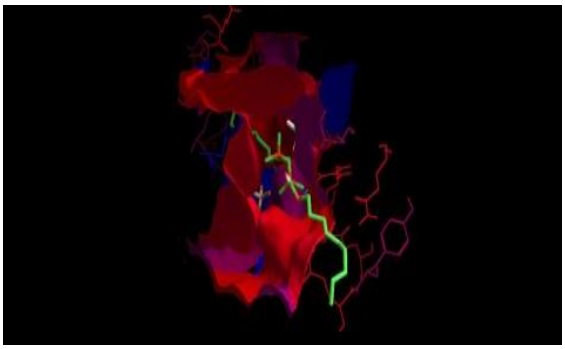
Compound	Energy	E(pharma)	H-S-HIS-145	H-S-ARG-427	H-S-SER-428	H-S-ARG-458
		Z-Score	0	0	0	0
		W(pharma)	0	0	0	0
S_1OTfC_9	-139.4	-144.5	0	-13.975	-8.1821	0
S_4OTFC_3	-131.6	-138.1	-7.5317	0	-4.8924	-3.5
S_3IC_9	-126.7	-126.7	0	0	0	0
$S_2BF_4C_{19}$	-124.7	-124.7	0	0	0	0
S_4OTFC_8	-124.1	-124.1	0	0	0	0
S_3OTFC_5	-122.5	-122.6	0	0	0	0
S_2OTfC_3	-121.1	-126.7	0	0	0	0
S_2OTfC_{20}	-120.7	-123.8	0	0	0	0
S_3BrC_{20}	-120	-120	0	0	0	0
S_3OTFC_8	-119.8	-127.3	0	0	0	0

Table 3: List of top 10 derivatives of Gemini surfactant with effective hydrogen bonding value with PDB ID 4F5S.

C. No.	Energy	E (pharma)	V-S-TYR-400	V-S-ASN-404	V-S-PHE-506	V-M-LYS-524	V-S-LYS-524
		Z-Score	48.25	18.14	18.22	1.92	25.89
		W (pharma)	0.88	0.33	0.33	0.04	0.47
S_3OTfC_8	-139.2	-169.4	-8.4662	-5.6361	-5.762	-3.1998	-7.7581
S_3IC_9	-135.4	-164.2	-3.0861	-3.7989	-9.5683	-1.8193	-3.9294
$S_3BF_4C_{11}$	-133.7	-165.7	-4.1331	-5.2819	-8.6658	-1.9814	-2.8454
$S_3C_lC_{11}$	-133.1	-156.3	-3.7478	-3.2798	-9.9333	-2.6878	-3.5771
S_4IC_{10}	-132.4	-156.9	-5.9426	-3.7964	-9.6830	9.8804	-4.1941
S_4IC_9	-128.7	-151.5	-3.1299	-2.8971	-11.913	-3.1897	-3.9522
S_3BrC_8	-128	-149.8	0.1959	-5.1009	-10.333	-1.6460	-6.4026
S_3BrC_7	-127.7	-138.9	-1.2528	-1.7652	-12.765	-3.2330	-2.4555
$S_2BF_4C_{11}$	-127.2	-150.4	-13.3661	-3.9327	-8.6551	-4.6887	-2.4969
S_4OTFC_6	-124.8	-155.3	-9.8203	-7.0752	-2.2810	-4.9527	-9.592



S1OTfC9



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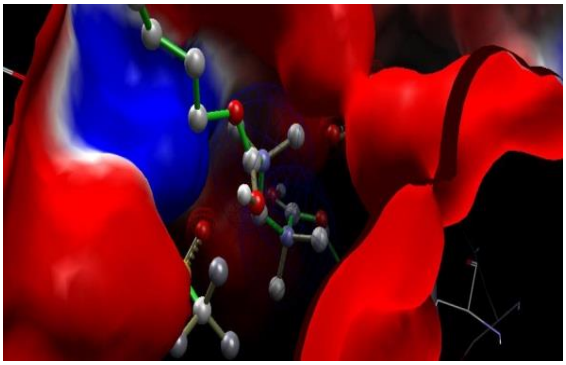

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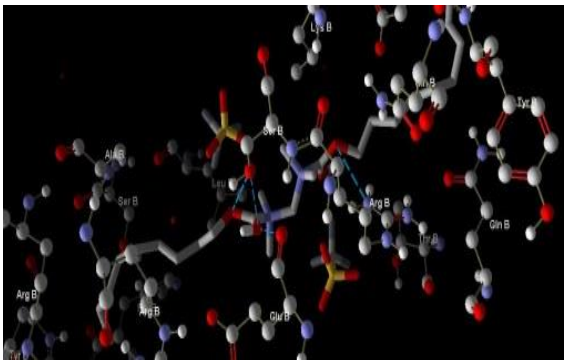

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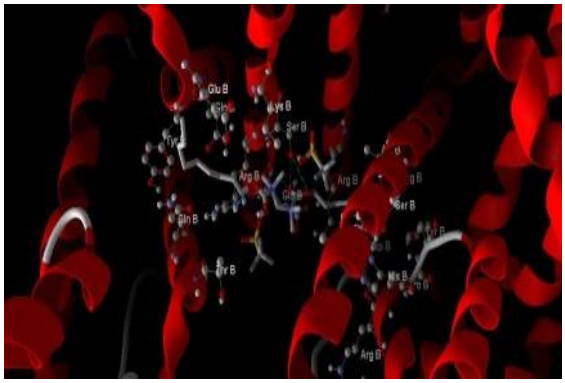
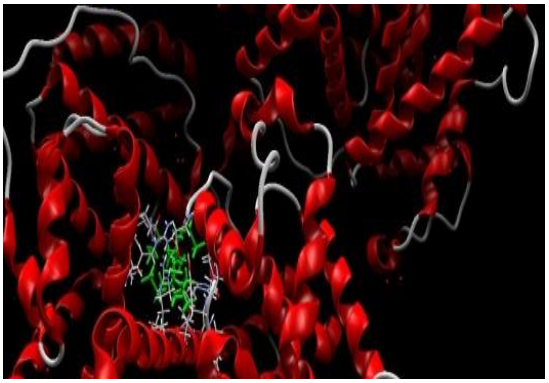
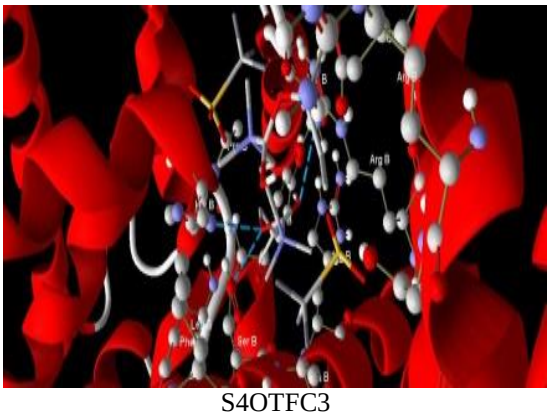


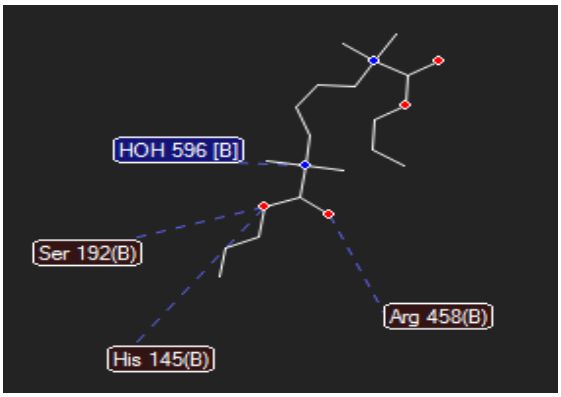
S1OTfC9

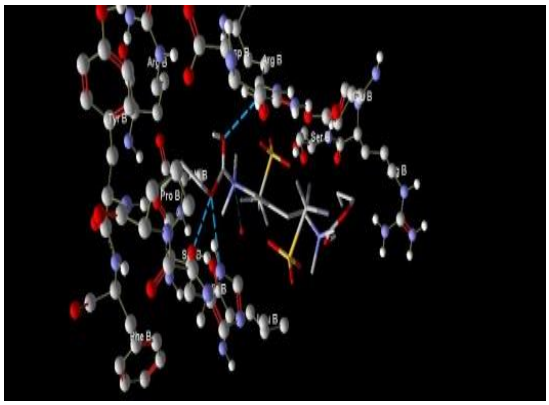


S4OTFC3

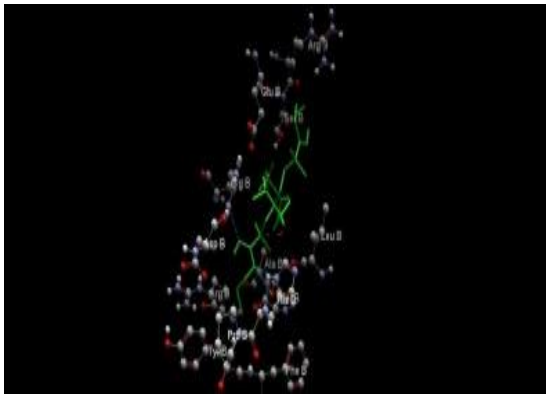


S4OTFC3





S4OTFC3



S4OTFC3

Figure 2: Docking poses of top 2 compound listed in Table 1.

Another docking simultaneous work with another PDB of Bovine serum albumin is done with PDB ID 4F5S, which contains the ligand by default neans, we specifie the binding site for the molecular docking. But the result were not much satisfactory as we expecting from the docking simulation. Herein, we found that top scorer derivative does not show any hydrogen bonding interaction with the proveded side of interaction, although second scorer is also not showing interaction, that's why we resulted that the target specific docking have specific and will be continue when we need specic amino acid interction with ligand. Although here we talking about the stabilization of BSA protein, hence we prefer the random docking as we do in case of 3V03 and get better result. But in case lead output of drug molecule usually scientists prefer the binding site specific interaction with drug molecule. The details of energy, pharma and hydrogen bonding interaction of BSA (PDB ID 4F5S) are given in T**able 3**. Herein we find that S3OTFC8 have highest score in the all derivatives

4 Conclusion

Stabilization of BSA by Gemini surfactant can be achieved successfully via two molecular docking simulation viz., random docking and binding site specific docking. Where we found that, the surfactants showed strong interactions with the protein predominantly via their hydrpphillic part via hydrogen bonding, Vander Waals interactions. The

favorable electrostatic and van der Waals interaction energies calculated for the association between BSA and Gemini surfactant also show remarkable point to accept this model as a novel work. For the stabilization purpose we found that the random docking access more powerful tool to check the interaction between macromolecule and ligand. The result also shows that the Gemini surfactant could be used as powerful stabilizer to preventing protein aggregation. There is a lot possibility to tune the properties of novel Gemini surfactant. This type of theoretical work is also useful in the searching new binding pocket in the protein molecules, these binding pockets may also serve in the new discoveries leading to the desired conformational change in the molecule by binding many types of ligand molecules.

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