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Short Communication

Theoretical model to investigate the alkyl chain and anion dependent interactions of gemini surfactant with bovine serum albumin

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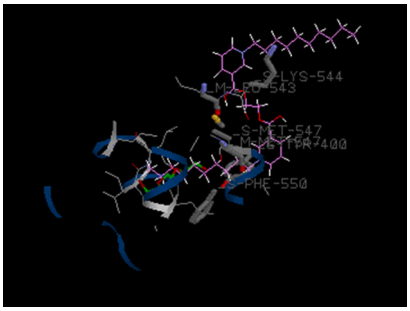
HIGHLIGHTS

- A theoretical model to study the interactions of gemini surfactants with BSA.
- Interaction was predominantly through hydrogen bonds, Vander Waals and hydrophobic interactions.
- Gemini surfactants bind to non-specific surface regions on the BSA.
- Formation of clusters of gemini surfactants with BSA could increase the protein conformational stability.

GRAPHICAL ABSTRACT



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ABSTRACT

Surfactants are used to prevent the irreversible aggregation of partially refolded proteins and they also assist in protein refolding. We have reported the design and screening of gemini surfactant to stabilize bovine serum albumin (BSA) with the help of computational tool (iGEMDOCK). A series of gemini surfactant has been designed based on bis-N-alkyl nicotinate dianion via varying the alkyl group and anion. On changing the alkyl group and anion of the surfactant, the value of Log *P* changes means polarity of surfactant can be tuned. Further, the virtual screening of the gemini surfactant has been carried out based on generic evolutionary method. Herein, thermodynamic data was studied to determine the potential of gemini surfactant as BSA stabilizer. Computational tools help to find out the efficient gemini surfactant to stabilize the BSA rather than to use the surfactant randomly and directionless for the stabilization. It can be confirmed through the experimental techniques. Previously, researcher synthesized one of the designed and used gemini surfactant to stabilize the BSA and their interactions were confirmed through various techniques and computational docking. But herein, the authors find the most competent gemini surfactant to stabilize BSA using computational tools on the basis of energy score. Different from the single chain surfactant, the gemini surfactants exhibit much stronger electrostatic and hydrophobic interactions with the protein and are thus effective at much lower concentrations. Based on the present study, it is expected that gemini surfactants may prove useful in the protein stabilization operations and may thus be effectively employed to circumvent the problem of misfolding and aggregation.

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Introduction

Serum albumin, the transport protein present in plasma, is known as a major ligand binding protein. A relatively globular protein bovine serum albumin (BSA) is one of the extensively studied proteins of this kind. Due to its structural homology (80%) with human serum albumin, water solubility and versatile binding ability of BSA and it has been used as a model protein for a great variety of biophysical and physicochemical studies [1–8]. On changing the conformation, they lose their biological activities and therefore, for the stabilization of proteins, various reagents have been proposed like detergent, lipid colloidal nanoparticles, ionic liquids etc. but, all have some limitations. Their interactions with proteins lead to denaturation and to the formation of poorly soluble complexes. Surfactants do not denature the globular and favour a progressive loss of their secondary and tertiary structure [8–16]. Amongst various proteins, serum albumins are said to be the most abundant soluble proteins in the circulatory system of various organisms, and possess several physiological functions. That's why, BSA attracted the researchers/academicians and became the hot topic of research.

Protein–surfactant interactions hold greater importance since they are more relevant in the fields of detergents, cosmetics, biosciences, foods, pharmaceuticals etc. Gemini surfactants have attracted much attention due to their special behaviours like high surface activity, low critical micelle concentration (CMC), diverse aggregate structures, good transfection ability etc. [13,15–20]. Therefore, gemini surfactants are being used in oil recovery, drug encapsulation, and gene therapy and further, can also be used as a soft template in biomimetic synthesis to solubilise the materials to moderate the photoelectric inorganic nanomaterials. Activity of gemini surfactants depends on the length and nature of the alkyl chain, spacer and anion present. Structural based virtual screening involves automated and fast docking of a large number of chemical compounds against a protein-binding or active site. Computational tools have gained huge attraction of the researchers, scientists, academicians in designing potent molecules via interaction which can be explained thermodynamically and biologically parameters [5,6,17,18,20,21].

Previously Ya Wang et al. have used gemini surfactant glycol (bis-N-tetradecyl nicotinate dibromide) to stabilized BSA and studied through various experimental techniques and molecular docking, wherein they proposed the π–π stacking between heterocyclic ring and pyrole ring of amino acid residue of BSA, H-bonding and hydrophobic interaction [22].

In the present work, we designed 100 gemini surfactants based on bis-N-alkyl nicotinate dianion via varying alkyl part (C_1–C_{20}) and anions (–Cl, –Br, –I, $–BF_4$, –OTf). Further, computational tools were used to investigate the interaction between the designed gemini surfactants and BSA via varying the alkyl chain and anion. Further, to find the potential surfactant to stabilize the BSA.

Experimental

Selection of molecule

The low cmc values of gemini surfactants lower the concentration of free non-micellized surfactant which in turn reduce the toxicity and enhances the ability to dissolve the water insoluble biomolecules and stabilize them. Their behaviour towards biomolecules like proteins is entirely different than conventional surfactants and offer better result in terms of stability and solubility.

Derivative preparation

Derivatives of parent compound were prepared by changing alkyl side chain and anion. Via changing different alkyl group and anions, we made a library of 100 surfactants. The details can be understood by Table 1. The basic structure of the gemini surfactant is as Fig. 1. These all structure is drawn in CS Chemdraw 12 in the native format and then Hyperchem 8.0 and Gaussian 03 program were used for the optimization of the derived molecules via energy and geometry using minimization protocol.

Table 1
Details of parent, side chain and anions.

S. no.	Anion	–R or alkyl part (normal)	Compound no.
1	Br	$–C_nH_{2n+1}$	a1–a20
2	Cl	n = 1–20	b1–b20
3	I		c1–c20
4	BF_4		d1–d20
5	OTf		e1–e20

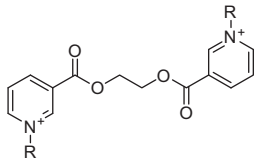

Fig. 1. Structure of the bis-N-alkyl nicotinate dianion.

Optimization of derivatives

These 100 derivatives are imported in ACD. ACD ChemSketch generate only 3D geometry of the molecule but optimization is done by HyperChem and minimum energy optimization by applying amber99 molecular mechanics using polark rebiere conjugate gradient in which RMS gradient set to 0.1 kcal/A° mole and maximum number of cycle is set as to find minimum energy geometry. Now output optimized geometry were exported out in .pdb format from Hyperchem and in .mol format from ACD Chemsketch for carrying out the molecular docking.

Protein preparation

Protein preparation is most important for accurate result in molecular docking; therefore we also perform by Chimera and perform preceptor preparation. In this, for the protein preparation, authors focused on to removing ligands, adding hydrogen, deleting solvents and adding charges. We also concerned to make receptor torsion free and finely extracted in .pdb format.

Methodology

Herein, a computer-aided docking process was followed and indentified the lead compound by determining the minimum energy between the ligand and protein. Computational tools were used to determine the interaction between the protein and ligand. Docking problem involves two critical elements: a good scoring function and an efficient algorithm for searching conformation and orientation spaces. A good scoring function should be able to screen a large number of potential solutions rapidly and simply, while effectively discriminating between correct binding states and non-native docked conformations. iGEMDOCK energy function consists of electrostatic, steric and hydrogen-bonding potentials. Steric and hydrogen bonding potentials uses a linear model that is simple and recognizes potential complexes rapidly. There are four main steps which is used here. First, we developed an empirical scoring function having fewer local minima to replace the relatively complicated AMBER-based energy function. Second, we added a