Presented by:
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DETERMINATION OF BINDING FREE ENERGIES OF CUCURBITURIL CLIP WITH GUESTS USING BEDAM SAMPL5 CHALLENGE:

Binding energy distribution analysis method (BEDAM) is used for determining the free energies of complexes of cucurbituril clip host with various guests' as a part of SAMPL5 challenge. As a part of the project, I performed molecular dynamic simulations of host-guest complexes and analyzed the results. With the help of this project, I learnt about the BEDAM methodology and have understood about its applications on the host-guest systems.

Methods and Preparations

Firstly, the molecular models were prepared for the host and guests using ligprep workflow of the 2013 version of maestro program. It was observed that some guests molecules have more than one protonation state at pH = 7 ± 2. The force field parameter used is OPLS_2005. The complex of these guests with the cucurbituril host were prepared by placing these guests manually in the cavity of the Clip. Once these complexes were prepared, these files were exported to BEDAM workflow and input files were generated. These input files were then used for the molecular dynamic simulations by means of IMPACT program. Furthermore, the resulting binding free energy values obtained after simulations were corrected by means of UWHAM analysis. The implicit solvation model used for these calculations is AGBNP2. The simulation temperature for BEDAM is 300 K. All sulfonate groups of cucurbituril clip are deprotonated and has charge of -4.

BEDAM (Binding Energy Distribution Analysis Method)

The BEDAM method computes absolute binding free energy by means of equation:

$$u(x;\beta, \lambda) = \beta[U_0(x) + \lambda b(x)]$$

Where λ is an alchemical progress parameter ranging from 0, corresponding to the unbound state of the complex, to 1, corresponding to the bound state of the complex and is the inverse of temperature. $U_0(x)$ is the potential energy of the complex when receptor and ligand are unbound, that is as if they were separated at infinite distance from each other. The quantity b(x), called the binding energy, is defined as the change in effective potential energy of the complex for bringing the receptor and ligand rigidly from infinite separation to the given conformation x of the complex.

AGPNP2 (Analytic Generalized Born plus Non Polar version 2)

It is the implicit solvation model which determines the hydration sites in the cucurbituril host and hence is used for the computation of the binding energy of the complex. It takes into account various interactions such as electrostatic interaction, non-polar interaction and hydrogen bonding interaction. It computes hydration free energy by means of solvent potential of a mean force of solute in water.

ASyncRE- Asynchronous replica exchange algorithm is a conformational sampling tool which is used for yielding convergence while carrying out MD simulations. ASyncRE is much better and faster than synchronous RE because in ASyncRE, processors undergo replica exchanges independent of other processors, and hence increases the speed and efficiency while running algorithm.

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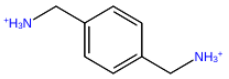
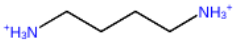
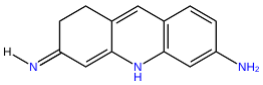
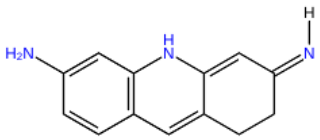
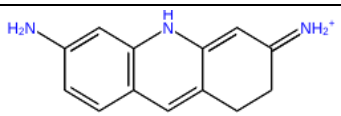
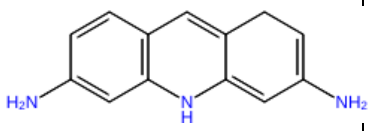
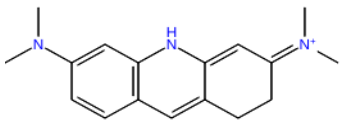
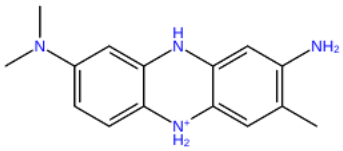
IMPACT (Integrated modeling Program, applied chemical theory) is a program used along with force field parameters to carry out MD simulations .IMPACT program generates input file which further uses force field parameters and energy functions to carry out binding energy calculations.

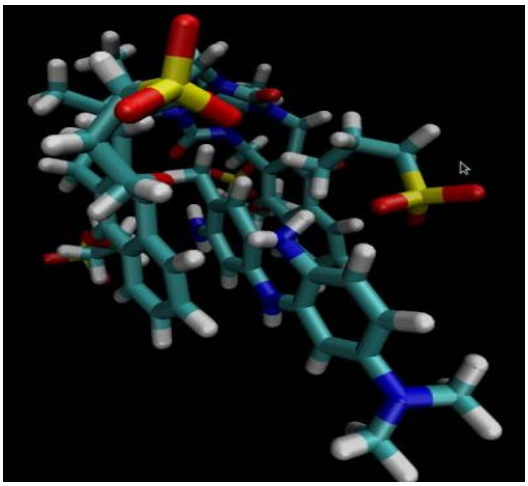
Table:

Guest no.		Binding energy(Kcal/mol)	State Penalty(Kcal/mol)	Corrected Binding Energy(Kcal/mol)
1		-4.6924	0.0485	-4.6439
2		-1.1551	0.001	-1.1541
4		-4.0265	0.6005	-3.426
4-2		-9.7851	0.6005	-9.1846
4-3		-7.5275	0.8613	-6.6662
4-4		-4.1566	1.9005	-2.2561
5		-5.5283	0.1068	-5.4215
9		-12.8895	0.0306	-12.8589

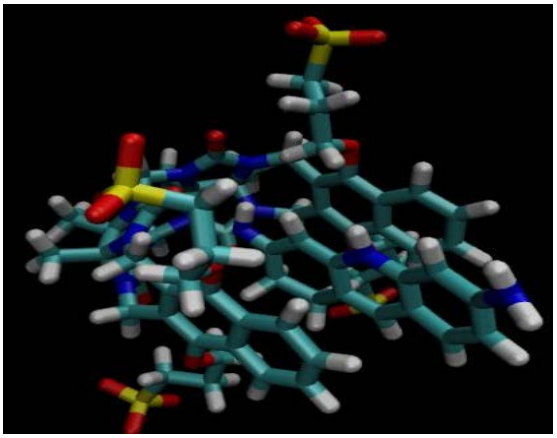
Results and Discussions:

The table represents the binding free energy values of cucurbituril clip with various guests. Some guests have more than one protonation state structures and therefore different binding energies were obtained accordingly. It was observed that guests having fused rings have more favorable values of binding free energies than substituted benzene and linear analogues. This is due to the hydrophobic interactions between the fused rings and cucurbituril clip.

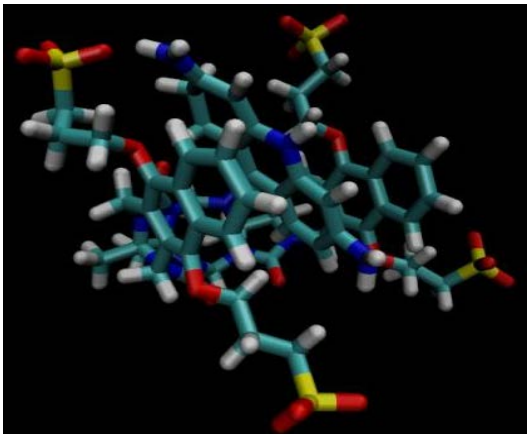
Guest 9 has largest value of binding energy amongst the other guest molecules and is the strongest binder. This is so because addition of two nitrogen in the fused rings will increases hydrogen bonding interaction with the clip. Also there is hydrophobic interaction between fused rings and clip.



One of the protonation state of guest 4(Guest 4-2) is second strongest binder with the clip because it has both hydrogen bonding interactions and hydrophobic interactions with the cucurbituril clip. Also, another protonation state of guest 4(Guest 4-3) has positively charged ammonium which forms ion dipole interaction with the sulfate oxygen of sulfonate group of cucurbituril clip which also enhances binding affinity of the guest-clip complex. Furthermore, fused rings has hydrophobic interactions with the naphthalene rings of cucurbituril clip which leads to the favorable binding energy.

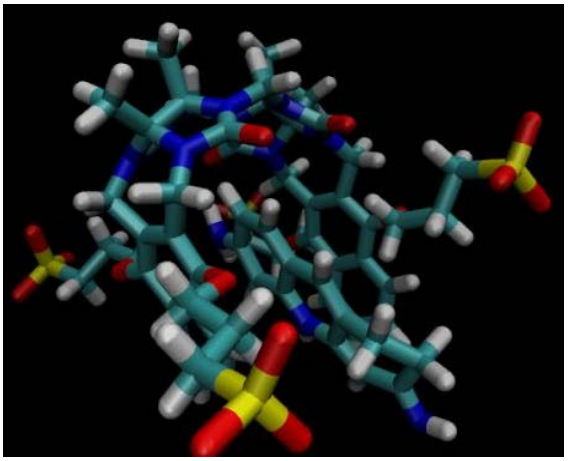


Guest 4-2

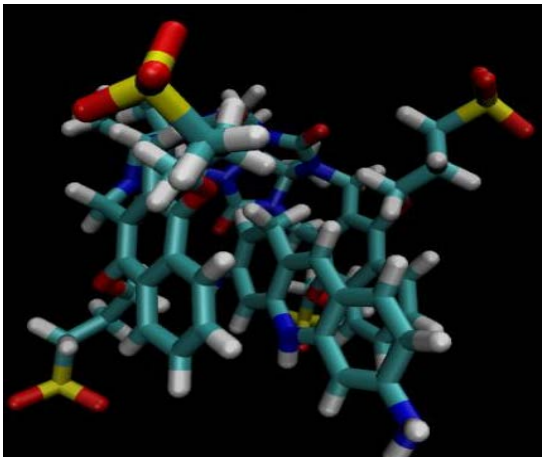


Guest 4-3

Also, the other structures of guest 4(Guest 4 and 4-4) has similar values of binding which has only hydrophobic interaction with the clip. The slight variation the values of binding energy is due to different state penalty values. The binding energy values of the complexes are lower than complexes of guest 1 and 5.

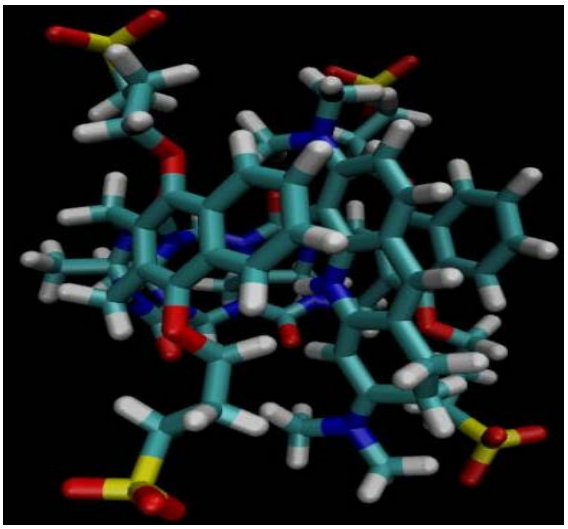


Guest 4

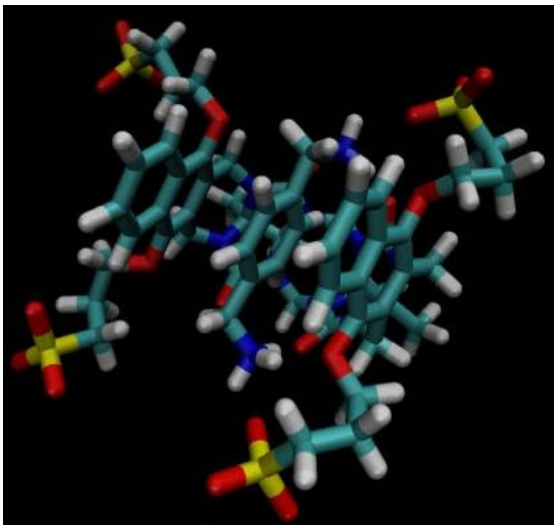


Guest 4-4

Guest 5 is third strongest binder because the structure is neutral and has methylated ammonium which contributes to favorable binding energy. It has hydrophobic interactions between the fused rings and clip. Guest 1 is ranked 4 as it has two positively charged methyl ammonium ion at first and fourth position of the benzene ring which forms two ion dipole interactions with the sulfate oxygen of the sulfonate oxygen of the clip. The guest 1molecule has +2 charge and is achiral due to equivalent substituent at first and fourth position.

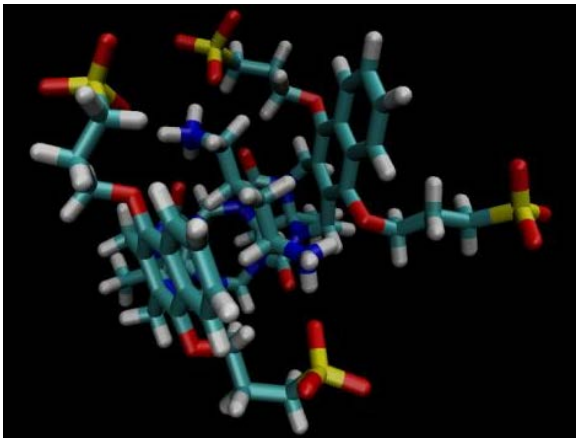


Guest 5



Guest 1

Guest 2 is the weakest binder amongst all other guest molecule although it has two positively charged ammonium ion. The reason is that the molecule is linear and the length of the chain is so small that the molecule is inside the cavity of the clip. Therefore, the positively charged ammonium ion cannot interact with sulfate oxygen of the sulfonate group of the clip which is outside the cavity of the clip. This leads to the unfavorable value of the binding energy.



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