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Computational Analysis of Dipeptide Boc-Val-Val-NHMe as a Drug Carrier

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Abstract: Micelles are the clustering of hydrophobic groups of amphiphilic molecules when placed in aqueous medium. It has been previously determined that the dipeptide Boc-Val-Val-NHMe, forms micelles, when placed in non aqueous medium, chloroform. The potential of these inverted micelles as carriers of drugs are analyzed by insilico methods. Here, the dipeptide is being shown by computational analysis that it can be used as a drug carrier. Also, the free energy values of the peptide, correlates with the experimental value.
Key words: dipeptide, aggregation, aggregation number, free energy.

Introduction:

Recently, colloidal carrier systems have been receiving much attention in the field of drug targeting because of their high loading capacity for drugs as well as their unique disposition characteristics in the body. This paper highlights the utility of polymeric micelles formed through the multi molecular assembly of block copolymers as novel core–shell typed colloidal carriers for drug and gene targeting (1). A polymeric micelle is a macromolecular assembly composed of an inner core and an outer shell, and most typically is formed from block copolymers. In the last two decades, polymeric micelles have been actively studied as a new type of drug carrier system, in particular for drug targeting of anticancer drugs to solid tumors. (2). Polymeric micelles were expected to increase the accumulation of drugs in tumor tissues utilizing the enhanced permeability and retention effect and to incorporate various kinds of drugs into the inner core by chemical conjugation or physical entrapment with relatively high stability (3). Molecular dynamic simulation using empirical force fields provides one of the most direct methods of theoretically investigating the behaviors of complex molecular systems and is well-suited for the simulation of protein-surface interactions(4). Peptide folding simulations and experiments characterize the dynamics and molecular mechanisms of the early events of protein folding. Computationally, peptides present a more tractable system than proteins. Experimentally, peptides fold at very fast rates, requiring probing on the nanosecond time resolution. Peptides offer a unique opportunity to bridge the gap between theoretical and experimental understanding of protein folding (5). Surfactants and cosolvents can be toxic at high doses and may be limited in their daily and per-dose uptake levels Formulators aim to develop systems with maximum drug loading capacity while using minimum possible amounts of surfactants and cosolvents. These limitations lead formulators to a limited range of compositions (6). Predictive ability and quick methods for assessment of such problems could be very useful to the formulators in selecting lead formulations (6). To efficiently deliver therapeutics into cancer cells, a number of strategies have been recently investigated (7). The close interaction between sophisticated experiments and specialized simulations has led to a general understanding of the mechanism of protein folding (8). One of the true facts in molecular dynamic simulations is that, the simulation time is extended from to a range of nano to micro seconds, to analyse biological phenomena (9). But, with the time resolution extended to femtoseconds, the reactions involved in

chemical reactions could be observed (10, 11). Insilico analysis of dipeptide predicted to be a drug carrier has already been done (13). The aggregation of dipeptide, to form reverse micelles in non aqueous medium has also studied (14).

Materials & Methods:

Boc-Val-Val-NHMe – Construction:

The structure of the dipeptide, Boc-Val-Val-NHMe, was drawn using the tool ChemSketch. The template window of the tool offers the structures of several moieties like sugar, alkaloids, etc. SMILES notation of these structures were generated using the Generate SMILES option, in ChemSketch tool. The structure is developed from Chemsketch.

Selection of the drug:

An extension of the work on inverted micelles as an application is to unravel the potentiality of the constructed inverted micelle. This was analysed computationally to carry drugs. Insilico methods were employed to calculate the inner volume of the inverted micelle. The drug, Meprobamate, was selected, whose volume is lesser than that of the inner core of the inverted micelle. The drug Meprobamate, which is used as a sedative with muscle relaxing property was selected and is shown to be carried by the inverted micelle at the different aggregation numbers.

Packmol Program:

The software Packmol was used in creating the inverted micelles of the dipeptide. Here the path for the packmol program was set in the specified directory.

For example,

C:\set path=packmol

The structure file of the dipeptide, the required parameters along with the structure file of the water and chloroform molecules was typed in a wordpad. The parameter used:

1) tolerance 2.0
structure valval.pdb
number 27
atoms 51
inside sphere 0. 0. 0. 7.
end atoms
atoms 7
outside sphere 0. 0. 0. 12.
end atoms
end structure
structure chlor.pdb
number 540
inside box -25. -25. -25. 25. 25. 25.
outside sphere 0. 0. 0. 14.
end structure
output 27mol.pdb

2) tolerance 2.0
structure valval.pdb
number 32

```
        atoms 51
        inside sphere  0. 0. 0. 8.
        end atoms
        atoms 7
        outside sphere  0. 0. 0. 15.
        end atoms
        end structure
structure chlor.pdb
            number 200
            inside box  -25. -25. -25.   25. 25. 25.
                  outside sphere  0. 0. 0. 16.
end structure
        output  32mol.pdb
        3)tolerance 2.0
structure valval.pdb
        number 44
        atoms 51
        inside sphere  0. 0. 0. 9.
        end atoms
        atoms 7
        outside sphere  0. 0. 0. 17.
        end atoms
        end structure
structure chlor.pdb
            number  341
            inside box  -25. -25. -25.   25. 25. 25.
                  outside sphere  0. 0. 0. 18.
                  end structure
        output  44mol.pdb
        4) tolerance 2.0
        structure valval.pdb
        number 56
        atoms 51
        inside sphere  0. 0. 0. 12.
        end atoms
        atoms 7
        outside sphere  0. 0. 0. 16.
        end atoms
        end structure
        structure chlor.pdb
            number  180
            inside box  -25. -25. -25.   25. 25. 25.
                  outside sphere  0. 0. 0. 18.
end structure
```

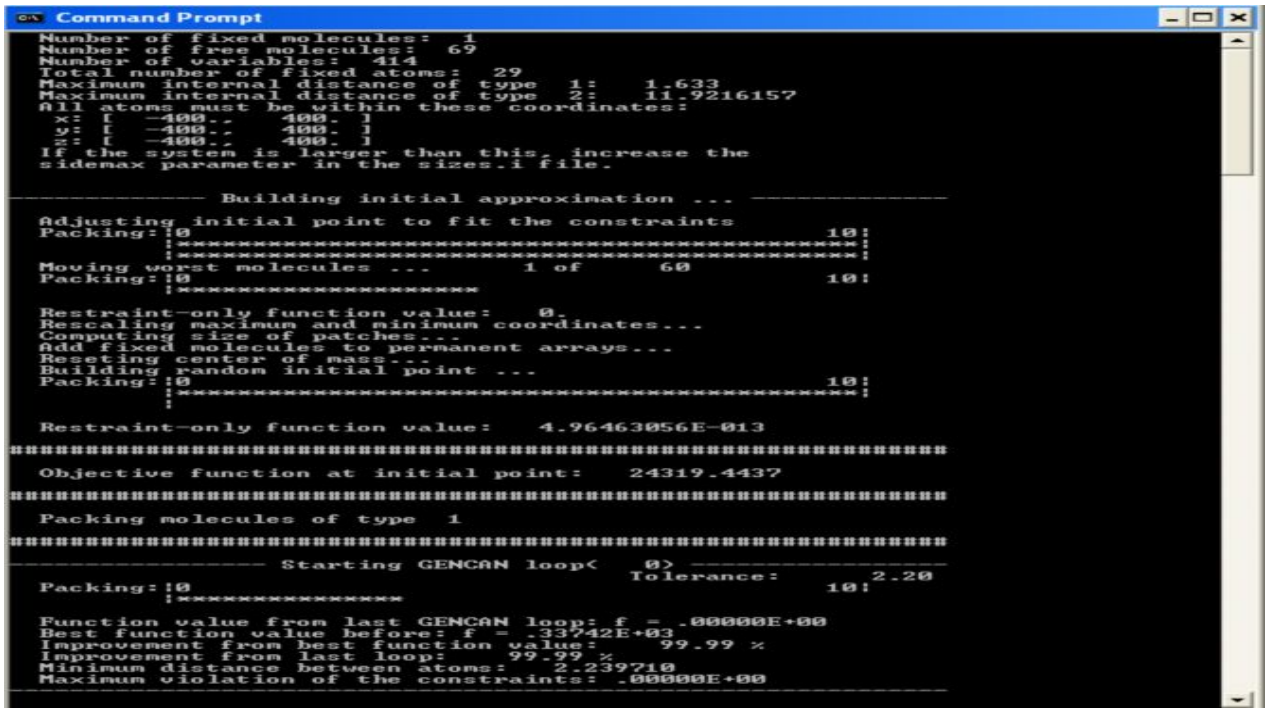
output 56mol.pdb

Save the wordpad with .inp extension.

Running packmol:

The saved wordpad file was run in the command line. The command to run the file

packmol<filename.inp



Results and Discussion:

Construction of Dipeptide Boc-Val-Val-NHMe:

The dipeptide Boc-Val-Val-NHMe was found to form micelles at four different temperatures. The aggregation number of the inverted micelles, were determined experimentally (12). The structure of the dipeptide was constructed using the tool ChemSketch. The SMILES notation was used to generate the structure (Fig.1).

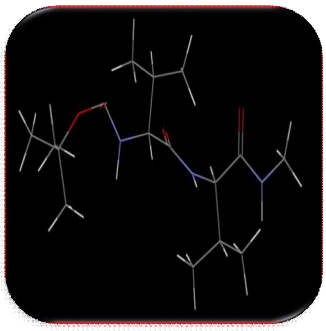


Fig.1. Structure of dipeptide Boc-Val-Val-NHMe

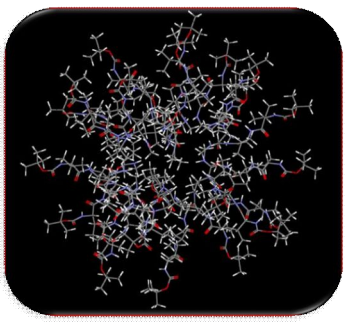


Fig.2. Structure of inverted micelle

Construction of Inverted Micelles Using Packmol Program:

The inverted micelle structure of Boc-Val-Val-NHMe was created using packmol package (Fig.2). The dipeptide forms aggregates with different aggregation number at four different temperatures. Water was added to the inner core of the inverted micelle and chloroform molecules were added to the outer surface of the inverted micelle. Initial configuration was done using packmol package and later, after the initial configuration, the inverted micelle structures were minimized using Discovery Studio2.0 and the different energy values were calculated. The constructed inverted micelles were subjected to minimization using the Steepest Descent Method algorithm in Discovery Studio 2.0 Figure 3 shows the micelles, with different aggregation numbers.

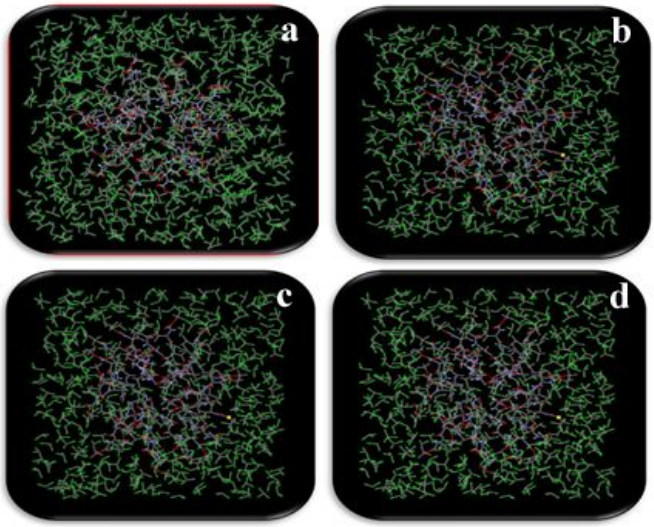


Fig.3. Inverted micelles of different aggregation numbers viz., 27-a, 32-b, 56-cand 44-d.

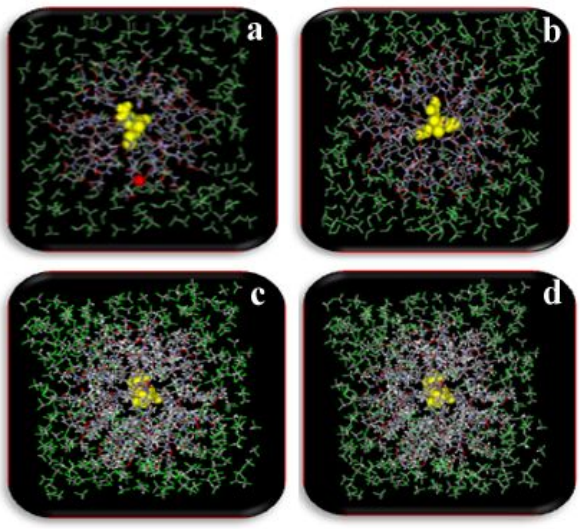


Fig.4: **Reverse micelles with Different Aggregation Number Having Meprobamate**

Fig.4 shows the micelles, carrying the drug, Meprobamate in the inner core**.** The drugs were chosen such that they pack inside the inverted micellar core. The inverted micelle was subjected to energy minimization with and without the drug, using Steepest Descent Method algorithm. The free energy value of the dipeptide, experimentally and computationally determined is shown in the table 1.

Table:1. **The Free Energy Values of the dipeptide – experimental and computational.**

S.No	Temperature In Kelvin	Aggregation No of micelles	ΔG ($KJmol^{-1}$)	
			Experimental Value	Simulated value
1	297	27	-15.0	-15.0792
2	305	32	-15.0	-15.0121
3	310	44	-14.7	-14.7184
7	320	56	-14.8	-14.8513

Conclusion:

The Reverse Micelles with different aggregation numbers were constructed and their free energy was calculated. The Free energy of the dipeptide, by computational method was shown to be same as the experimental value. The free energy of the dipeptide micelle and other thermodynamic parameters has already been determined (12).

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