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1.4-DHP-Lipid Forms a Tubular Micellae

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The cationic lipid 1,1.-[3,5-bis(dodecyloxycarbonyl)-4-phenyl-1,4-dihydropyridin-2,6-diyl] dimethylene bispyridinium dibromide (1,4-DHP lipid), a gene transfection agent, formed a tubular micellae during the molecular dynamics simulation with AMBER 8.0 force field. Result was confirmed with the electron microscopy showing extended, worm-like structures.

1 Introduction

Non-viral gene delivery based on self-assembling structures is an effective medical tool. The cationic lipid 1,1.-[3,5-bis(dodecyloxycarbonyl)-4-phenyl-1,4-dihydropyridin-2,6-diyl] dimethylene bispyridinium dibromide (1,4-DHP lipid, charge q=+2) (Fig. 1) is a gene transfection agent.[1,2] The electronic structure of 1,4-DHP lipid molecule was investigated by ab initio quantum mechanics, and the supramolecular structure formed by 1,4-DHP lipid molecules was investigated by means of molecular dynamics simulation.

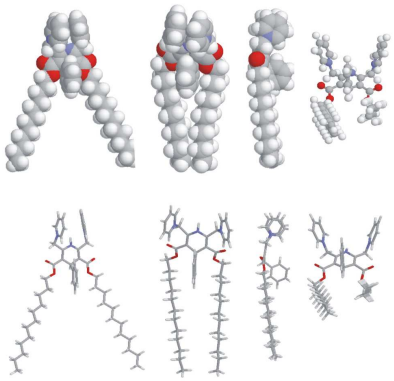

Figure 1. 1,4-DHP lipid molecule.

2 Methods, Results and Discussion

1,4-DHP lipid structure was calculated by Restricted Hartree-Fock (RHF) *ab initio* quantum mechanics, 6-31G* bases set, to obtain the charges for molecular dynamics using RESP algorithm (electrostatical potential based method using charge restrains for determining atom-centered charges). 72 molecules of 1,4-DHP-lipid were subjected to MD (AMBER 8.0 force field, NTP protocol) from the initial structure of a periodic lipid bilayer-water box, with a small amount of excessive water on the lipid edges to ensure the mobility of lipid molecules. Temperature was risen gradually from T=10 K by step of 10 degrees till 300 K. After 35 ns of MD simulation few lipid molecules turned with their charged heads to the side of the lipid bilayer and after 100 ns a profound tubular micelle structure began to form. The tubular micelle structure (Fig. 2) becomes more perfect during the course of simulation of 300 ns.

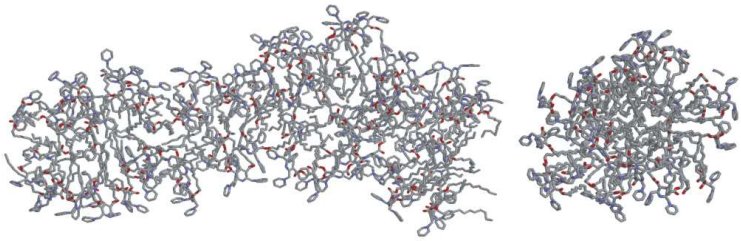

Figure 2. 1,4-DHP lipid tubomicellae side view and top view.

The results of MD simulation were confirmed by electron microscopy, showing the interwinding tubular structures (Fig. 3).

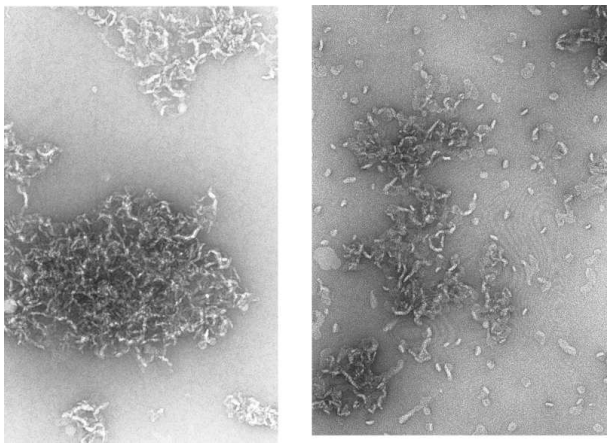

Figure 3. Electron microscopy of the 1,4-DHP lipid.

Conclusion is that one of the gene transfection agent 1,4-DHP lipid structures is a tubular micellae, and we could expect that such the micellaes are capable to form a lipoplex for the DNA transfection

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References

1. Z. Hyvonen, A. Plotniece, I. Reine, B. Chekavichus, G. Duburs, A. Urtti, *Novel cationic amphiphilic 1,4-dihydropyridine derivatives for DNA delivery*, Biochim. Biophys. Acta **1509**, 451-466, 2000.
2. Z. Hyvonen, S. Ronkko, M.-R. Toppinen, I. Jaaskelainen, A. Plotniece, A .Urtti,*Dioleoyl phosphatidylethanolamine and PEG-lipid conjugates modify DNA delivery mediated by 1,4-dihydropyridine amphiphiles*, J. Controlled Release **99**, 177-190, 2004.