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Theoretical Investigation of Solvent Effects on The Structural Changes of 1 - Pentadecanoyl - 2 - Docosahexaenoyl - Sn – Glycerol - 3 –Phosphocholin

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ABSTRACT

Theoretically predictions of the solvent effects of 1 - pentadecanoyl - 2 -docosahexaenoyl - Sn – glycerol - 3 - phosphocholin have been studied using Hartree-fock quantum chemical approximation and STO - 3G basis set within the Onsager Self-Consistent Reaction field (SCRF) model. All optimized conformers of 1 - pentadecanoyl - 2 -docosahexaenoyl - Sn – glycerol - 3 - phosphocholin as well as their total relative energies in terms of the most stable confooner in gas phase and different solvent media such as water, ethanol, methanol and DMSO have been calculated. According to the obtained results the 1 - pentadecanoyl - 2 - docosahexaenoyl - Sn – glycerol - 3 - phosphocholin configuration has the most negative energy values and then has been found to be the most stable conformer. In this aspect the graph of relative energy values versus dielectric constants (ε) as well as Ln (1/ε) of employed solvents has been plotted and the observed trend has been analyzed.

For further investigation, the effect of solvent's polarity on the dipole moments of 1-pentadecanoyl - 2 - docosahexaenoyl - Sn – glycerol - 3 - phosphocholin in various solvent media have been reported and compared with the gas phase. We would like to note that the dipole moment variations revealed that the values of the computed dipole moment seems to be solvent - dependent because this property is closely related to the environmental effects the greatest dipole moment brings more stability which is under influence of solvation

Keywords: Pentadecanoyl; Docosahexaenoyl; - Sn – glycerol; Phosphocholin; Solvent effect; SCRF; Dielectric constant; Energy values

INTRODUCTION

Long chain polyunsaturated fatty acids are highly enriched in the nervous system. The early model of biological membranes, which called "fluid-mosaic model", was proposed in 1972 explaining an idea that the lipid membrane could be considered as a two dimensional fluid and the proteins can diffuse around [1].

Lipid molecules are the main constituents of the biological membranes. They exist in numerous structural forms which the glycerophospholipids (or phosphoglycerides) are the most abundant lipids in membranes [2].

Cells which are more metabolically active need more flexible membranes and for this purpose, these membranes are better to have phospholipids carry long chain unsaturated fatty acids [3-5]. Long

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chain polyunsaturated fatty acids are highly enriched in the nervous system Docosahexaenoic acid (22:6n-3, DHA), in particular, is the most abundant polyunsaturated fatty acid in the brain, and is concentrated in amino phosphalipids of cell membranes[6-10](see Fig.1)

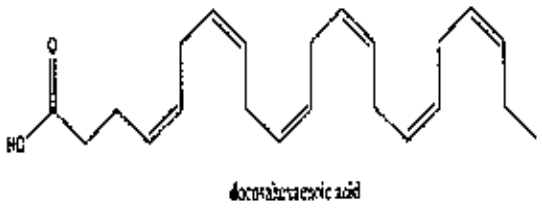

Fig.1. Molecular structure of docosahexaenoic acid (DHA).

DHA is paired in glycerophnspholipids often with palmitic acid (16:0) and stearic acid (18:0) and in some cases with another long-chain polyunsaturated fatty acid such as 22:6 in position sn-1 and accumulates in phosphatidylethanolamines[11]. It has been postulated that optimal neurological development, information processing, the capacity of nerve cells to conduct electrical signals [10] and cognitive functions[11-13]. DHA is major structural and functional buildings of the brain about 30% of the structural lipids of the grey matter are DHA Hence, it is not surprising that the deficiency DHA in early life has been associate with a variety of learning and cognitive disorders[13].

As DHA can only produced by the body in limited quantities it has to supply by dietary sources [14-15].

Currently, some fatty fishes. Such as tuna and salmon is the main source of DHA and these supplies are unreliable because of unpleasant taste, marine pollution, seasonal variation and high processing costs [14-17]. Microorganisms are used to provide DHA and also microalgae biomass is particularly suitable for providing polyunsaturated fatty acids due to their stable composition, contaminant free and good tastes [18].

Schizochytrium sp is an algae-like microorganism used for industrial production of docosahexaenoic acid (DHA) - rich oil and dried microorganism for its usage as a source of this fatty acid in foods, and nutritional supplements [19]. Nowadays, it is obvious that the major phospholipids in the Schizochytrium sp. Straia F26 - b is a novel PC which contains pentadecanoicacid (C15:0) at sn-1 and docosahexaenoic acid at sn-2, i.e., the systematic name of this new phospholipid is 1 - pentadecanoyl - 2 - docosahexaenoyl - Sn – glycerol - 3 -phosphocholin (see Fig.2) and if it is possible to extract and purify DHA from this microorganism a new insight upen into the methods of producing DHA [14].

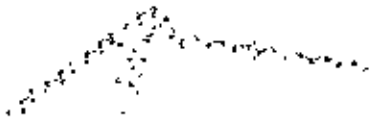

Fig.2 The optimized structure of 1-pentadecanoyl-2-docosahexaennyl-Sn-glycerol-3-phosphocholin.

In the early study of Demel et al, the force-area characteristics of unsaturated PC minelayers were determined[20]. Numerous experimental observations explain that the existence of DHA and other polyunsaturated fatty acids in the membrane bilayer result in dramatic changes in material properties[21].

The structure and dynamics of these polyunsaturated lipid chains at the molecular level are profoundly different from their saturated counterpart with correlation times and extremely low chain order as revealed by NMR spectroscopy[22].

Ab - initio quantum chemical studies of segments of DHA with classical molecular dynamics simulations of DHA-containing have been explained. In the recent review, biochemical mechanisms for enriching and metabolizing DHA in neural cells are discussed in the context of biological significance in neuronal function[23].

The lack of theoretical investigation of solvent effect on the biological stability of DHA in a variety of solvents motivated us to perform the computational molecular modeling to better understand the - structural changes due to solvation as well as variations of energy values and dipole moments of DHA in solvents.

Hartree - fock (HF) approximation has been used to study the structural changes of hydrated forms of 1 - pentadecanoyl - 2 - docosahexaenoyl - Sn - glycerol - 3 - phosphocholin as well as variation of solvation energies in different solvent media.

The purpose of the present study is to analyze the solvent effects on the energy values which reveal the relative structural stability caused by solvents on 1 - pentadecanoyl - 2 - docosahexaenoyl - Sn - glycerol - 3 - phosphocholin within various solvents.

To estimate the effect of polarity of solvent media on the relative biological stabilities of the coosidered compounds we have employed the Onsager SCRF solvent model at the level of RHF/STO-3G theory.

COMPITITIONAL DETAIL

For membrane's phospholipids, the experimental studies are so difficult and NMR studies nf unsaturated fatty acids in membranes provide equilibrium and dyoamic properties. but to ohtain data in atomic level of those properties for such molecules, we have to use eomputer simulation. Surely, molecular dynamics (MD) is the most common technique tn simulate membranc systems [18]. However, one may gain more detailed description of a system in shnrt time range simulation, generally in the order of picoseeonds [1].

In our study, first, we have optimized the 1 - pentadecanoyl - 2 - doeosahexaenoyl - Sn - glycerol - 3 - phosphocholin molecule with HYPER 6 software For this purpose, we have chosen different water boxes and have considered 310K for all of them the same as body temperature. Then insert the 1 - pentadecanoyl - 2 - dococsahexaenoyl - Sn - glycerol - 3 - phosphocholin in eaeh of boxes and hyperchem softwarc optimized them .the sceond step was to obtain volume of each optimized solute cavity with Gaussian 98 softwarc [24].
So, we calculated all molecules' volumes at the Hf / STO-3G level of theory. Then put the optimized molecules with definite volume in six solvents with different dielectric constant water (ε = 78.39), DMSO (e = 46.8), nitro methane (e = 38.2), methanol (e = 32.63), ethanol (c = 24.55) and acetone (c = 20.7), then obtained energy values as well as dipole moments have been analyzed (Table 1).

RESULTS AND DISCUSSION

The investigation of molecular energies in a wide variety of solvents, polarities of 1 - pentadecanoyl - 2 - docosahexaenoyl - Sn - glycerol - 3 - phosphocholin will be of great interest for obtaining a logieal relationship between the delicate balance of dielectric constant and energy values caused by intermolecular interactioos within solvation process.

Solvent effects on the structural stability

Amongst studied molecules in different solvent media the highest energy value and con sequent the least stability observed in the solvents with dielectric eonstant in the range of 20 up to 40. Also through increasing the dielectric constant of solvent the structural energy has been decreased (see Fig.3).

Strikingly supposing two cases which the 1 - pentadecanoyl - 2 - docosahexaenoyl - Sn - glycerol - 3 - phosphocholin has been optimized within 548 and 561 water molecules the plotted graphs of relative energies in different solvent media considerably resemble to each other. So, we ean realize that the most structural stability has been observed in acetone and in the other eases the stability has been increased through increasing dielectric constants. The optimized 1 - pentadecanoyl - 2 - docosahexaenoyl - Sn - glycerol - 3 - phosphocholin in 566 and 629 water molecules exhibited the similar plotted graphs and the least stability is corresponded to ethanol (ε = 24.55) and through going to the highest dielectric constant and then the highest polarity ,the molecular stability has been increased.

However the optimized molecule within 566 water molecules exhibited different trend to the both above cases .in spite of such a significant difference , we ean clearly find a point that these three curves crossed each nthers .it is notable that this point has been located in the moderate polarity .i.e. c=20.5 up to 24.55 (see Fig.3).

For the conformer which has been optimized in 613 water molecules the most stability has been found in acetone and eonversely the least stability has been corresponded to ethanol (see Fig.3).

Table 1. Dipole moment and energy values for the optimized structure of 1 - pentadecanoyl - 2 - docosahexaenoyl - Sn - glycerol - 3 – phosphocholin

	ε	Ln(1/ε)	E(HF)	ΔE relative (kcal/Mol)	Dipole moment
DHA-containing molecule optimized in 548 water molecules	78.39	-4.36169	-2732.705880	-0.000042	3.4741
	46.8	-3.84588	-2732.705886	0.000036	3.4794
	38.2	-3.64283	-2732.705891	-0.000031	3.4862
	32.63	-3.48523	-2732.705899	-0.000023	3.4951
	24.55	-3.20071	-2732.705913	-0.000009	3.5354
	20.7	-3.03013	-2732.705922	0.0000	3.5220
DHA-containing molecule optimized in 561 water molecules	78.39	-4.36169	-2732.705852	-0.000043	3.4741
	46.8	-3.84588	-2732.705858	-0.000037	3.4794
	38.2	-3.64283	-2732.705863	-0.000031	3.4862
	32.63	-3.48523	-2732.705871	-0.000023	3.4951
	24.55	-3.20071	-2732.705885	-0.000009	3.5354
	20.7	-3.03013	-2732.705894	0.000	3.5220
DHA-containing molecule optimized in 566 water molecules	78.39	-4.36169	-2732.610806	-0.000014	3.3776
	46.8	-3.84588	-2732.610808	-0.000012	3.3816
	38.2	-3.64283	-2732.610812	-0.000009	3.3868
	32.63	-3.48523	-2732.610818	-0.000003	3.3938
	24.55	-3.20071	-2732.610821	0.000	3.3904
	20.7	-3.03013	-2732.610812	-0.000009	3.3984
DHA-containing molecule optimized in 576 water molecules	78.39	-4.36169	-2732.620918	-0.288750	3.1134
	46.8	-3.84588	-2732.909663	-0.000005	3.1611
	38.2	-3.64283	-2732.909664	-0.000004	3.1626
	32.63	-3.48523	-2732.909668	0.000	3.1648
	24.55	-3.20071	-2732.620920	-0.288748	3.1147
	20.7	-3.03013	-2732.620912	-0.288756	3.1224
DHA-containing molecule optimized in 613 water molecules	78.39	-4.36169	-2732.638098	-0.000027	3.4438
	46.8	-3.84588	-2732.638101	-0.000024	3.4461
	38.2	-3.64283	-2732.638104	-0.000021	3.4487
	32.63	-3.48523	-2732.638104	-0.000021	3.4523
	24.55	-3.20071	-2732.638125	0.000	3.4884
	20.7	-3.03013	-2732.638094	-0.000031	3.4520
DHA-containing molecule optimized in 629 water molecules	78.39	-4.36169	-2732.630060	-0.000010	3.1663
	46.8	-3.84588	-2732.630063	-0.000007	3.1687
	38.2	-3.64283	-2732.630066	-0.000004	3.1719
	32.63	-3.48523	-2732.630070	0.000	3.1740
	24.55	-3.20071	-2732.630067	-0.000003	3.1870
	20.7	-4.36169	-2732.630060	-0.000010	3.1663
	78.39	-4.36169	-2732.611858	-0.000014	3.4392
	46.8	-3.84588	-2732.611860	-0.000012	3.4422
	38.2	-3.64283	-2732.611861	-0.000011	3.4460
	32.63	-3.48523	-2732.611844	-0.000028	3.4270
	24.55	-3.20071	-2732.611853	-0.880019	3.4316
	20.7	-3.03013	-2732.611872	8.000	3.4606
DHA-containing molecule optimized in 707 water molecules	78.39	-4.36169	-2733.108537	-0.000017	3.3261
	46.8	-3.84588	-2733.108540	-0.000014	3.3281
	32.63	-3.48523	-2733.18854	0.000	3.3275
	24.55	-3.20071	-2733.108534	-0.000020	3.3189
	20.7	-3.03013	-2733.108531	-0.000023	3.3358
	78.39	-4.36169	-2733.108537	-0.000017	3.3261

Table1. Continue...

DHA-containing molecule optimized in 777 water molecules	78.39	-4.36169	-2735.061353	-0.000002	2.9547
	46.8	-3.84588	-2735.061355	0.000	2.9555
	38.2	-3.64283	-2735.061354	-0.000001	2.9556
	32.63	-3.48523	-2735.061355	0.000	2.9525
	24.55	-3.20071	-2735.061354	-0.000001	2.9596
	20.7	-3.03013	-2735.061342	-0.000013	2.9539
DHA-containing molecule optimized in 884 water molecules	78.39	-4.36169	-2735.061353	-0.000001	2.9547
	46.8	-3.84588	-2735.061354	0.000	2.9555
	38.2	-3.64283	-2735.061354	0.000	2.9556
	32.63	-3.48523	-2735.061354	0.000	2.9521
	24.55	-3.20071	-2735.061354	0.000	2.9596
	20.7	-3.03013	-2735.061341	-0.000013	2.9539

For the 1-pentadecanoyl-2-docosahexacnoyl-Sn-glycerol-3-phosphocholin which has been optimized in 692 water molecules the most positive energy values and the least one have been observed in acetone and methanol, respectively (see Fig.3).

Finally, for the optimized conformer in 777 and 884 water molecules the most stability has been observed in acetone and strikingly the obtained energy values appeared with significant difference in comparison to other employed solvents. Although, the least stability has been caused by hydration in water .

Solvent effects on the structural polarity

Solvent-induced effect has been investigated for all considered conformer which have been optimized in different water molecules and different values of dipole moments concerning the structural polarity of studied compounds have been obtained in different solvent media. The highest values of dipole moment have been yielded in the range of 20 up to 30 of dielectric constant (see Fig.4).

According to our obtained theoretical data, the values of dipole moment exhibited the decreasing trend through increasing dielectric constant and the highest value of dipole moment have been observed in the polar solvents such as acetone, ethanol and methanol. In the case of optimized 1 - pentadecanoyl - 2 - docosahexaenoyl - Sn - glycerol - 3 - phosphocholin in 548 and 561 water molecules the highest Pic on the graphs of relative dipole moment versus dielectric constaut which is corresponded to acetone and after passing that region the decreasing trend has been obvious and in water solvent the pick reaches to the lowest value (see Fig.4).

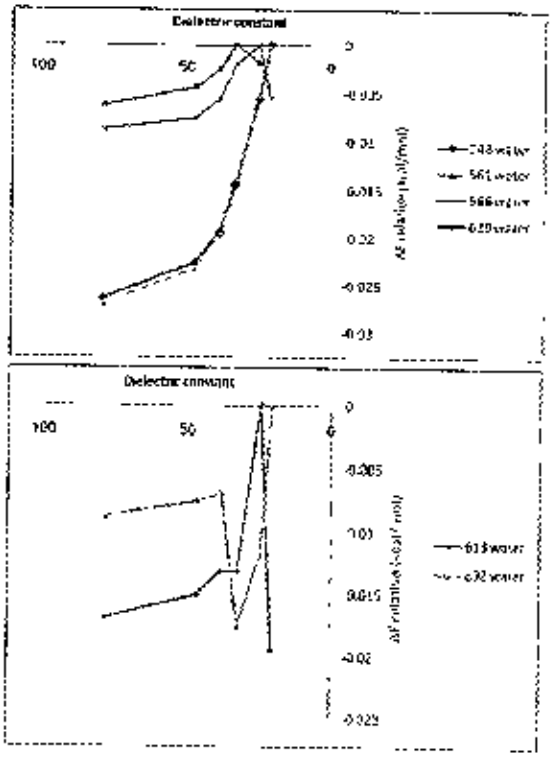

Fig.3. The graphs of relative energy values for optimized 1 - pentadecanoyl - 2 - docosahexaenoyl - Sn - glycerol - 3 - phosphocholin in different water molecules.

For the 1 - pentadecanoyl - 2 - docosahexaenoyl - Sn - glycerol - 3 - phosphocholin which has been optimized in 566 water molecules the highest dipole moment value and the least one have been observed in acetone and water, respectively. and for the next molecule which optimized in 576 water molecules the mentioned values have been obtained in methanol and water ,respectively(see Fig.4).

In the case of 1 - pentadecanoyl - 2 - docosahexaenoyl - Sn - glycerol-3-phosphocholin which has been optimized with 613 and 629 water molecules the plotted graphs exhibited the same pattern and the highest points corresponded to ethanol and after this region the decreasing trend has been obvious and finally the pick reaches to the lowest value in water.

The last two 1 - pentadecanoyl - 2 - docosahexaenoyl - Sn - glycerol - 3 - phosphocholin molecules which have been optimized in 777 and 884 water molecules respectively, exhibited the similar plotted graphs and the highest values dipole moment have been observed in ethanol and the least value corresponded to methanol(see Fig.4).

CONCLUSION

Computer technology has an important role in the conformational energetics of the DHA chain in biological membranes especially in nerve cell's membrane and should be considered when understanding the unique properties of this fatty acid. The large number of conformers accessible with the thermal energy of physiological conditions far exceeds those of saturated lipids, even in their fluid state. A novel DHA - containing phosphocholin have found in Schizochytrium sp. Strain F26-b which is expected to consider as a new, safe and better source for DHA and DHA-contaning phospholipids. This new molecule has been chosen for solvent effect's study in computational methods.

Due to some conditional variations may change cell's membrane as well as cell integrity. so, understanding the of different solvent effect on unsaturated chains in all membranes will be fruitful to identify membranes behaviors in different conditions. In this research, the influence of employing different solvent media on the structural stability has been investigated with quantum chemical calculations.

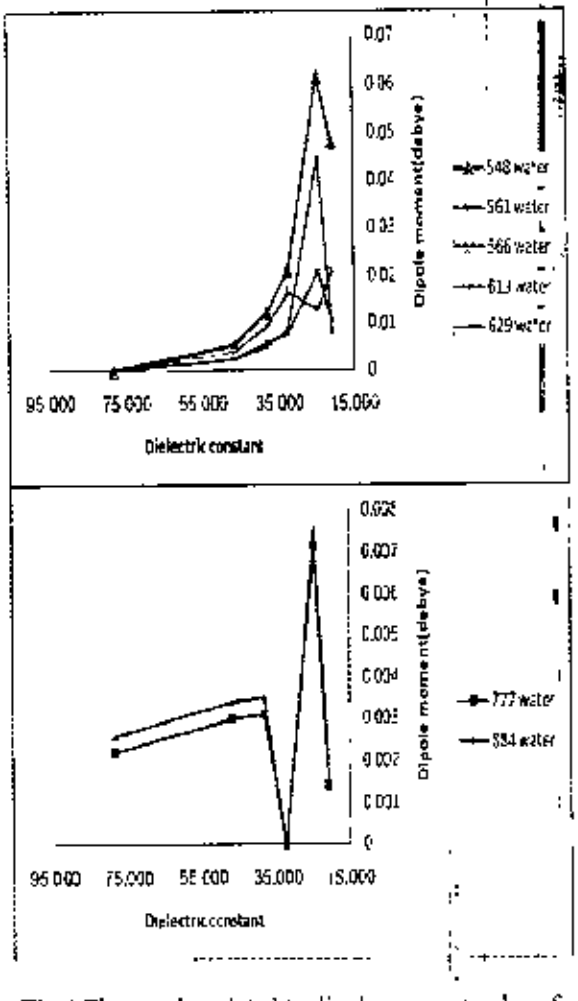

Fig.4. The graphs related to dipole moment values for optimized 1 - pentadecanoyl - 2 - docosahexaenoyl - Sn - glycerol - 3 - phosphocholin in different water molecules.

The Solvent - induced effect on conformational energies and structural stability of DHA is a critically important feature that should be seriously identified in order to find out the unique Physico - chemical properties of this fatty acid. Structural investigations of 1 - pentadecanoyl - 2 - docosahexaenoic - Sn - glycerol - 3 - phosphocholin in general show a relation between the solvent's polarities and the structural stability of similar biolngical compounds. These results are in agreement with the common chemical concepts.

It has been found that in different solvent media the highest energy value and then the least stability correspond to solvents with dielectric

constant in the rauge of 20 up to 40 and also through increasing the dielectric constant of solvent the structural energy values decreased.

In the case of solvent effect on dipole moment the result show that the highest value of dipole mument have been obtained in the range of 20 up to 30 dielectric constant which have been observed in the polar solvents such as acetone, ethanol and methanol.

We hope the observation from simulations of specific DHA – eontaining phosphocholin help people to have a new source of DHA which would be contaminant free and good taste.

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