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Full Length Research Paper

Structural changes of DHA-containing phospholipids by K^+ and Na^+ cations in nerve cell membranes

N.Khodayari, F.Mollaamin , M. Monajjemi

[1]Ph.D Student, Science and Research Branch, Islamic Azad University, Tehran, Iran.
[2]Department of Chemistry, Science and Research Branch, Islamic Azad University, Tehran, Iran.
[3] Department of Chemistry and Biochemistry, Institute for Theoretical Chemistry, Visitor Researcher, The University of Texas at Austin, Austin, Texas, USA.

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Understanding the structure and dynamics of a docosa hexaenoic acid (DHA) containing phospholipid monomer within membranes is essential for recognizing the bilayer function in central nervous system. It has been recognized that the electrical impulses in nerve cells arise from the movement of electrical charges in the form of ions across the plasma membrane. In this study, we have modeled a novel DHA-containing phosphatidylcholine (PC) found in a marine single cell eukaryote, "Schizochytrium sp F26-b" and we were focused on understanding the physico-chemical nature of K^+ and Na^+ movement toward DHA-containing phospholipid through its structural changes. To know more about the temperature dependence of the structural stability of 1-pentadecanoyl-2-docosahexaenoyl-sn–glycerol-3-phosphocholin frequently calculations have been carried out at different biological temperatures and the plotted graphs of energy values at all employed temperatures have been analyzed. Our findings confirmed the usefulness of Quantum chemical calculations for determination of dynamics of a phospholipid and prediction of their biological activity in bio-membranes.

Key words: Docosahexaenoic acid-containing phospholipid, nerve cell membranes, K^+ and Na^+, Ab initio.

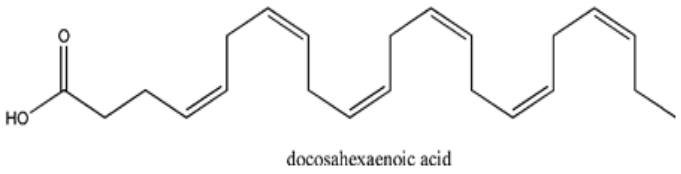
INTRODUCTION

Experimental studies have shown that understanding of the structure and dynamics of a phospholipid monomer within an assembly is essential for recognizing the bilayer functional role in bio-membranes (Krishnamurty et al., 2008; Aussenac et al., 2003). Numerous experimental observations revealed that the presence of DHA (docosahexaenoic acid) or other polyunsaturated fatty acids in the cell membrane causes dramatically changes in material properties (Scott, 2008; Olbrich et al., 2000; Rawicz et al., 2000).The structure of Docosahexaenoic acid (DHA) has been displayed in Figure 1. Since the membrane phospholipid bilayer forms the matrix within membrane proteins such as receptors and ion channels, membrane proteins may also associate with a sufficient number of specific or non-specific lipids which form coat or annulus around the mentioned proteins (Hallahan and Garland, 2005; Battaglia and Schimmel, 1997; Litman et al., 2001).

There is an agreement in the literature that mammalian brain accretes its DHA during specific periods of intrauterine and postnatal life and its fatty acid composition does not change (Farkas et al., 2000). Indeed, the electrical impulses in nerve cells arise from the movement of electrical charges in the form of ions across the plasma membrane Wilson et al. (1983).

Cell membrane transport of two ions Na^+ and K^+ is of interest to physiologists due to the wide range of cellular functions of these ions in the cells Hoffman (1964). Transport processes are driven by differences in electro-chemical gradient of the transported ions in the two sides

*Corresponding author. E-mail: m_monajjemi@cm.utexas.edu.



docosahexaenoic acid

Figure 1. The structure of docosahexaenoic acid (DHA).

of the membrane, cytoplasm and extra cellular matrix (Halperine et al., 1988; Abe, 2006).

Moreover, according to the most accepted membrane theory the main key of this regulation is based on the Na^+, K^+-ATPase pumps K^+ into and Na^+ out of the cell with hydrolyzing one ATP molecule to ADP (Bongeret al., 1998; Glynn, 1993).

For the first time, computer-based modeling of the conformation and packing properties of docosa hexaenoic acid was performed in 1986(Kenneth and Applegate, 1986; Evertset al., 2000; Teague et al., 2002).

The question how the movement of K^+ and Na^+ makes the structural changes of this phospholipid in membrane still remains open. Despite a large body of evidence relating activity of a given drug with its structure, there are no simple rules, which would allow drawing conclusions on biological activity of a compound on the basis of its chemical structural changes. Hence, we were focused on understanding of the nature of K^+ and Na^+ interactions during movement toward DHA-containing phospholipid through exploring structural changes of this biological system. Because our considered molecule is a novel molecule, so for the first time we have performed the computer-based modeling of this DHA-containing phospholipid and in this way, after obtaining the optimized specific dihedral (θ_4, α_5), the variations of optimized dihedral angles of 1-pentadecanoyl-2-docosahexaenoyl-sn–glycerol-3-phosphocholin which are under influence of Na^+ and K^+ cations have been evaluated. So, we have found out some useful facts regarding structural changes of DHA-containing phospholipid in neural cell membranes.

To accomplish our goal, we have modeled the DHA-containing phospholipid within the membrane against Na^+ and K^+ ions adjacent polar head of molecule individually at the level of RHF/3-21G theory and then calculated the Gibbs free energies of the considered molecule and analyzed the structural stability as well as the polarity of the phospholipid in different regions.

To know more about the temperature dependency of the structural stability of 1-pentadecanoyl-2-docosahexaenoyl-sn–glycerol-3-phosphocholin, frequency calculations have been carried out at 300 K (lab temperature), 310K (body temperature) and 313K (fever temperature) and the plotted graphs of energy values at all employed temperatures have been analyzed.

COMPUTATIONAL DETAILS

Computers have permitted the activation of many approaches in sciences that were dormant, or limited in their applications to the level of simple model, for the lack of appropriate computational tools (Tomasi et al., 2005). The geometry of 1-pentadecanoyl-2-docosahexaenoyl-sn–glycerol-3-phosphocholin has been fully optimized at the level of RHF/3-21G with G98 (Gaussian98) program (Frisch et al., 1998).

Secondly, we considered the two common ions around membrane, namely Na^+ and K^+ and set them individually in different regions close to polar head of phospholipid and explored the potential energy surface of each ions. Furthermore, frequency calculations have been performed to characterize the stationary points and evaluate the energy shifts at different temperatures. We have investigated the effect of temperature on the structural stability of 1-pentadecanoyl-2-docosahexaenoyl-sn–glycerol-3-phosphocholin at 300, 310, and 313K using UFF method (Sairam et al., 2005). Then two K^+ and Na^+ ions were located in specific distance from polar head of the conformer and optimized the 1-pentadecanoyl-2-docosahexaenoyl-sn–glycerol-3-phosphocholin close to these two ions were evaluated and observed as dihedral angles. These two dihedral angles are θ_4 angle (O_{32}, C_{26}, C_{31}, O_{30}) and α_5 angle (N_2, C_9, C_{11}, O_{17}) has been considered in the structure and at this distance the energy values of the phospholipid and dipole moments during the variation of mentioned dihedral angles have been analyzed.

RESULTS AND DISCUSSIONS

The energy values (kcal/mol) of optimized 1-pentadecanoyl-2-docosahexaenoyl-sn-glycerol-3-Phosphocholin molecules in different water boxes using UFF method at different temperatures are reported in Table 1. Also, the graph of energy values (kcal/mol) of 1 – pentadecanoyl – 2 – docosahexaenoyl – sn – glycerol – 3 – phosphocholin at different temperatures has been displayed in Figure 2.

According to the observed trend in Figure 2, the lowest energy value and the highest structural stability has been yielded at 310 K which is body temperature, however, supposing the highest temperature that is 313 K. The energy (kcal/mol) and dipole moment values (Debye) of optimized 1 – pentadecanoyl – 2 - docosahexaenoyl – Sn – glycerol – 3 - phosphocholin with different θ_4 and α_5 angles toward Na^+ ion have been listed in Tables 2 and 3, respectively. Within variation of torsion angles (θ_4 and α_5) of 1-pentadecanoyl-2-docosahexaenoyl-sn–glycerol-3-phosphocholin in the considered distance of Na^+ and K^+ from polar head of the phospholipid, for θ_4 angle the lowest energy value and consequently the most stable structural position has been observed at about -171.6 degree. Generally by changing the θ_4 angle increasing trend in structural energy values was obvious and consequently the structural stability decreased.

Table 1. The energy (kcal/mol) of optimized 1-pentadecanoyl-2-docosahexaenoyl-sn-glycerol-3-phosphocholin molecules in diffe-rent water boxes at different temperatures using UFF method.

Number of Water molecules	300 K	310 K	313 K
548 water	234.1378	229.1155	229.1397
561 water	235.1184	235.1232	235.1076
566 water	236.1091	236.13871	236.3579
578 water	116.0159	167.11903	215.3754
613 water	237.7326	219.2787	237.8413
629 water	239.1759	239.3568	239.4248
692 water	222.4502	239.8061	239.9235
707 water	241.0956	241.2791	241.0459
777 water	248.5212	250.2783	248.6568
884 water	254.6160	254.7821	254.9270

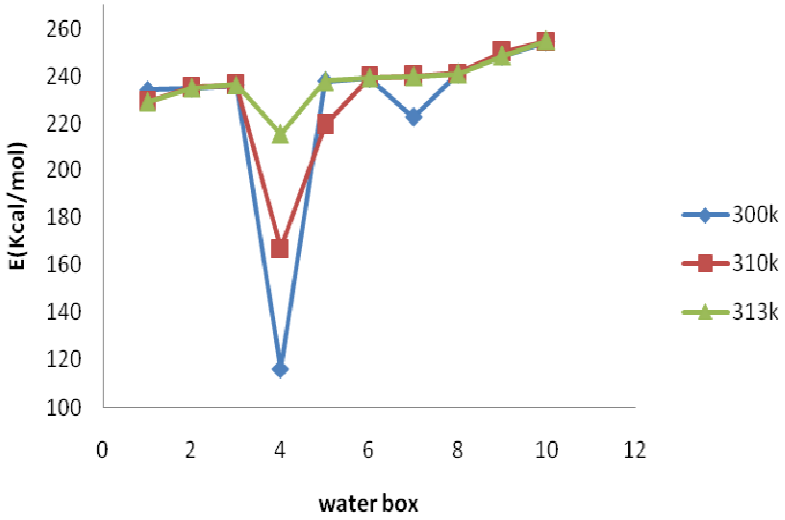


Figure 2. The graph of energy values (kcal/mol) of 1– pentadecanoyl–2–docosahexaenoyl– sn–glycerol–3–phosphocholin versus water box at different temperatures using UFF method.

The energy (kcal/mol) values of optimized 1 – pentadecanoyl – 2 - docosahexaenoyl – Sn – glycerol – 3 - Phosphocholin holding different θ_4 and α_5 angles toward Na^+ ion have been plotted in Figures 3 and 4. The energy (kcal/mol) and dipole moment values (Debye) of optimized 1 – pentadecanoyl – 2 - docosahexaenoyl – Sn – glycerol – 3 - phosphocholin with different θ_4 angles toward Na^+ ion have been reported in Table 2.

It is notable that the graph of structural polarity exhibited the similar pattern and during the increase in the θ_4 angle, the structural polarity also increases and the highest dipole moment can be seen when the θ_4 angle is about -178 degree. In the case of the second important torsion angle, that is, α_5 obtained considered in the graphs revealed that when α_5 angle increases from 110 degree to 135 degree, the energy values decreases and structural stability of the conformer increases. As a result the most positive stability has been yielded at 135 degree. In the next step, for K^+ movement toward phospholipid's polar head group which has been shown in Figures 5 and 6, meanwhile θ_4 angle reaches from -165 degree to -180 degree, the energy values have decreased and showed that when the angle changes from -165 degree to -170, the energy values have significant variations and at -180 degree, the energy value reaches the lowest value and after that it keep these energy values as well as the structural stability remain constant. The plotted graph of dipole moment has yielded

Table 2. The energy (kcal/mol) and dipole moment values (Debye) of optimized 1 – pentadecanoyl – 2 – docosahexaenoyl – sn – glycerol – 3 - phosphocholin with different θ_4 angles toward Na^+ ion.

$\theta_4$angle	E(H)	E(kcal/mol)	Dipole moment (Debye)
-180.01	-2699.4312406	-1693870.673	33.473947
-179.71	-2699.4285109	-1693865.029	33.473657
-179.51	-2699.4255234	-1693855.595	33.473456
-179.31	-2699.4215573	-1829999.035	33.473249
-179.11	-2699.4165815	-1829985.27	33.473037
-178.91	-2699.4105765	-1830006.051	33.472820
-178.71	-2699.4035401	-1829980.735	33.472598
-178.51	-2699.3954954	-1829991.703	33.472372
-178.31	-2699.3865001	-1704636.226	33.472143
-178.01	-2699.3714661	-1694316.587	33.471791
-177.77	-2699.358467	-1643847.4370	33.471505
-177.75	-2699.3573597	-1693846.7427	33.471481
-177.73	-2699.3562501	-1693846.0468	33.471457
-177.71	-2699.3551386	-1693845.3490	33.471433
-177.69	-2699.3540255	-1693844.6510	33.471409
-177.67	-2699.3529111	-1693843.9516	33.471385
-177.65	-2699.3517957	-1693843.2513	33.471361
-177.63	-2699.3506799	-1693842.5510	33.471336
-177.41	-2699.3384835	-1693834.8980	33.471068
-177.21	-2699.3278623	-1693828.2334	33.47822
-177.01	-2699.3182101	-1693822.1767	33.470574
-176.81	-2699.3101039	-1693817.0796	33.470325
-176.61	-2699.3041623	-1693813.3616	33.470074
-176.41	-2699.3010033	-1693811.3793	33.469821
-176.21	-2699.30118	-1693811.4904	33.469568
-176.01	-2699.3050776	-1693813.9361	33.469310
-175.81	-2699.3127271	-1693825.4628	33.469044
-175.61	-2699.3234468	-1693825.4623	33.468761
-175.41	-2699.3353526	-1693832.9333	33.468456
-175.01	-2699.350742	-1693842.5906	33.467723
-174.61	-2699.3517586	-1693843.2281	33.466120
-174.01	-2699.4107398	-1693880.2392	33.458422
-173.41	-2700.1061152	-1694316.5871	33.425434
-171.61	-2716.5517547	-1704636.2231	32.897639
-170.51	-2916.3214388	-1693825.463	11.8347
-170.01	-2916.3039601	-1693832.934	13.3900
-169.01	-2916.3443051	-1693842.591	10.5117
-168.01	-2916.311187	-1693843.229	10.0744
-167.01	-2916.333124	-1693880.239	11.3208

Table 3. The energy (kcal/mol) and dipole moment values (Debye) of optimized 1 – pentadecanoyl – 2 – docosahexaenoyl – sn – glycerol – 3 - phosphocholin with different α_5 angles toward Na^+ ion.

α_5 angle	E(H)	E(kcal/mol)	Dipole moment (Debye)
113.0	-2916.2924100	-1829973.4872750	3.1510
115.0	-2916.3235442	-1829993.0239855	3.3679
116.0	-2916.3289689	-1829996.4279848	3.4331
116.5	-2916.2464591	-1829944.6530853	3.4253
117.0	-2916.331678	-1829998.1279450	3.3418
117.5	-2916.2632778	-1829955.2068195	3.8409
118.0	-2916.3323758	-1829998.5658145	3.0178
118.5	-2916.3309668	-1829997.6816670	2.8383
119.0	-2916.3303808	-1829997.3139520	3.6501
119.5	-2916.3431959	-1830005.3554273	3.1116
120.0	-2916.3159320	-1829988.2473300	9.6554
120.5	-2916.3398172	-1830003.2352930	2.8850
121.0	-2916.3375635	-1830001.8210963	2.7926
121.5	-2916.3467451	-1830007.5825503	3.7034
122.0	-2916.3502604	-1830009.7884010	3.7172
122.5	-2916.3521619	-1830010.9815923	3.3753
122.9	-2916.3521985	-1830011.0045588	3.5135
123.0	-2916.3177261	-1829989.3731278	3.4573
123.4	-2916.3488051	-1830008.8752003	4.0242
123.7	-2916.3482986	-1830008.5573715	4.2275
124.0	-2916.3111791	-1829985.2648853	6.5731
124.6	-2916.3359069	-1830000.7815798	4.8370
124.9	-2916.3554064	-1830013.0175160	4.1040
125.0	-2916.3532089	-1830011.6385848	3.6203
125.2	-2916.3540138	-1830012.1436595	4.1641
125.5	-2916.3490442	-1830009.0252355	4.0911
126.1	-2916.3413200	-1830004.1783000	5.6937
126.5	-2916.3139750	-1829987.0193125	5.9885
126.8	-2916.3577159	-1830014.4667273	2.9253
127.1	-2916.3414408	-1830004.2541020	2.8133
127.4	-2916.3530014	-1830011.5083785	3.1197
127.8	-2916.3584572	-1830014.9318930	3.0825
128.1	-2916.3558325	-1830013.2848938	3.2830
128.5	-2916.3549054	-1830012.7031385	3.6668
129.0	-2916.3574018	-1830014.2696295	4.0443
130.0	-2916.3491121	-1830009.0678428	4.8674
131.0	-2916.3572837	-1830014.1955218	3.4321
132.0	-2916.3561455	-1830013.4813013	3.8836

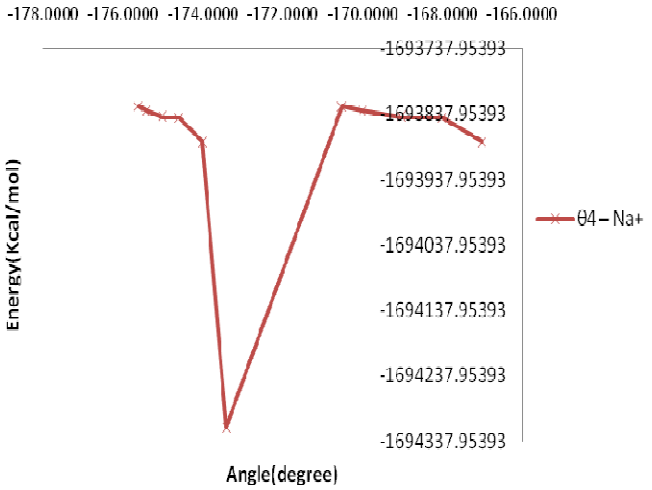


Figure 3. The graphs of energy values (kcal/mol) of 1-pentadecanoyl-2-docosahexaenoyl-sn- Glycerol - 3 - phosphocholin close to Na^+ versus θ_4 angles at HF/3-21G level.

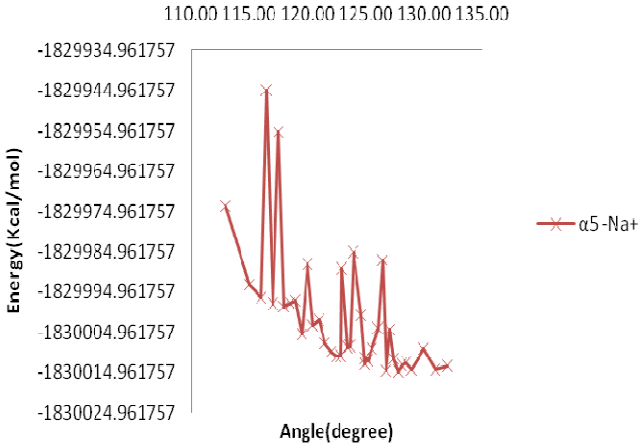


Figure 4. The graph of energy values (kcal/mol) of 1-pentadecanoyl-2-docosahexaenoyl-sn- glycerol-3-phosphocholin close to Na^+ versus α_5 angles at HF/3-21G level.

the similar trend as the graph of energy values.

Through the variation of α_5 angle, the obtained graph displayed that during the increase in α_5 angle, the increasing trend in energy values have been observed and then the structural stability reached to the lowest point. However, there were not any significant changes in dipole moment values.

CONCLUSION

Computer technology has an important role in the conformational energetic of the DHA chain in biological membranes especially in nerve cell's membrane and should be considered during understanding the unique properties of this fatty acid. This novel DHA - containing phosphocholin molecule has been chosen for investigation of structural and temperature changes against K^+ and Na^+ cations in nerve cell membranes.

Due to some conditions, changes may occur in cell membrane as well as cell integrity. So, understanding the different cation's movement effect on the unsaturated chains in all membranes will be fruitful to identify membranes behaviors in different conditions. In this research,

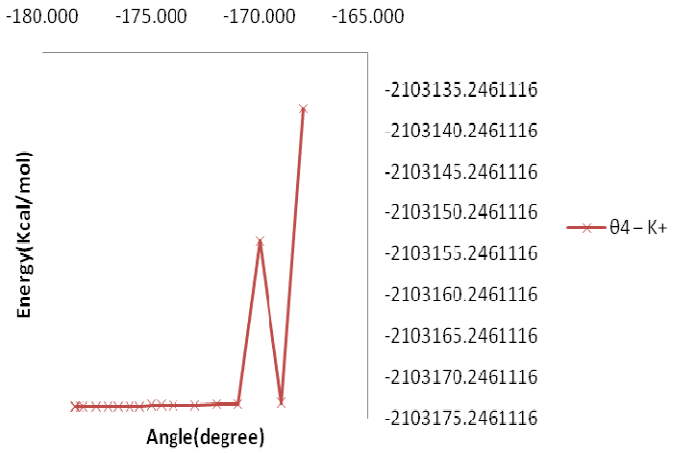


Figure 5. The graph of energy values (kcal/mol) of 1-pentadecanoyl-2-docosahexaenoyl-sn-glycerol-3-phosphocholin toward K^+ versus θ_4 angles at HF/3-21G level.

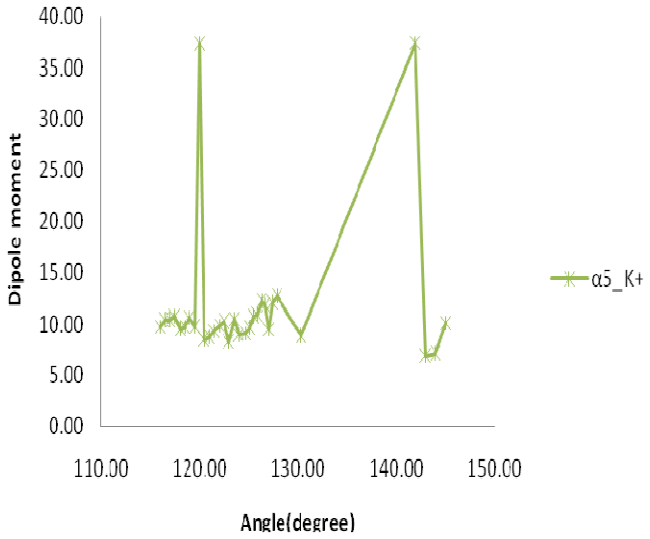


Figure 6. The graph of energy values (kcal/mol) of 1-pentadecanoyl-2-docosahexaenoyl-sn-glycerol-3-phosphocholin close to K^+ versus α_5 angles at HF/3-21G level.

Table 4. The energy (kcal/mol) and dipole moment values (Debye) of optimized 1 – pentadecanoyl- 2 – docosahexaenoyl – sn – glycerol – 3 - phosphocholin with different θ_4 angles toward K^+ ion.

$\theta_4$angle	E(H)	E(kcal/mol)	Dipole moment (Debye)
-183.11	-3351.6712211	-2103173.6912402	9.1060
-182.81	-3351.6712586	-2103173.7147715	9.1035
-182.51	-3351.6712938	-2103173.7368595	9.1015
-182.11	-3351.6713373	-2103173.7641557	9.0995
-181.81	-3351.6713672	-2103173.7829180	9.0983
-181.41	-3351.6714035	-2103173.8056962	9.0970
-181.01	-3351.6714358	-2103173.8259645	9.0960
-180.71	-3351.6714574	-2103173.8395185	9.0954
-180.41	-3351.6714768	-2103173.8516920	9.0948
-180.11	-3351.6714939	-2103173.8624222	9.0944
-179.81	-3351.6715088	-2103173.8717720	9.0939
-179.41	-3351.6715252	-2103173.8820630	9.0934
-179.01	-3351.6715376	-2103173.8898440	9.0929
-178.71	-3351.6715443	-2103173.8940482	9.0925
-178.53	-3351.6715473	-2103173.895930	9.0923
-178.51	-3351.6715476	-2103173.896119	9.0923
-178.31	-3351.6715498	-2103173.897499	9.0920
-178.11	-3351.6715511	-2103173.898315	9.0917
-177.51	-3351.6715488	-2103173.896872	9.0908
-177.01	-3351.6715401	-2103173.891412	9.0900
-176.51	-3351.6715251	-2103173.882000	9.0891
-176.01	-3351.6715037	-2103173.868571	9.0880
-175.51	-3351.6714759	-2103173.851127	9.0869
-175.01	-3351.6714418	-2103173.829729	9.0855
-174.51	-3351.6714013	-2103173.804315	9.0839
-174.01	-3351.6713544	-2103173.774876	9.0819
-173.01	-3351.6712411	-2103173.703790	9.0767
-172.01	-3351.671102	-2103173.616505	9.0723
-171.01	-3351.6710939	-2103173.611422	9.0839
-170.01	-3351.6393139	-2103153.669535	11.5742
-169.01	-3351.671000	-2103173.552500	9.3545
-168.01	-3351.6135437	-2103137.498232	13.5955

the influence of employing two important Na^+ and K^+ on the structural stability has been investigated with Ab initio chemical calculations.

The Na^+ and K^+ cations influenced the conformational energies and structural stabilities of phospholipid's torsion angles as a critically important feature that should be seriously identified in order to find out the unique physico - chemical properties of this phospholipid.

Moreover, structural investigations of 1 - pentadecanoyl - 2 - docosahexaenoic - Sn - glycerol - 3 - phosphocholin in general showed a relationship between the temperature and the structural stability of similar biological compounds. These results were well in agreement with the common chemical concepts. It has been found out that through increasing the temperature, the energy values increased. More interestingly, the most stable conformer has been obtained at 310 k which is corresponded to body temperature. The investigation of the conformer's θ_4 angle, showed that the lowest energy value and consequently the most stability observed for θ_4 angle about -171.6 degree. But, during changing the θ_4 angle increasing trend in structural energy values when Na^+ moved to the phospholipid. For the other torsion angle, α_5, the obtained graphs displayed that, when α_5 angle increased from 110 degree to 135 degree, the energy values decreased and structural stability of the conformer increased and the most positive stability was at 135 degree. When K^+ moved toward 1 - pentadecanoyl 2 –

Table 5. The energy (kcal/mol) and dipole moment values (Debye) of optimized 1 – pentadecanoyl – 2 – docosahexaenoyl – sn – glycerol – 3 - phosphocholin with different α_5 angles toward K^+ ion.

α_5Angle	Energy(H)	Energy(kcal/mol)	Dipole moment (Debye)
116.0	-3351.6237405	-2103143.897164	10.3272
116.5	-3351.6192771	-2103141.096380	10.3206
117.0	-3351.6330240	-2103149.722560	10.7397
117.5	-3351.6391997	-2103153.597812	9.4270
118.0	-3351.6165865	-2103139.408029	9.7535
118.5	-3351.6199856	-2103141.540964	10.6737
119.0	-3351.6477672	-2103158.973918	9.6761
119.5	-3351.5755513	-2103113.658441	37.2676
120.0	-3351.6518667	-2103161.546354	8.4444
120.5	-3351.5664880	-2103107.971220	8.6863
121.0	-3351.5749858	-2103113.303590	9.3849
121.5	-3351.6406095	-2103154.482461	9.8498
122.0	-3351.5839667	-2103118.939104	10.2169
122.5	-3351.6565992	-2103164.515998	8.1822
123.0	-3351.6547282	-2103163.341946	10.4958
123.5	-3351.6698335	-2103172.820521	9.0176
124.0	-3351.6446119	-2103156.993967	12.6736
124.77	-3351.6718716	-2103174.0994290	9.1530
125.07	-3351.6695349	-2103172.6331498	9.5843
125.47	-3351.6591486	-2103166.1157465	10.7397
125.87	-3351.6572522	-2103164.9257555	10.8475
126.27	-3351.656375	-2103164.3753125	12.3213
126.67	-3351.6593384	-2103166.2348460	11.7092
127.07	-3351.6745544	-2103175.7828860	9.4768
127.47	-3351.6570174	-2103164.7784185	11.9714
127.87	-3351.6530293	-2103162.2758858	12.6024
128.27	-3186.5454565	-1999557.2739538	38.201071
128.67	-3173.5862558	-1991425.3755145	39.726073
129.07	-3188.4939422	-2000779.9487305	38.797948
129.47	-3189.360303	-2001323.5901325	38.714596
129.87	-3199.2948712	-2007557.5316780	37.318115
130.27	-3351.6737666	-2103175.2885415	8.8317
130.97	-3249.1828366	-2038862.2299665	28.031514
140.97	-3351.5676009	-2103108.6695648	37.4373
141.97	-3351.6211461	-2103142.269178	6.7826
142.97	-3351.6445685	-2103156.966734	7.0359
143.97	-3351.6388515	-2103153.379316	10.1365
144.97	-3351.6546461	-2103163.290428	9.7868

docosahexaenoic - Sn - glycerol - 3 – phosphocholin, when θ_4 angle reached from -165 degree to -180 degree, the energy values have been decreased and showed that when the θ_4 angle changes from -165 degree to -170, the energy values had significant variations and at -180 degree, the energy value reached to the lowest value. During increasing the α_5 angle the increasing trend in energy values observed and then the structural stability declined to the lowest point. No significant change in dipole moment values has been observed.

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