Structural analysis of phosphatidyl choline lipids and glycerol precursors

Annick Goursot, Tzonka Mineva, Sailaja Krishnamurty, and Dennis R. Salahub

Abstract: The structures and stabilities of the glycerol (G) and glycerol 3-phosphate (G3P) isomers have been calculated in the gas phase, using an ab initio density functional theory (DFT) method. The different conformational structures are shown to be at the origin of the various phospholipid conformers, except, obviously, for the alkyl chain torsions. The G3P conformations have been examined taking into account the experimental structures of the complexation sites in the glycerol kinase (GK) and glycerol 3-phosphate acyl transferase (G3PAT) enzymes, which correspond to the first and second steps of the “de novo” phospholipid biogenesis, respectively. The conformational analysis of the glycerophosphate skeleton is shown to determine most of the structural characteristics of the phosphatidyl choline lipids, which differ by the length of their diacyl chains, i.e., dilauroyl (DL), dimyristoyl (DM), and dipalmitoyl (DP) phosphatidylcholines (PC). Higher energy conformers with kinks in the acyl chains have been found, in preparation for molecular dynamics studies of the chain melting phase transformation.

Key words: glycerol, glycerol 3-phosphate, phosphatidylcholines, DLPC, DMPC, DPPC, conformational analysis, density functional theory, DFT-D.

Résumé : Les structures et stabilités relatives du glycérol (G) et du glycérol 3-phosphate (G3P) ont été calculées en phase gaseuse avec une méthode ab initio, basée sur la théorie de la fonctionnelle de la densité (TFD). A l’exception des formes gauches des chaînes alkyles, les différentes conformations de ces molécules sont effectivement à l’origine des conformères possibles des phospholipides. Les conformations de G3P ont été analysées en considérant les structures expérimentales des sites de complexation des enzymes glycérol kinase (GK) et glycérol 3-phosphate acyl transférase (G3PAT) qui correspondent, respectivement, aux deux premières étapes de la biosynthèse « de novo » des phospholipides. L’analyse conformationnelle du squelette glycérophosphate montre qu’il détermine la plupart des caractéristiques structurales des lipides phosphatidylcholines qui diffèrent par la longueur de leurs chaînes alkyles, c.-à-d. dilauroyl (DL), dimyristoyl (DM) et dipalmitoyl (DP) phosphatidylcholines (PC). Des conformères d’énergie plus élevée, présentant des formes gauches dans les chaînes alkyles, ont été étudiés en relation avec les simulations par dynamique moléculaire des transformations structurales des chaînes, au cours de la transition principale de phase.

Mots-clés : glycérol, glycérol 3-phosphate, phosphatidylcholine, DLPC, DMPC, DPPC, analyse conformationnelle, théorie de la fonctionnelle de la densité, TFD-D.

Introduction

Phospholipids and proteins are the main components of biological membranes, separating the cell and its various constituents from their environment. Cell membranes also have different functional roles, including protein synthesis, ion pumps and channels, receptor molecules, energy production and storage, and so forth. This versatility is due to the large range of phospholipid and protein structures, which can be involved in the membrane bilayers. The necessary fluid plasticity of these bilayers is obtained by the regulation of the lipid composition in the membrane. This regulation is accomplished by the “de novo” synthesis of the lipids in the various compartments of the cells of all living organisms.1

The synthesis protocol, in particular for the glycerophospholipids studied in this work, is a long and complex pathway, which starts with the enzymatic phosphorylation of the glycerol molecule and proceeds by three further successive enzymatic reactions.2,3 The phospholipid molecule is thus built step by step through different enzyme-catalyzed reactions. The location in the enzymes of the different substrate-binding sites and their selectivity have not been identified unambiguously.4–8 The structures of the phospholipid molecules synthesized and transferred to the membranes have thus not been determined, and there is no information concerning the existence of possible different conformers.

The presence of such conformers within phospholipid bilayers in their liquid-crystalline state has, however, been
suggested from NMR experiments, that have also provided some structural information on the overall structure of the lipids.\textsuperscript{9,10} X-ray diffraction data demonstrate the possible presence of two structurally different molecules in the solid-crystalline state of a few phospholipids.\textsuperscript{11,12} In a previous theoretical work on the dimyristoyl phosphatidylcholine (DMPC) molecule, we have shown that several conformational structures can exist (minima on the potential-energy surface), a number of them having comparable energies.\textsuperscript{13} The dynamics of the individual DMPC has been studied for a series of temperatures, and the nature of lipid melting has been elucidated.\textsuperscript{14} The existence in the membranes of different lipid conformers, even iso-energetic ones, depends, of course, on the barriers for their in situ interconversion. One may also infer that the synthesis pathway itself selects the lipid conformations within the specific enzymatic catalytic sites at one or at several steps of the synthesis.

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### Computational methods

#### Models

The carbon numbering (C1, C2, and C3), illustrated in Figs. 1 and 2, refers to the standard biochemical nomenclature defined for the glycerol molecule: if the hydroxyl group on C2 is oriented to the left, C1 is the carbon below and C3 the carbon above. When the hydroxyl on C3 is phosphorylated, the glycerol 3-phosphate molecule formed is chiral. Its in vivo synthesis produces, following the stereospecific numbering (sn) system, the sn-glycerol 3-phosphate. The diacyl phosphatidylicoline lipids have been generally characterized as a head group or a chain that is connected through one CH\textsubscript{2} group (C3 carbon) to two glycerolipid β and γ chains, as shown in Fig. 1b. The nomenclature defining the characteristic lipid torsion angles is illustrated in Fig. 1.

In addition, for a better understanding of the torsion angles, we have chosen to partition the molecule into four building blocks, labelled as head (H), neck (N), body (B), and tails. The head is built from the N(CH\textsubscript{3})\textsubscript{3}–CH\textsubscript{2}–CH\textsubscript{2}–PO\textsubscript{4} atoms and is described by the α\textsubscript{1} to α\textsubscript{6} torsion angles. The neck includes the glycerol C3–C2–C1 fragment, characterized by the q\textsubscript{1} and q\textsubscript{2} angles, and defines the orientation of the head with respect to the carbonyl groups and the tails. The body is formed by the next two O–CO–CH\textsubscript{2}–CH\textsubscript{2}...
Fig. 2. The glycerol conformers with the standard nomenclature: C2, secondary carbon; C3, carbon where phosphorylation will occur.

(a) OH
      (b) OH
      (c) OH
      (d) OH
      (e) OH
      (f) OH

Methods

The calculations were performed in the framework of density functional theory (DFT), using a linear combination of Gaussian orbitals, as implemented in the deMon2k program. All calculations were performed using the revised PBE exchange functional (revPBE) and the LYP correlation functional, augmented by a damped empirical correlation for dispersion-like interactions, referred to as DFT-D. This DFT-D approach is necessary to account for the stabilizing interaction between the alkyl chains.

DFT-optimized double-zeta plus valence polarization (DZVP) basis sets were employed for all atoms, associated with automatically generated functions up to 1 = 2 for fitting the density. The exchange-correlation potential was numerically integrated on an adaptive grid. The grid accuracy was set to 10^-5 in all calculations. The Coulomb energy was calculated by the variational fitting procedure proposed by Dunlap, Connolly, and Sabin. A quasi-Newton method in internal redundant coordinates with analytical energy gradients was used for the structure optimization. The convergence was based on the Cartesian gradient and displacement vectors with a threshold of 10^-4 and 10^-3 au, respectively.

Results and discussion

Conformational analysis of the glycerol and glycerol 3-phosphate molecules

The in vivo phosphatidyl choline lipid synthesis involves first the phosphorylation of glycerol in the GK enzyme, at the expense of ATP (adenosine triphosphate). The product formed is exclusively the G3P molecule (phosphate group at C3), which is further esterified at the free primary alcohol with one fatty acid molecule by an acyl transferase enzyme using an acyl carrier protein (ACP) or an acyl coenzyme A (CoA) as substrate. A second esterification at the secondary carbon leads further to a phosphatidate or phosphohydric acid including two fatty acid chains. The phosphatidate phosphatase enzyme, which regulates the glycerolipid synthesis, catalyzes its hydrolysis into diacylglycerol (or diglyceride). The reaction of this molecule with the cytidine diphosphate (CDP)-choline (via a transferase enzyme) leads finally to a phosphatidyl choline lipid.

The G3P molecule provides, in some sense, the precursor of the neck–body skeleton (Fig. 1) that is common to all glycerophospholipids. The catalytic reaction forming G3P occurs at a site of the GK enzyme, which forms a complex with Mg-ATP and the G molecule. Structural information on this site has been provided by several X-ray studies and molecular dynamics simulations.

Chemically, the G molecule is achiral, since the two –CH2OH groups are equivalent. The total number of combinations of the three OH relative positions reduces to six, taking into account mirror-image structures. Figure 2 illustrates these isomers.

The GK active site for glycerolphosphorylation is a deep cleft where ATP and glycerol are stabilized. The X-ray structures of GK show that the glycerol molecule forms hydrogen bonds with several residues. Therefore, it is reasonable to assume that, during the glycerophosphate synthesis, external hydrogen bonds rather than internal ones are favoured. The calculated relative stabilities of the G isomers without internal hydrogen bonds are displayed in Table 1, along with the dipole-moment values and characteristic torsion angles, as defined in Fig. 1. These torsion angles are also characteristic of the final phospholipid, once the phosphocholine head and acyl chains have been bound. It is interesting to note that three glycerol structures are competitive at the lowest energy, i.e., the a, b, and f isomers (Fig. 2), which correspond very clearly to the largest dipole moments. The calculated \( \Delta E \) values are only indicative of the possible conformers in the GK channel, since they do not take into account the interaction of glycerol with the surrounding residues. It is interesting to note that two types of “necks” (180/60 and 60/–60) and “bodies” (180/–60 and –60/60) are represented among the a, b, and f isomers.

The crystallization of GK leads to tetrameric structures, which are inactive forms of the enzyme. Among the mono-
mers, a “closed” and an “open” form were distinguished.27 The glycerol conduction to the GK enzyme-binding site could be facilitated by its hydrogen bonding with the surrounding GK residues more than with water molecules, due to the deepness of the GK cleft that argues for poor accessibility to the solvent.27 The processing of glycerol from the cleft opening to the catalytic site could be helped by fluctuations of its large dipole moment interacting with the electric field along the cleft. MD simulations have shown that the protein attracts a substrate with a strong dipole moment, requiring its change of orientation at some positions in the cleft.28 Binding the glycerol at the catalytic site is performed through tight hydrogen bonds to the closest residues (Asp245, Arg83, and Tyr135). All of these features would be in favour of promoting the a, b, and f isomers in the GK site.

X-ray structures of GK (pdb access 1glf26 and 1glj27) also contain glycerol molecules. The structures of the glycerol molecule inside the tetramers are different in the “closed” and the “open” forms, with neck and body torsion angles very comparable to the conformer a for pdb.1glf (“closed” GK structure) and to a deformed f conformer (torsions of about 100°–120° instead of 60°–70°) for pdb.1glj (“open” GK structure).

The phosphorylation of one –CH2OH group of glycerol leads to a chiral C2 carbon in the sn-glycerol-3-phosphate. Starting from each of the six glycerol isomers allows one to generate the possible glycerol phosphate isomers. There are, in fact, nine topologically different structures, due to the lowering of the molecular symmetry. The presence of the phosphate group generates also additional rotational isomers, taking into account the rotation of the –PO3H2 group around the C3–O bond. Variations of the C2–C3–O–P torsion angle, α1, when sterically possible, leads to more rotational isomers. It must be noted that most of these rotations generate a steric strain due to the P=O or P–OH groups being confined too close to the atoms of the free primary CH2OH group. In the same spirit as for the glycerol molecule, intramolecular hydrogen bonds have been avoided. After geometry optimization, 12 isomers were obtained with relative total energies within a range of 0 to about 4.0 kcal/mol. The five most stable structures (between 0 and 1.5 kcal/mol) are reported in Table 2. They are labelled by priming the letter of the original glycerol conformers. The isomers a’ and f’ are the counterparts of the a and f glycerol isomers mentioned above. They could thus both exist as products of the GK phosphorylation. These two isomers have different θ1/θ2 and θ3/θ4 values. It is thus not clear why the other isomers of equivalent energies, differing by either 01/02 or 03/04, could be much less stabilized through their interaction with the GK residues. It seems possible that the glycerol 3-phosphate, already before binding the acyl chains and the phosphate group generates also additional rotational isomers, lowering of the molecular symmetry. The presence of the phosphate, already before binding the acyl chains and the glycero-3-phosphate most stable isomers. The primed labels correspond to the non-primed labels used for glycerol (Fig. 1).

Table 2. Relative energies and characteristic torsion angles of the glycerol-3-phosphate most stable isomers. The primed labels correspond to the non-primed labels used for glycerol (Fig. 1).

<table>
<thead>
<tr>
<th>Isomers</th>
<th>ΔE (kcal/mol)</th>
<th>θ1/θ2</th>
<th>θ3/θ4</th>
<th>α1</th>
</tr>
</thead>
<tbody>
<tr>
<td>a’</td>
<td>0.7</td>
<td>180/60</td>
<td>180/–60</td>
<td>180</td>
</tr>
<tr>
<td>b’</td>
<td>0.8</td>
<td>70/–60</td>
<td>180/–60</td>
<td>180</td>
</tr>
<tr>
<td>c’1</td>
<td>0.8</td>
<td>60/185</td>
<td>70/–60</td>
<td>90</td>
</tr>
<tr>
<td>c’2</td>
<td>0.8</td>
<td>50/180</td>
<td>–70/180</td>
<td>70</td>
</tr>
<tr>
<td>f’</td>
<td>0.0</td>
<td>60/–70</td>
<td>–70/60</td>
<td>–100</td>
</tr>
</tbody>
</table>

Fig. 3. Damped empirical dispersion energies for the DLPC (triangles), DMPC (circles), and DPPC (squares) ground-state isomers. The isomers are ordered from left to the right as follows: H1N1BA1, H1N3BA1, H2N3BA1, H1N1BA2, H1N2BA2, H2N2BA2, and H2N2BB1. The filled symbols are for T1 isomers and the open symbols are for T2 isomers.

Structural analysis of the DLPC, DMPC, and DPPC molecules

Ground-state conformers with all trans chains

As in the case of the DMPC molecule, the DFT-D energy optimization for the DLPC and DPPC isomers led to 14 conformers in the range between 0 and 2 kcal/mol. The 14 lowest isenergetic conformers are subsequently grouped into two sets of structures, differing by the mutual orientations of the carbon skeletons of the β and γ alkyl chains: in the first group of seven lowest energy structures, these two carbon skeletons are in two parallel planes (T1), and in the second half of the minimum-energy conformers, the two carbon skeletons are in two perpendicular planes (T2) (Fig. 1c). For a given T1 or T2 orientation of the hydrocarbon chains, the ground-state conformers arise from the following combinations between two heads (H1, H2), three necks (N1, N2, and N3) and three bodies (B1, B2, and B3): H1N1BA1, H1N3BA1, H2N3BA1, H1N1BA2, H1N2BA2, H2N2BA2, and H1N1BB1.

These conformational structures are described in detail for the DMPC molecules in ref. 13. Their averaged α, β, and γ
angles and their mutual combinations leading to those ground-state isomers are not affected by the chain length, e.g., the same arrangement of $a$, $b$, and $g$ chains is obtained for the DLPC, DMPC, and DPPC molecules. As a consequence, the characteristic geometries of the head, body, and neck conformations display very similar structural parameters. The displacement of the polar head with respect to the $b$ or $g$ alkyl chains in the various isomers is characterized by the distances of the closest C=O oxygen to the choline N atom ($N/C_1/C_1/C_1C=O$) and to the non-ester phosphate O atom ($P=O/C_1/C_1/C_1O=C$). These distances do not vary with the chain length.

The 14 isomers have the same relative energy stability for the DLPC, DMPC, and DPPC molecules. The computed damped empirical dispersion energies, $E_{\text{disp}}$, plotted in Fig. 3, indicates an increase of approximately 3.1 kcal/mol per CH$_2$ unit for the lipids with 12, 14, and 16 carbons in the alkyl chains in their T1 and T2 arrangements. This value is somewhat smaller than the $E_{\text{disp}}$ increase of 3.8 kcal/mol per CH$_2$ in the case of $n$-alkane dimers (from butane to docadecane) in their most stable arrangement.$^{19}$ The averaged DFT-D empirical dispersion in the T1 isomers is higher than the average value for the T2 isomers. This difference increases slightly with the chain length, e.g., $E_{\text{disp}}$ of T1 isomers is higher by 3.8, 4.0, and 5.2 kcal/mol for the DLPC, DMPC, and DPPC molecules, respectively. The $E_{\text{disp}}$ difference for both tail arrangements correlates with the difference between the $b$ and $g$ hydrocarbon chain separation in T1 and T2. The relative dispersion energy in the case of isomers with parallel tails (T1) follows a very similar trend for the three lipid molecules as seen from Fig. 3. This regular behaviour is not so well-respected for the T2 isomers for a particular diacyl PC lipid. It indicates, thus, some influence of the chain length when T2 chains are coupled with a specific head and body conformation. However, this “discrepancy” is less than 3%–4% of the dispersion energy values.

### Higher energy structures with gauche conformers in the alkyl chains

Gauche chain conformers are predominantly formed in phospholipid aggregates in their liquid phase. The relative energies of the possible gauche conformers with one kink per alkyl chain, optimized at $T = 0$ K, with respect to the all trans structures are presented in Table 3 for the DLPC, DMPC, and DPPC H1N1B$_{A2}$T2 isomers. For comparison, relative energies between gauche and trans isomers of tetradecane are reported in the same table. The torsions in Table 3 follow the nomenclature indicated in Fig. 1 for the $b$ and $g$ chains. In contrast to tetradecane, the gauche conformers in DLPC, DMPC, and DPPC are not degenerate with, however, insignificant relative energy variations for three of the four possible gauche conformers in the DLPC molecule. Interestingly, comparable stability is obtained for the structures with a kink at the free end of the C12, C14, and C16 chains. The DPPC gauche conformers follow the behaviour of DMPC: the least stable structures are those with kinks in the middle of the hydrocarbon chains (at $\beta_n$, $\gamma_n = 8, 10, 12$ for DPPC and $\beta_n$, $\gamma_n = 8, 10$ for DMPC); the most stable conformation is the one with a torsion of 300° at $\beta_n$, $\gamma_n = 6$. The latter is obtained also for the DLPC molecules.

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**Table 3.** Relative energies in kcal/mol with respect to all-trans conformers of the DPPC, DMPC, and DLPC gauche isomers (H1N1B$_{A2}$T2) at various positions of the chain.

<table>
<thead>
<tr>
<th>Kinks position $n$</th>
<th>DPPC (16C)</th>
<th>DMPC (14C)</th>
<th>DLPC (12C)</th>
<th>Tetradecane C$<em>{14}$H$</em>{30}$</th>
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<tr>
<td>$n = 16$</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>60</td>
<td>0.72</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>300</td>
<td>0.80</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Average</td>
<td>0.76</td>
<td>—</td>
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<td>$n = 14$</td>
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<td></td>
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<tr>
<td>60</td>
<td>0.85</td>
<td>0.75</td>
<td>—</td>
<td>0.65</td>
</tr>
<tr>
<td>300</td>
<td>1.10</td>
<td>0.66</td>
<td>—</td>
<td></td>
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<tr>
<td>Average</td>
<td>0.98</td>
<td>0.70</td>
<td>—</td>
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<tr>
<td>$n = 12$</td>
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<tr>
<td>60</td>
<td>1.09</td>
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<td>0.88</td>
<td>0.46</td>
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<tr>
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<td>$n = 10$</td>
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<td>1.11</td>
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<tr>
<td>300</td>
<td>0.24</td>
<td>0.20</td>
<td>0.30</td>
<td></td>
</tr>
<tr>
<td>Average</td>
<td>0.63</td>
<td>0.53</td>
<td>0.51</td>
<td></td>
</tr>
</tbody>
</table>

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Comparison of the G3P and phospholipid conformers

The precursor G3P values of $\theta_1/\theta_2$ and $\theta_3/\theta_4$, characterizing the “neck” and “body”, respectively, correspond to those found for the complete phospholipid structures. Indeed, if one considers all the isomers of Table 2, the three phospholipid necks are found with the combinations 180/60 (N1), 60/–60 (N2), and 60/180 (N3). Since G3P has no acyl chains, only three types of body exist: two of them correspond to those found for the phospholipids: $B_A$ and $B_B$, with the $\theta_3/\theta_4$ values of 180/60 and 60/–60, respectively. The value of $–70/180$, ($\epsilon_5^2$ in Table 2), related to two opposite OH groups at the C1 and C2 carbons, i.e., acyl chains in opposite directions, would not lead to the formation of phospholipid bilayers. Actually, this configuration (opposite acyl chain will), would not lead to the formation of phospholipid bilayers. Actually, this configuration (opposite acyl)

energies along the alkyl chains.

ent thermodynamical behaviour at the melting transition

of the phosphatidyl choline lipids, which differ by the length of their diacyl chains, i.e., DLPC, DMPC, and DPPC.

Higher energy conformers with kinks in the acyl chains have been found, in preparation for molecular dynamics studies of the chain melting phase transformation, which will be published elsewhere. The comparison of their relative energies with respect to the acyl chain length shows that DLPC, the shortest lipid to form bilayers, may have a different thermodynamical behaviour at the melting transition from the other two lipids, displaying more similar gauche energies along the alkyl chains.

Conclusion

The different conformational structures of the glycerol (G) and glycerol 3-phosphate (G3P) molecules have been shown to be at the origin of the various phospholipid conformers, except, obviously, for the alkyl chain torsions. Conformations lacking internal hydrogen bonds are imposed by the enzymes involved in the synthesis, and these persist through the various subsequent steps of the synthesis, adding the tails and the head. The conformational analysis of the glycerophosphate skeleton determines most of the structural characteristics of the phosphatidyl choline lipids, which differ by the length of their diacyl chains, i.e., DLPC, DMPC, and DPPC.

References

(2) Kennedy, E. J. Biol. Chem. 1953, 201, 399.

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