Vitamin E promotes the inverse hexagonal phase via a novel mechanism: implications for antioxidant role

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Abstract

Vitamin E (α-tocopherol) and a range of other biological compounds have long been known to promote the H_{II} (inverted hexagonal) phase in lipids. Now, it has been well established that purely hydrophobic lipids such as dodecane promote the H_{II} phase by relieving *extensive* packing stress. They do so by residing deep within the hydrocarbon core. However, we argue from X-ray diffraction data obtained with 1-palmitoyl-2-oleoylphosphatidylcholine (POPE) and 1,2-dioleoylphosphatidylcholine (DOPE) that α-tocopherol promotes the H_{II} phase by a different mechanism. The OH group on the chromanol moiety of α-tocopherol anchors it near the aqueous interface. This restriction combined with the relatively short length of α-tocopherol (compared to DOPE and POPE), means that α-tocopherol promotes the H_{II} phase by relieving *compressive* packing stress. This observation offers new insight into the nature of packing stress and lipid biophysics. With the deeper understanding of packing stress offered by our results, we also explore the role molecular structure plays in the primary function of vitamin E, which is to prevent the oxidation of polyunsaturated membrane lipids.

Introduction

The H_{II} or inverted hexagonal phase (See Fig. 1) in lipids has long been appreciated as a window offering insight into the both the biophysical properties of lipids and their interactions with proteins and other biomolecules.[1] The degree to which lipids curl, or their spontaneous curvature,[2] is revealed in the H_{II} phase and has been shown to exert a powerful effect on the conductance of the ion channel alamethicin.[3] Lung surfactant protein promotes curvature in the H_{II} phase and this is thought to be connected to its essential role for proper pulmonary function.[4] It is known that the wasp venom mastoparan promotes the H_{II} phase and that, interestingly, inhibitors of the venom do the reverse.[5] These are just a few examples of a whole host of membrane disruptive compounds, including anti-microbial peptides, that actively promote or inhibit the H_{II} phase.[6,7]

α-Tocopherol is the form of vitamin E retained by the human body. It is a lipid soluble antioxidant that is an essential micronutrient.[8] Symptoms of deficiency include nerve and muscle damage.[9,10] The primary role of α-tocopherol is to protect polyunsaturated phospholipids from oxidation in membranes,[11] although modulation of membrane architecture is another mode of action that has recently been examined.[12] Its molecular structure consists of a chromanol group with a hydroxyl group on the benzene ring at one end and a phytanyl chain attached at the other end (See Fig. 2). In phospholipid bilayers, the hydroxyl group usually sits near the aqueous interface while the phytanyl chain extends towards the middle of the bilayer.[13–16] The effect of α-tocopherol on the phospholipid is, somewhat akin to cholesterol, to disrupt chain packing in the gel state and to increase order in the liquid crystalline state.[17,18] Vitamin E is known to promote the H_{II} phase.[19–21] Here we present data on phosphatidylethanolamine (PE) lipids that we propose reveals that α-tocopherol induces the H_{II} phase by a new mechanism.

In terms of understanding the energetics of H_{II} phase, there are two key components, namely the curvature energy and the packing energy. Following Gruner et al.[2] and more recent studies,[22–26] curvature energy represents an elastic free energy term that depends on bending rigidity and intrinsic curvature, while packing energy refers to hydrocarbon-packing free energy. The curvature energy is strongly influenced by the overall shape of the lipid and for lipids with high intrinsic curvature generally promotes curved phases such as H_{II}. On the other hand, the anisotropy of lipid lengths in the H_{II} phase gives rise to unfavorable packing energy (See Fig. 1). This foundational model was established by a classic series of experiments that showed a purely hydrophobic compound, such as dodecane, could relieve the packing stress by filling in the interstitial corners of the H_{II} phase.[2] With the packing stress relieved, the curvature energy dominates and the lipid can express its spontaneous curvature.[27] This basic model has been used and extended with a great deal of success,[28,29] but open questions remain[30] and experimental measurements of curvature interactions remain an active area.[24,31]

We explore in this work the contrasting changes α-tocopherol and dodecane make to the H_{II} structure in POPE and DOPE and argue that these differences are due to the quite different interactions each compound has on lipids in general and the packing energy stress in particular.

Materials and Methods

Sample Preparation

POPE (16:0-18:1 PE or 1-palmitoyl-2-oleoyl-*sn*-glycero-3-phosphoethanolamine) and DOPE (18:1-18:1 PE or 1,2-dioleoyl-*sn*-glycero-3-phosphoethanolamine) were obtained from Avanti Polar Lipids (Alabaster, AL), while α-tocopherol was prepared as previously described[15] and Sigma (St. Louis, MO) was the source for dodecane. Phospholipid (POPE or DOPE) was co-dissolved in chloroform with dodecane or α-tocopherol in a 2:1 or 4:1 mol ratio, respectively. The organic solvent was removed under a stream of nitrogen gas followed by vacuum pumping overnight. The dried lipid was thoroughly mixed with water and was then transferred to an Eppendorf tube, with the final composition being 3 wt% lipid (approx. 15 mg) in water. Samples containing α-tocopherol were frozen and thawed three times to abet uniform dispersion before recording X-ray measurements. Samples containing dodecane were *not* frozen and thawed as we found this procedure actually resulted in the dodecane separating out, possibly due to dodecane's lower density. We note that freezing dodecane-lipid mixtures was not part of the mixing procedure in a previous X-ray study.[32] Equivalent mol, weight and volume compositions are listed in Table 1.

X-ray diffraction measurements

X-ray diffraction data were taken using a fixed-anode Bruker Nanostar U system (Bruker AXS, Madison, WI), with a typical exposure being 14,400 seconds (4 hours) in duration. The integrated sum of three such exposures for POPE and α-tocopherol at 40 °C is shown in

Fig. 3. The peaks were integrated using the software package FIT2D and were Lorentz and multiplicity corrected.[33] The peak amplitudes thereby extracted from the data are given in Table 2.

Results

The H_{II} phase is depicted in Fig. 1 and consists of a hexagonal unit cell in which a layer of lipids wraps around a cylindrical water core. The distance from the center of the cell to the edge is at a minimum along the short direction and a maximum along the long direction. The lattice spacing, a, is the distance between the centers of adjacent water cores or, equivalently, twice the distance from the center of the cell to the edge along the short direction. The radius of the water core is r_p; it has been shown that it is located at the electron density maximum.[32,34] The thickness of the lipid layer varies from l_{min} to l_{max}, each of these being respectively measured along the short and long directions of the unit cell. The average lipid length, l_{ave}, is calculated using an area weighted average.[33] Consequently, the average lipid length assumes a value that yields roughly equal areas of compression and expansion (see Fig. 1).

X-rays scatter primarily off electrons and so diffraction data can be used to reconstruct the electron density of the lipid structures. Note that this method only gives relative electron density, $\Delta\rho$, where $\rho_{electron} = \rho_{average} + \Delta\rho$. The relative electron density can be reconstructed from the measured X-ray diffraction amplitudes and their phasings via

$$\Delta\rho = \sum_{(h,k)\neq(0,0)}^{h,k\ max} \alpha_{hk} F_{hk} \cos(\boldsymbol{b}_{hk} \cdot \boldsymbol{r}) \tag{1}$$

where h and k are the Miller indices and $\boldsymbol{r}$ is position. The α_{hk}, F_{hk} and $\boldsymbol{b}_{hk}$ terms are, respectively the phase, amplitude and reciprocal lattice vector for each pair of Miller indices. Electron density reconstructions were performed and the proper phasing was determined by selecting the most physically plausible combination; i.e., one that resulted in a uniform

electron density peak ring corresponding to the phospholipid heads, an electron density valley in the center for the water region and a deeper valley for the low electron density region of the hydrocarbon tails. For basic, detailed information on performing reconstructions, the reader is referred to Harper et al.[33] For recent, innovative work on reconstructions one can also consult Frewein et al.[35] The resulting phasings were in agreement with the rubric developed in Turner and Gruner,[32] which states that for $r_p/a > 0.258$, the correct phasing is $+,-,-,+,+,+,+$ and for $0.237 < r_p/a < 0.258$, the correct phasing is $+,-,-,-,+,+,+$. These phasing combinations are also in agreement with subsequent reconstructions of lipids in H_{II} phase.[33,36,37]

A 3-D plot of the relative electron density ($\Delta\rho$) of POPE and α-tocopherol at 40 °C is shown in Fig. 4 (left panel). The phospholipid headgroups form a fairly uniform peaked ring that steeply drops off in the hydrocarbon region. Slices of the electron density through the short and long directions (See Fig. 1) are also shown in Fig. 4 (right panel). Note that there is a good deal of rotational symmetry, which is typical for these systems. Nonetheless, there is a noticeable difference in the relative electron density along the short and long directions. The peak relative electron densities along each direction are designated $\Delta\rho_{short}$ and $\Delta\rho_{long}$.

Fig. 5 illustrates the contrasting effect that dodecane and α-tocopherol have on the structural parameters derived from our data that characterize the H_{II} phase (see Table 3). It can be seen that dodecane slightly increases the lattice parameter, a, for DOPE, whereas α-tocopherol substantially reduces it (Fig. 5, left panel). A similar trend is apparent with POPE (Fig. 5, right panel). As alluded to earlier, the radius r_p of the water core is the average of the radii measured for the electron density maxima along the short and long directions. Both dodecane and α-tocopherol reduce the value of r_p in DOPE (Fig. 6, left panel) and POPE (Fig. 6, right panel). The reduction is greater with α-tocopherol than dodecane.

Geometry (see Fig. 1) readily suffices to determine the minimum length of the lipid

monolayer, l_{min}, which is

$$l_{min} = a/2 - r_p \tag{2}$$

and the maximum length of the lipid monolayer, l_{max}, which is

$$l_{max} = \frac{a/2}{\cos \pi/6} - r_p \tag{3}$$

The average lipid length can be calculated by taking an area weighted average of the length of the lipid monolayer. Note that in this paper lipid includes both the membrane forming lipid (DOPE or POPE) and the additive (dodecane or α-tocopherol). It can be shown[33] that the average lipid length is well approximated by

$$l_{ave} = (a/2 - r_p)\left[1.1084 + 0.0572\left(\frac{r_p}{a/2 - r_p} - 1\right)\right]. \tag{4}$$

We accordingly see that dodecane increases the average lipid length, as opposed to α-tocopherol that leaves it generally unchanged (See Fig. 7).

The cross-section area per lipid A at the lipid-water interface (Fig. 1) can be found by

$$A = V_{total}\left(\frac{2\pi r_p}{\sqrt{3}a^2/2 - \pi r_p^2}\right), \tag{5}$$

where, as before, a is the lattice size, r_p is the water core radius and $V_{total} = V_{lipid} + V_{additive}$.[33] Note that this definition of the area per lipid follows a volumetric decomposition of the unit cell as introduced by Luzzati et al.[1] and shown in Fig. 1. Since the volume fraction for both additives is about 0.13 (See Table 1), we note that therefore $V_{total} = V_{lipid} + 0.13\ V_{total}$ and hence $V_{total} = V_{lipid}/0.87$. It is apparent that the area stays roughly the same with the addition of dodecane but, in contrast, increases with α-tocopherol (See Fig. 8).

Discussion

It has long been appreciated that the extension of lipids in the long direction in the H_{II} phase is energetically costly, with this cost being known as the packing energy.[2] What is less appreciated is that an essential consequence of this energetically costly extension in the long direction must be necessarily accompanied by similarly costly compression in the short direction (see Fig. 1). This is readily understood by the following argument. Overextension in the long direction can be relieved by shrinking the thickness of the lipid monolayer in the H_{II} unit cell. One would then expect that shrinking to continue until opposed by the energetic cost of compression along the short direction. A similar argument can be made by modeling the free energy of the lipid as a harmonic function of lipid length with the minimum sensibly located at the average lipid length. Then, both lipid lengths longer and shorter than the average would necessarily result in free energy costs.

A. α-Tocopherol and dodecane stabilize the H_{II} phase by different mechanisms

With this model in mind, we can consider how dodecane relieves packing strain and promotes the H_{II} phase. The wholly hydrophobic structure of dodecane ensures that it will be located in the tail region of the H_{II} phase as schematically depicted in Fig. 9 (middle panel). This location has been confirmed by neutron scattering experiments.[38] Consequently, it is not surprising that the interfacial area per lipid remains basically unchanged (See Table 4). Classic packing energy theory informs us that it alleviates stress in the long direction, thereby promoting the H_{II} phase.[2] Hence the dodecane should be primarily be located in this region (See Fig. 9). At this point, our deeper appreciation of the dual stresses of extension and compression can now lead us into a fuller understanding of the host lipid and dodecane structure. By effectively extending the lipid lengths (See Fig. 9, middle panel), the dodecane not only relieves the extension stress, but consequently also relaxes the compression stress,

allowing the lipid along the short direction to relax to its optimum value. This can be seen quantitatively in that the l_{min} for DOPE and dodecane matches the l_{ave} for DOPE only (See Table 4).

Turning to α-tocopherol, we see a rather different situation. Instead of increasing l_{max} as dodecane does, l_{max} is reduced by α-tocopherol (See Table 4). For this reason alone, it seems highly unlikely that α-tocopherol works as a lipid length extender as dodecane does. Furthermore, though mostly non-polar, α-tocopherol does have a polar OH group at its tip. This group would tend to locate in the vicinity of the aqueous interface,[14–16,39] suggesting α-tocopherol would not find an energetic minimum deep in the non-polar region as dodecane does. Support for this position is seen in the interfacial area per lipid, which goes up upon the addition of α-tocopherol (See Fig. 8). Therefore, we propose that α-tocopherol relieves stress and promotes the H_{II} phase by replacing lipids along the short direction (See Fig. 9, right panel). As noted earlier, the extensive and compressive stresses are inter-locked - one drives the other - so that if one of the stresses is relieved, the other is also reduced. Hence by alleviating the compressive stress, α-tocopherol allows a reduction in the extensive stress, resulting in a reduced l_{max}, which is what we observe (See Table 4).

In addition to our central argument, there is a suggestive pattern in how the electron density head group maximum varies. We have calculated $\Delta\rho_{long}/\Delta\rho_{short}$, the ratio of the electron density maximum along the long direction relative to the short direction. The electron density maximum is due to the electron dense phosphorous headgroups; with α-tocopherol as the additive, these headgroups are displaced in the short direction, presumably resulting in a reduced electron density maximum. This would result in an increase in $\Delta\rho_{long}/\Delta\rho_{short}$, which is what we see for our data in Table 4. However, the magnitude of the difference of this ratio between samples with and without α-tocopherol is approximately equal to its uncertainty, making this only a suggestive observation in support of our model.

We do not mean to imply, however, that his mechanism is exclusive to α-tocopherol. Other lipophilic molecules that anchor a head group at the aqueous interface, such as choles-

terol also induce the formation of the H_{II} phase.[22] In fact, the contrasting effects of α-tocopherol and dodecane might generalize to other similar chemical compounds.

Biological implications

Vitamin E is a lipophilic antioxidant.[11] To protect lipids from oxidative attack is the primary function of this essential constituent in membranes and is also the basis for its use as a preservative in food and cosmetics. The chemistry involved, whereby the OH group on the chromanol group is sacrificed to terminate the chain of reactions by which the lipid peroxidation progresses, is well understood.[40]. Whether there is a structural component that encourages proximity to polyunsaturated phospholipids, the lipid species most vulnerable to oxidation, remains an unanswered question.[18] The behavior of PE when vitamin E is introduced offers potential insight.

Promotion of negative curvature is revealed by the reduction in temperature of the lamellar to H_{II} phase transition for POPE when α-tocopherol is added. It has been suggested that membranes with intrinsic, negative curvature are less permeable to oxygen.[41] The impact of vitamin E on the local architecture of membranes around PE, thus, may contribute to prevention of oxidation. Interestingly, moreover, polyunsaturated fatty acids (PUFA) are often preferentially taken up into PE.[42] From the results presented here, we also can affirm that matching lipid lengths - avoiding hydrophobic mismatch - is a profound driving force behind lipid organization. It makes sense that in a lipid bilayer, as illustrated in Fig. 10, α-tocopherol will seek to be next to lipids of a similar length. As the length of the chain (12 carbons) in α-tocopherol's tail is less than the chain in a typical membrane phospholipid (16-18 carbons), this means that α-tocopherol will generally find its best match with membrane lipids that have effectively shorter chains (Fig. 9, middle panel). The projected length of PUFA chains is shorter because their multiple double bonds confer tremendous disorder[43] so, we suggest, α-tocopherol will naturally gravitate towards polyunsaturated lipids (Fig. 10).

Conclusions

In summary, we present evidence from electron density reconstructions that α-tocopherol promotes the H_{II} phase in PE by a new means, by relieving compressive stress. This mechanism contrasts with the well studied means by which dodecane promotes the H_{II} phase, which is by reducing extensive stress. Our findings give us new insight both into the nature of packing stress and the interactions of molecules within the lipid membrane, offering potential insight into the biological function of α-tocopherol.

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Table 1: The molecular weight and density, respectively, are 744 g and 1.00 g/cm^3 (DOPE) and 718 g and 1.00 g/cm^3 (POPE), each at 50 °C.[33,34,36] The molecular weight and density, respectively, are 431 g and 0.9 ± 0.1 g/cm^3 (α-tocopherol) and 170 g and 0.8 ± 0.1 g/cm^3 (dodecane).[44] Note that the equivalent compositions for DOPE and POPE are practically identical.

Lipid	Additive	Equivalent Compositions		
		Mole fraction	Weight fraction	Volume fraction
DOPE	α-tocopherol	0.20	0.13	0.13
POPE	α-tocopherol	0.20	0.13	0.14
DOPE	dodecane	0.33	0.10	0.13
POPE	dodecane	0.33	0.11	0.14

Table 2: Lorentz and multiplicity corrected amplitudes calculated from measured peak intensities in X-ray data. Amplitudes for our data have been normalized to the first order peak. [a] Data from Turner and Gruner[32] The phasing for these peaks is $+, -, -, +, +, +, +, +, -, -$. Uncertainties in the amplitudes are of order ± 0.03 relative to the first peak.

	Temp.	Amplitudes									
	(°C)	(1,0)	(1,1)	(2,0)	(2,1)	(3,0)	(2,2)	(3,1)	(4,0)	(3,2)	(4,1)
POPE and	40	1.00	1.00	0.83	0.18	0.21	0.14	0.15			
α-tocopherol	50	1.00	0.95	0.81	0.16	0.22	0.20	0.13			
POPE and	40	1.00	0.84	0.71	0.00	0.31	0.23	0.17			
dodecane	50	1.00	0.81	0.69	0.04	0.17	0.20	0.14			
DOPE and	40	1.00	0.68	0.66	0.00	0.00	0.09	0.06			
α-tocopherol	50	1.00	0.64	0.62	0.00	0.00	0.11	0.08			
DOPE and	40	0.97	0.64	0.58	0.02	0.09	0.18	0.15	0.05		
dodecane[a]	50	0.97	0.61	0.56	0.02	0.07	0.17	0.15	0.05		
DOPE[a]	40	0.95	0.87	0.73	0.13	0.18	0.17	0.14	0.02	0.03	0.04
	50	0.97	0.84	0.71	0.09	0.16	0.17	0.14	0.03	0.02	0.02

Table 3: Dimensional parameters for the lipid and additive combinations measured in this study. See Fig. 1 for the geometric definitions of the parameters and the Results section for how the parameters were calculated. Note that the average lipid length, l_{ave}, includes both the lipid and additive (if present). Uncertainties for the linear quantities (a, r_p, l_{ave}) are $\pm$ 0.5 Å, with the uncertainty for the volume being $\pm$ 20 Å^3 and for the area being $\pm$ 2 Å^2.

Structural Parameters						
	Temperature (°C)	a (Å)	r_p (Å)	V_{lipid} (Å^3)	l_{ave} (Å)	A (Å^2)
POPE and α-tocopherol	40	74.8	20.6	1185	18.8	50.2
	50	72.6	20.0	1190	18.3	52.0
POPE and dodecane	40	82.2	22.2	1185	21.1	44.1
	50	79.5	21.1	1190	20.8	44.5
DOPE and α-tocopherol	40	63.0	15.5	1230	17.7	51.4
	50	61.6	15.2	1238	17.3	53.0

Table 4: In depth comparative listing of DOPE H_{II} dimensions for DOPE only and with either dodecane or α-tocopherol at a single temperature (40 °C). Note that the lipid lengths include both the lipid and additive (if present). [a] Data from Turner and Gruner.[32] Uncertainties are as in Table 3, with the uncertainty in $\Delta\rho_{long}/\Delta\rho_{short}$ being $\pm$ 0.06.

Detailed DOPE Dimensions at 40 °C								
	a (Å)	r_p (Å)	$\Delta\rho_{long}/\Delta\rho_{short}$	l_{ave} (Å)	l_{min} (Å)	l_{max} (Å)	$l_{max} - l_{min}$ (Å)	A (Å^2)
DOPE only[a]	71.0	19.6	1.09	17.8	15.9	21.4	5.5	47.9
DOPE and dodecane[a]	72.0	18.4	1.09	19.5	17.6	23.2	5.6	47.7
DOPE and α-tocopherol	63.0	15.5	1.15	17.7	16.0	20.8	4.9	51.4

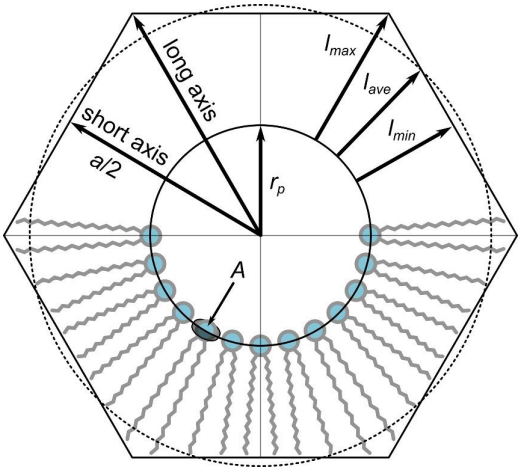

Figure 1: Diagram of a unit cell of the H_{II} phase, which consists of a lipid monolayer wrapped around a cylindrical water core. Lipids are explicitly shown in the bottom half of the diagram, with the hydrophilic heads drawn as circles and the hydrophobic tails as zig-zag lines. Going from the center, one can get to the edge of the cell via the short path (which is one half of the lattice parameter a) or via the long path. Lipid lengths are at a maximum, l_{max}, along the long path and a minimum, l_{min}, along the short path, with the average length, l_{ave}, lying in between. A circle with a radius equal to $r_p + l_{ave}$ is drawn with a dashed line. The radius of the water core is r_p and the average cross sectional area per lipid at the Luzzati interface is A.

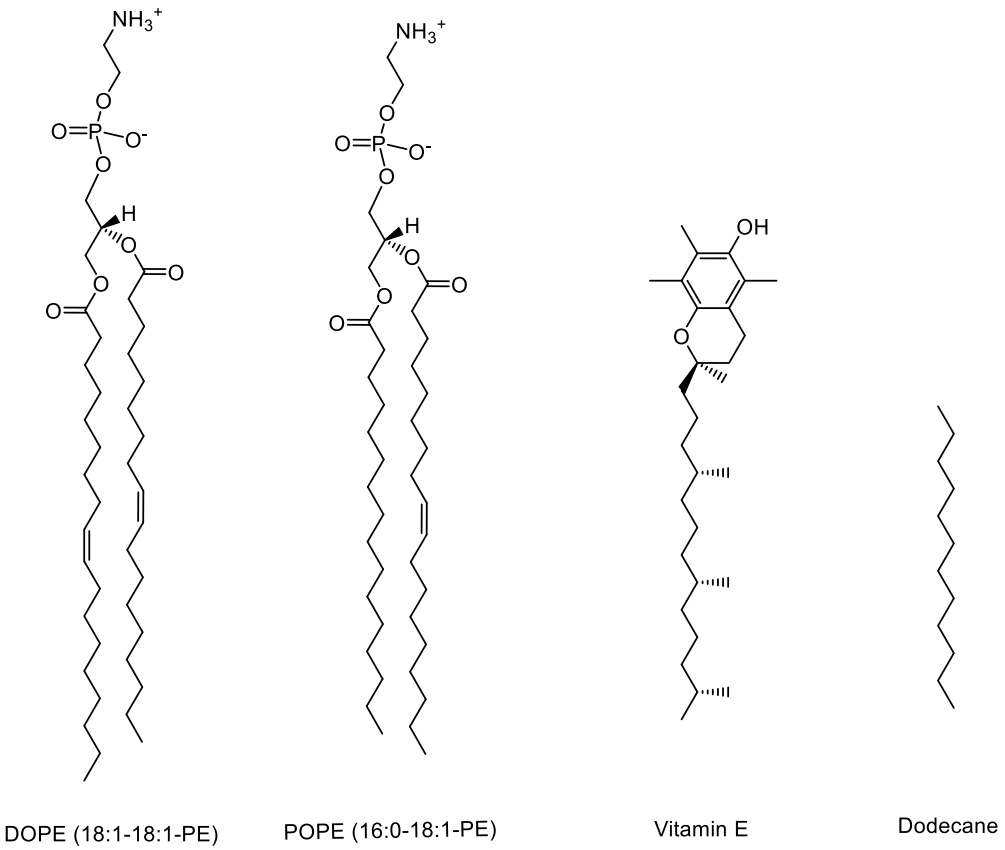

Figure 2: Chemical structures of DOPE, POPE, α-tocopherol and dodecane.

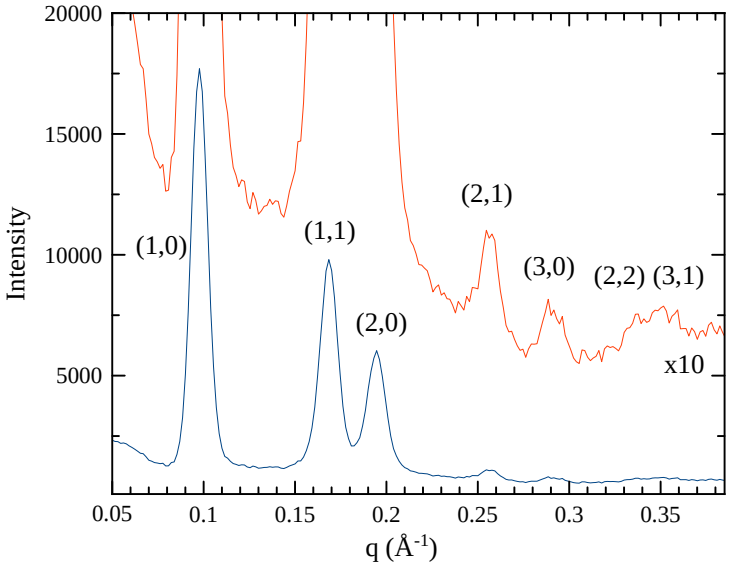

Figure 3: Integrated X-ray scattering intensity of POPE and α-tocopherol at 40 °C. The scattering pattern is typical for the H_{II} phase and each peak is labeled by its Miller indices. The intensity x10 is also plotted to better reveal the weaker, higher order peaks.

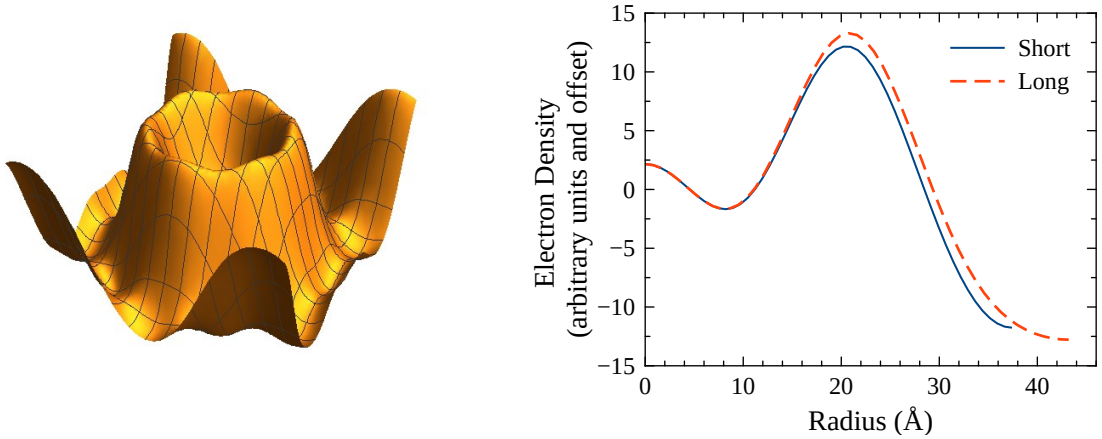

Figure 4: Relative electron density of POPE and α-tocopherol at 40 °C. Left: 3-D plot of the electron density (vertical axis) of the H_{II} phase. The high electron density phospholipid headgroups generate a ring peak with a shallow inner central valley for the aqueous region and a deeper outer valley for the hydrocarbon region. Right: Slices of the electron density along the short and long directions (See Fig. 1). Note that the relative electron density maximum along the long direction ($\Delta\rho_{long}$) is slightly higher than the electron density maximum along the short direction ($\Delta\rho_{short}$)

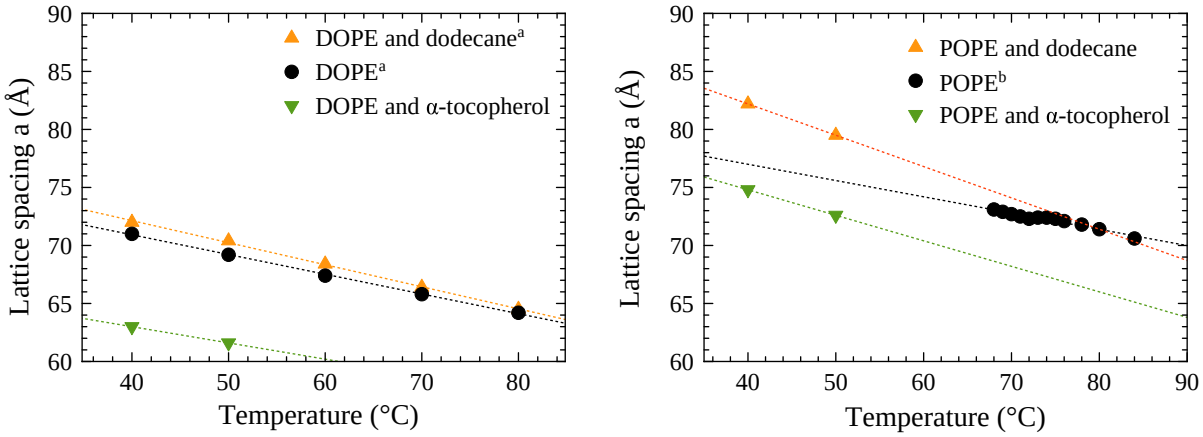

Figure 5: Lattice spacings (center of water core to center of water core distance) for DOPE (left) and POPE (right) for the lipid only, lipid with α-tocopherol and lipid with dodecane. Linear fits of the data are displayed as dotted lines to guide the eye. For both DOPE and POPE, α-tocopherol reduces the lattice spacing while dodecane increases it. [a] Data from Turner and Gruner.[32] [b] Data from Rappolt et al.[36]

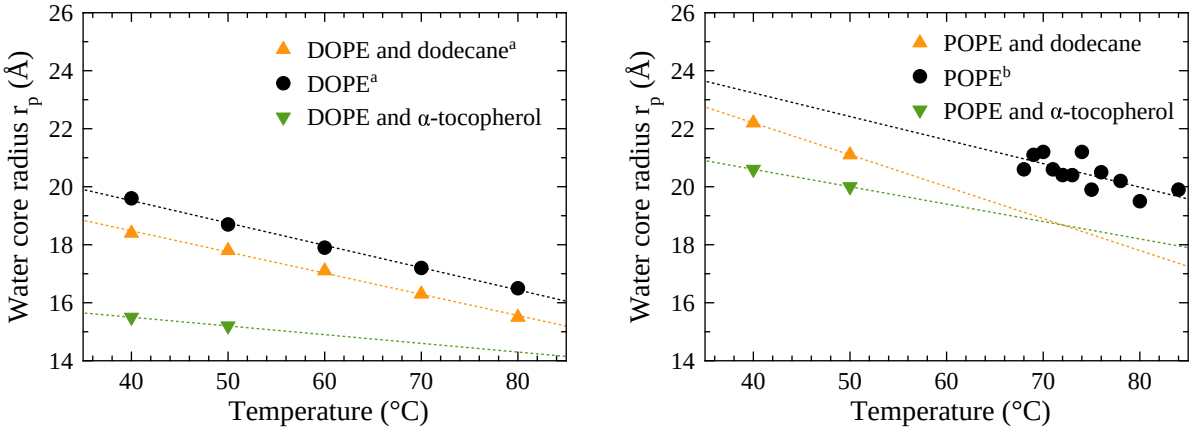

Figure 6: Water core radii for DOPE (left) and POPE (right) for the lipid only, lipid with α-tocopherol and lipid with dodecane. Linear fits of the data are displayed as dotted lines to guide the eye. For both DOPE and POPE, the water core radius is reduced by α-tocopherol and, to a lesser amount, dodecane. [a] Data from Turner and Gruner.[32] [b] Data from Rappolt et al.[36]

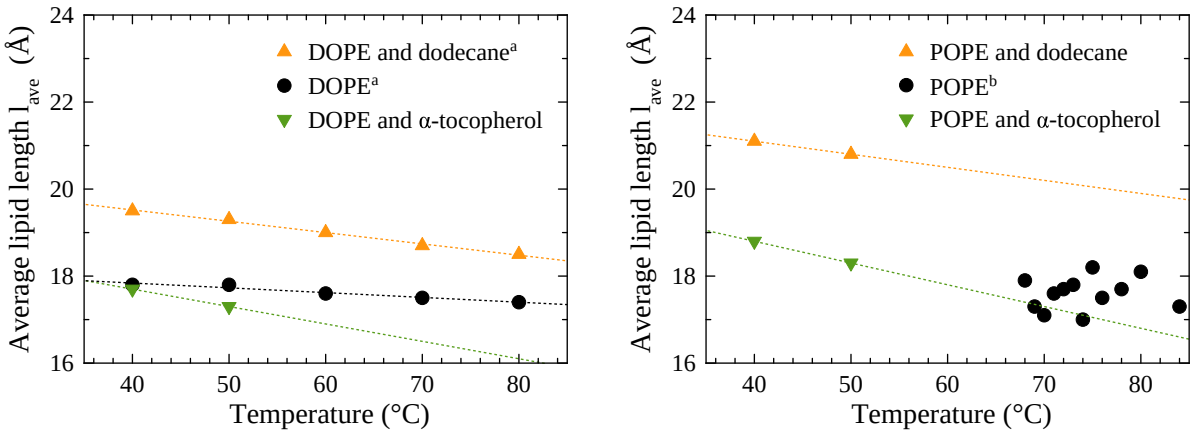

Figure 7: Average lipid lengths for DOPE (left) and POPE (right) for the lipid only, lipid with α-tocopherol and lipid with dodecane. Linear fits of the data are displayed as dotted lines to guide the eye. For both DOPE and POPE, α-tocopherol does not substantially change the average length but dodecane increases it. [a] Data from Turner and Gruner.[32] [b] Data from Rappolt et al.[36]

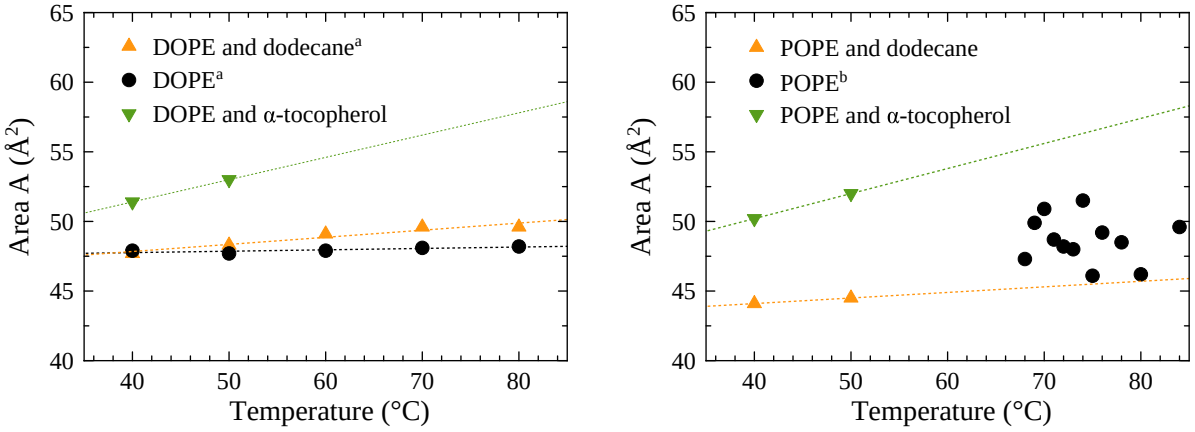

Figure 8: Average areas for DOPE (left) and POPE (right) for the lipid only, lipid with α-tocopherol and lipid with dodecane. Linear fits of the data are displayed as dotted lines to guide the eye. In general, α-tocopherol increases the area while dodecane does not seem to greatly change it. [a] Data from Turner and Gruner.[32] [b] Data from Rappolt et al.[36]

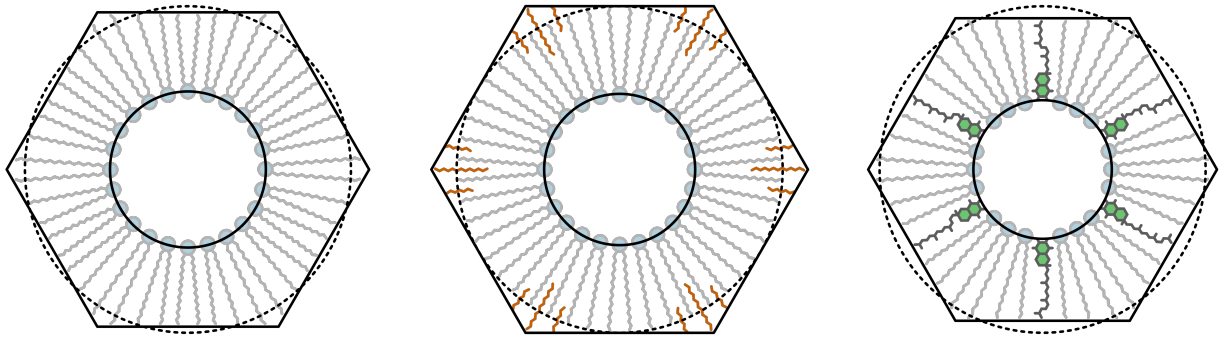

Figure 9: Models for PE only, PE and dodecane and PE and α-tocopherol in the H_{II} phase. Dodecane fits in deep in the hydrocarbon tail region, predominately along the long direction. By contrast, α-tocopherol fills in along the short direction and is relatively close to the lipid water interface. For all of the diagrams, the dashed circle indicates the average lipid length found in the PE only case. As discussed in the text, dodecane enlarges the unit cell so that the average lipid length in the PE only case matches the minimum lipid length in the PE and dodecane case. Likewise, α-tocopherol reduces the unit cell size and the average lipid length for the PE only case is closer to the maximum lipid length in the PE and α-tocopherol case.

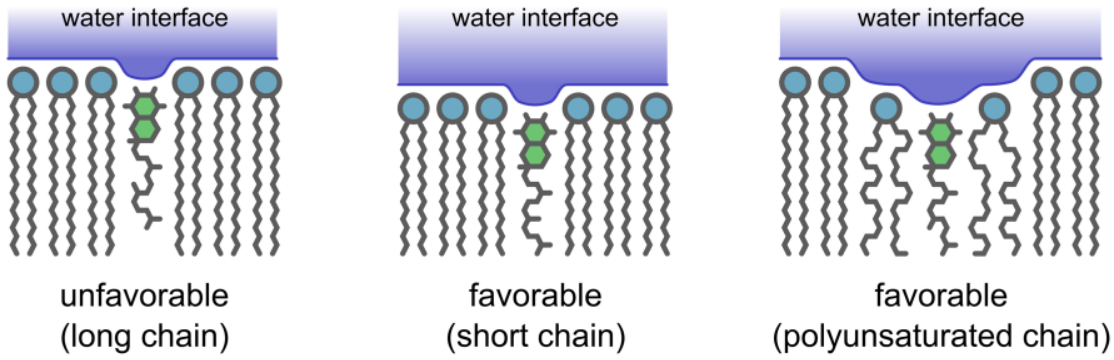

Figure 10: Model for the location of α-tocopherol in a membrane. A single monolayer is shown. The location is unfavorable when there is a mismatch between chain length (left panel) and favorable when chain lengths match (middle panel). In a mixed membrane, α-tocopherol locates next to polyunsaturated phospholipids in order to match chain length (right panel).

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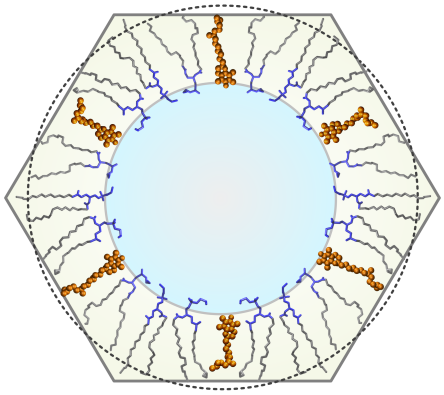
TOC (Table of Contents) Graphic



Vitamin E relieves compressive packing stress