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Comparative study of liponucleosides in Langmuir monolayers as cell membrane models

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ABSTRACT

Liponucleosides may assist the anchoring of nucleic acid nitrogen bases into biological membranes for tailored nanobiotechnological applications. To this end precise knowledge about the biophysical and chemical details at the membrane surface is required. In this paper, we used Langmuir monolayers as simplified cell membrane models and studied the insertion of five lipidated nucleosides. These molecules varied in the type of the covalently attached lipid group, the nucleobase, and the number of hydrophobic moieties attached to the nucleoside. All five lipidated nucleosides were found to be surface-active and capable of forming stable monolayers. They could also be incorporated into dipalmitoylphosphatidylcholine (DPPC) monolayers, four of which induced expansion in the surface pressure isotherm and a decrease in the surface compression modulus of DPPC. In contrast, one nucleoside possessing three alkyl chain modifications formed very condensed monolayers and induced film condensation and an increase in the compression modulus for the DPPC monolayer, thus reflecting the importance of the ability of the nucleoside molecules to be arranged in a closely packed manner. The implications of these results lie on the possibility of tuning nucleic acid pairing by modifying structural characteristics of the liponucleosides.

1. Introduction

Nucleosides and oligonucleotides are useful nanotechnological building blocks owing to their capability of molecular recognition. The specific molecular interaction between complementary nucleic acid strands serves to build the blocks of life, which stimulates the use of DNA-based duplexes [1–3]. Alkylated oligonucleosides structures, also called liponucleosides (other authors use the term 'nucleolipids' ref. [4]), have been exploited to improve anchoring of nitrogen bases of nucleic acids into biological membranes, which is important for biotechnology, cell biology and medicine [5–7], as in drug carriers for diagnostic and therapeutic applications [8,9].

The effect of lipophilic compounds into biological membranes can be investigated at the molecular level using models such as liposomes [10,11] and Langmuir monolayers [10,12]. From the literature it is known that lipophilic oligonucleosides inserted into preformed vesicles do not perturb the lipid bilayer structure significantly [13,14]. As for their mixture with Langmuir lipid monolayers, only a few studies have been reported so far [15–17]. In a previous paper [17], we showed that an isomer mixture of 2′-palmitoyluridin und 3′-palmitoyluridin could not only form stable Langmuir monolayers, but also be incorporated in dipalmitoylphosphatidylcholine (DPPC) monolayers.

In the current paper, the role of the hydrophobic chemical groups attached to the nucleosides has been studied, using lipidated nucleosides referred to as **1**–**5** and whose structures are shown in Fig. 1. In particular, we investigated their surface chemistry properties as well as their mixture with lipid monolayers of DPPC. In these lipidated nucleosides either one, two, or three lipid moieties are found, thus enabling to study the effect of the number of lipid anchors. Furthermore, the position where the lipophilic anchor is fixed to the nucleosides, i.e. at the sugar unit or at the nucleobase, is varied.

2. Materials and methods

The synthesis of the liponucleoside compounds **1**–**5** was carried out following the procedures described in literature [18,19]. The phospholipid dipalmitoyl phosphatidyl choline (DPPC), whose polar group is abundant in many biological membranes [20], was purchased from Avanti Polar Lipids. DPPC and compounds **1**–**5** were dissolved in chloroform (Merck) to yield a concentration of 0.4–0.8 mg/mL. Neat monolayers were obtained by spreading the chloroform solution of either DPPC or **1**–**5** on an aqueous subphase with pH 7.5 comprising 0.1 mol L^{-1} NaCl (Merck), and 0.001 mol L^{-1} phosphate buffer

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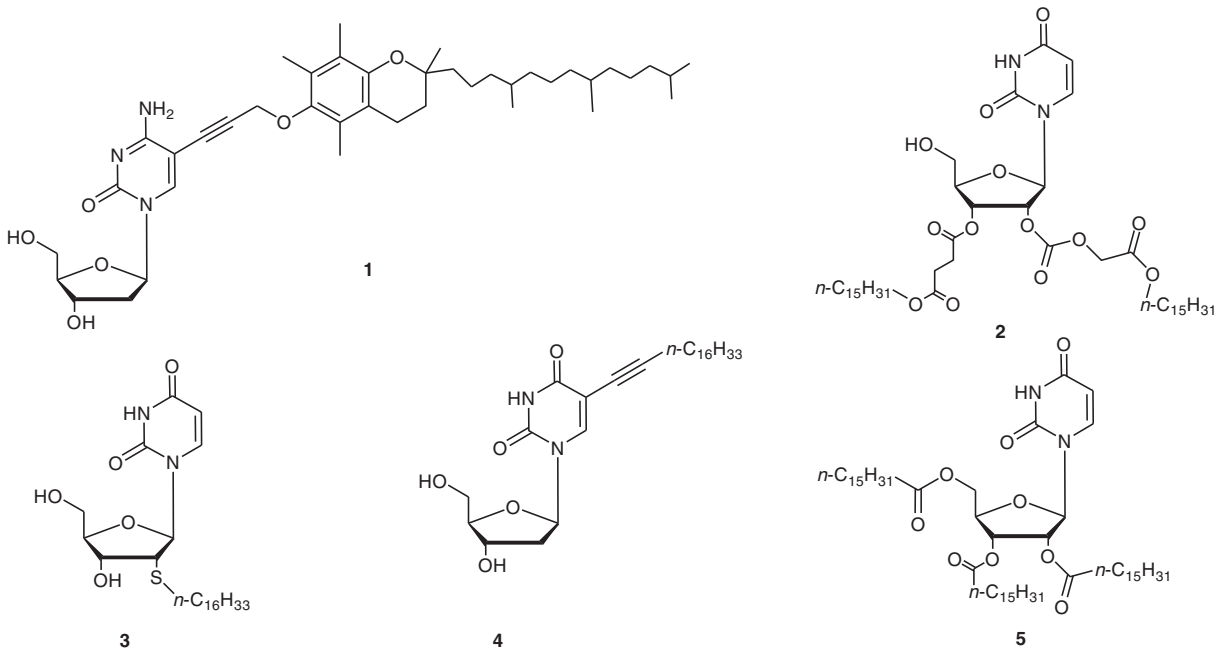

Fig. 1. Structure of the liponucleosides 1–5 used in this study.

(Na_2HPO_4:NaH_2PO_4 = 1:1, Merck). Mixed monolayers of **1–5** in DPPC were obtained by co-spreading a solution of the respective nucleoside with DPPC mixed in chloroform on a subphase containing the phosphate buffer as mentioned above. After 10–15 min of incubation to allow for solvent evaporation of spreading solutions of 0.4–0.8 mg/mL (volumes of 25–40 μL), the air–water interface was compressed with two movable barriers in a Mini-KSV trough (7.2 × 32.8 cm) at a rate of 2.9 $Å^2$/(molecule min). The surface pressure (π) and the surface potential (ΔV) were measured during compression using a Wilhelmy plate and a Kelvin probe, respectively.

For the neat monolayers of **1–5**, the area per molecule was calculated assuming that all molecules remained at the interface, with no loss to the buffer subphase. For mixed monolayers of DPPC and either one of the compounds, the area is given per DPPC molecule to allow for probing the effects from the liponucleosides on the phospholipid monolayers. From the surface pressure isotherms, we also obtained the surface compressibility modulus, K, defined [21] as $-A\,(\partial\pi/\partial A)_T$, where A is the molecular area and T is the absolute temperature. "K" is commonly related to the surface elasticity, and can be understood as the system response to an external mechanical perturbation.

3. Results and discussion

The pure liponucleosides spread onto a buffer subphase show very distinct surface pressure (π-area, Fig. 2) and surface potential isotherms (Fig. 3) reflecting the differences in the chemical structure of the compounds given in Fig. 1. Before discussing the isotherms in detail, a digression is in order to elaborate on the shape of the isotherms obtained for the Langmuir monolayers. For surface pressure isotherms, condensed films with high collapse pressures are normally obtained with the right balance between the hydrophilic and hydrophobic parts of the film-forming molecules, as is the case of fatty acids with long alkyl chains [22,23]. The isotherm may become more expanded if charges are present on the headgroup, which causes repulsion, or if hydrophilic groups (or even unsaturations) are incorporated in the alkyl chains. The latter groups generate long-range interactions with the water molecules and the subphase.

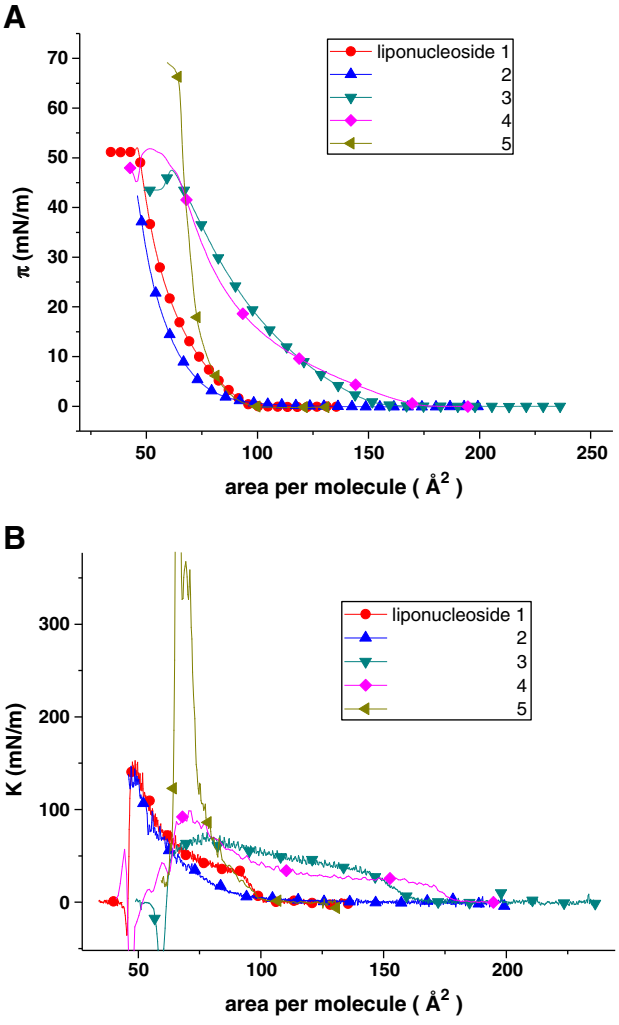

Fig. 2. (A) surface pressure-area (π-A) and (B) compressibility modulus-area (K–A) isotherms for the liponucleosides.

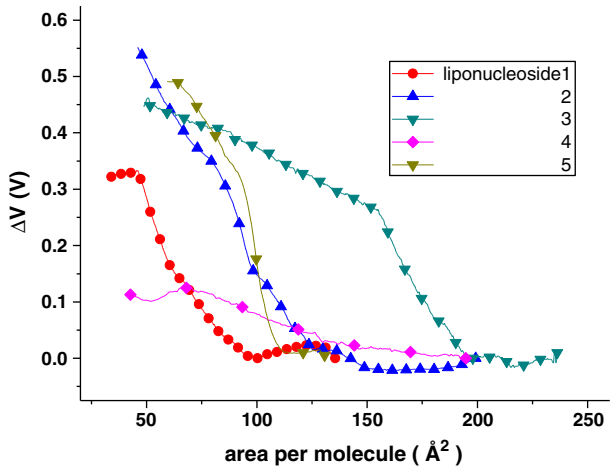

Fig. 3. Surface potential-area (ΔV–A) isotherms for the liponucleoside.

Expanded isotherms may also reflect the difficulty of the molecules to pack, either owing to steric hindrances or an imbalance in their hydrophobic/hydrophilic nature. In case packing is efficient, the area per molecule in the condensed films is generally proportional to the number of alkyl chains. The ability of the film-forming molecules to pack as flexible or ordered structures can be better probed by obtaining the surface compressibility modulus (K) from π-A curves. Fig. 2B shows that for compounds 3 and 4, the onset for K in K–A isotherms occurs at larger areas than for the other liponucleosides, but the maximum values do not exceed 100 mN/m, pointing to a flexible monolayer in a liquid-expanded phase. For compounds 1 and 2, the compressibility modulus reached values characteristic of a liquid-condensed phase, that is, around 150 mN/m. Compound 5 exhibited the highest structured monolayer among the liponucleosides studied, with K values above 400 mN/m, featuring a high ordered liquid-condensed state.

As for the surface potential isotherms, the structuring of the molecules is manifested at larger areas than is detected in the surface pressure measurement, and therefore the area for the onset of surface potential is usually higher than that for the onset in the pressure curve. For traditional amphiphiles, such as fatty acids and some phospholipids, the rise in potential is very abrupt, which is the reason why the area at the onset is referred to as critical area [24]. When the pressure starts to increase and the film becomes condensed the slope in the potential curve is significantly reduced, and the surface potential tends to level off. The surface potential is proportional to the normal component of the dipole moment of the film-forming molecules, which may be analyzed quantitatively using the Demchak–Fort model [25]:

$$\Delta V = 1/A\varepsilon_o(\mu_1/\varepsilon_1 + \mu_2/\varepsilon_2 + \mu_3/\varepsilon_3) + \psi_0,$$

where A is the molecular area, μ_1, μ_2, and μ_3 are the normal components of the dipole moment (polar groups, non-polar groups, and reoriented water molecules close to the monolayer), ε_o is the vacuum permittivity, and ψ_0 is the contribution of the Gouy–Chapman double layer that appears for ionized films. In this model, the monolayer is represented as a 3-layer capacitor to take into account dipoles in the tails, headgroups and arising from the reorientation of water molecules, which are embedded in the media of distinct dielectric constants. Phase transitions arising from ordering of chains and strong molecular reorientation yield considerable changes in the surface potential isotherm, as they may do in the surface pressure ones. However, this did not occur for any of the nucleosides investigated here, as is clear from Figs. 2 and 3.

In resuming the analysis of Figs. 2 and 3, we note that all compounds formed stable films, as one should expect from their amphiphilic nature. The compounds are not soluble in water, for in the synthesis in most cases the reaction mixture was washed with saturated $NaHCO_3$ leaving the liponucleoside in the organic layer. Compound **5** forms remarkably condensed films, with collapse pressure close to 70 mN/m and reaching a compressibility modulus above 300 mN/m (see Table 1), characteristic of a highly packed monolayer [26–28]. The area per molecule extrapolated to zero pressure is ca. 75 Å^2, which is consistent with the presence of three alkyl chains in the molecule (see Fig. 1). Therefore, this compound formed a Langmuir monolayer that is similar to traditional amphiphilic compounds, which is confirmed by the shape of its surface potential isotherm in Fig. 3. It is also possible that the palmitoyl chain in the opposite direction of the nucleoside may not fit with the other two chains in one layer. Either one of them stays outside or one anchors in another lipid layer than the other two (shown downwards in the drawing).

In contrast, the surface pressure isotherms for compounds **3** and **4** were very expanded, with relatively low collapse pressures. The difficulty in packing is better illustrated in the low compressibility modulus, whose maximum values for compounds **3** and **4** in Table 1 are typical of fluid phases (below 100 mN/m [28]). It is likely that such difficulty is related to the presence of only one alkyl chain for molecules with various polar groups (see Fig. 1). In spite of the similarity in the surface pressure isotherms for these compounds **3** and **4**, their surface potential isotherms differed considerably. For compound **3**, the difficulty in packing was reflected in an expanded surface potential isotherm, but the orientation of the polar groups must have been such as to yield large surface potentials. This could be due to the presence of the sulfur element, which is absent in compound **4**. For the latter, on the contrary, the surface potential remained small throughout the compression, from which one infers that either the polar groups had dipole moments parallel to the water surface or their contributions to the vertical component almost cancelled out. Unfortunately, a quantitative analysis of the surface potential is not possible for compounds **1** through **5** because one cannot predict with accuracy the orientation of the dipole moments. Nevertheless, the analysis of the surface potential isotherms is still useful for distinguishing the behaviors of the different liponucleosides in their interaction with DPPC.

Compounds **1** and **2** displayed similar surface pressure isotherms, also reaching the condensed state with compressibilities above 100 mN/m in Table 1, in spite of the differences in their structures, probably owing to a compensation of effects. On the one hand, compound **1** has only one alkyl chain, while compound **2** has two. On the other hand, the branched α-tocopherol unit in **1** is much more voluminous and bulky than the lean, straight alkyl chain of **2**. The differences appeared in the surface potential isotherms, with compound **1** exhibiting a considerably lower surface potential.

The effect of the liponucleosides into DPPC monolayers is illustrated in Fig. 4, which also shows the isotherm for neat DPPC that is in agreement with the literature [29]. The isotherms are different from those of the neat liponucleosides as expected. Significantly, the phase transition from the liquid-condensed to the

Table 1
Maximum surface compressional modulus (K_{max}) for the liponucleosides.

Liponucleoside	K_{max} (mN/m)
1	147.8
2	143.7
3	78.4
4	70.9
5	372.3

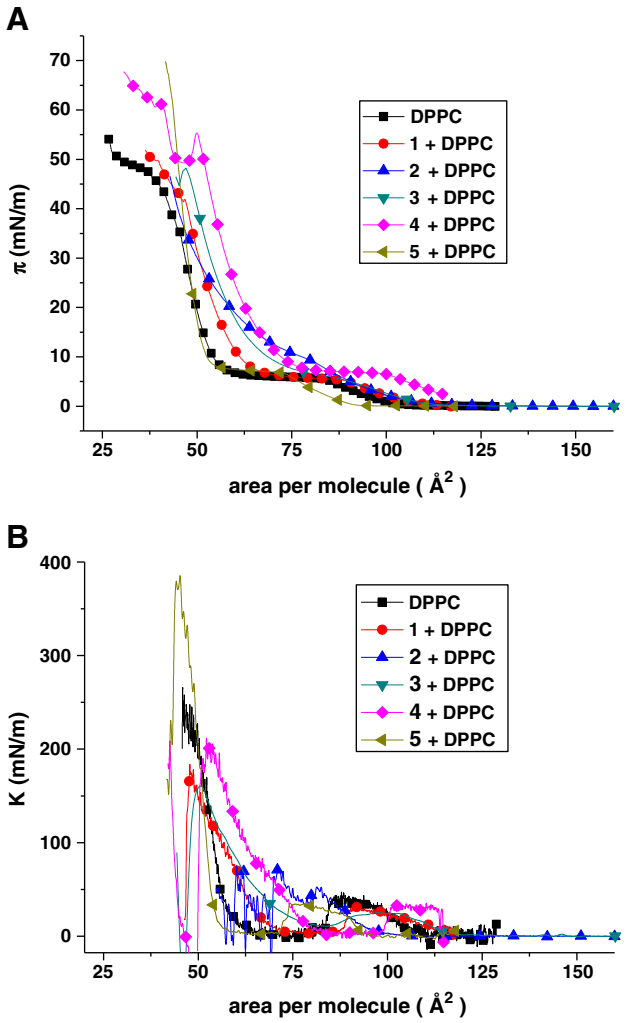

Fig. 4. Surface pressure-area (π-A) and (B) compressibility modulus-area (K–A) isotherms for mixed liponucleosides (10% in mol)-DPPC monolayers.

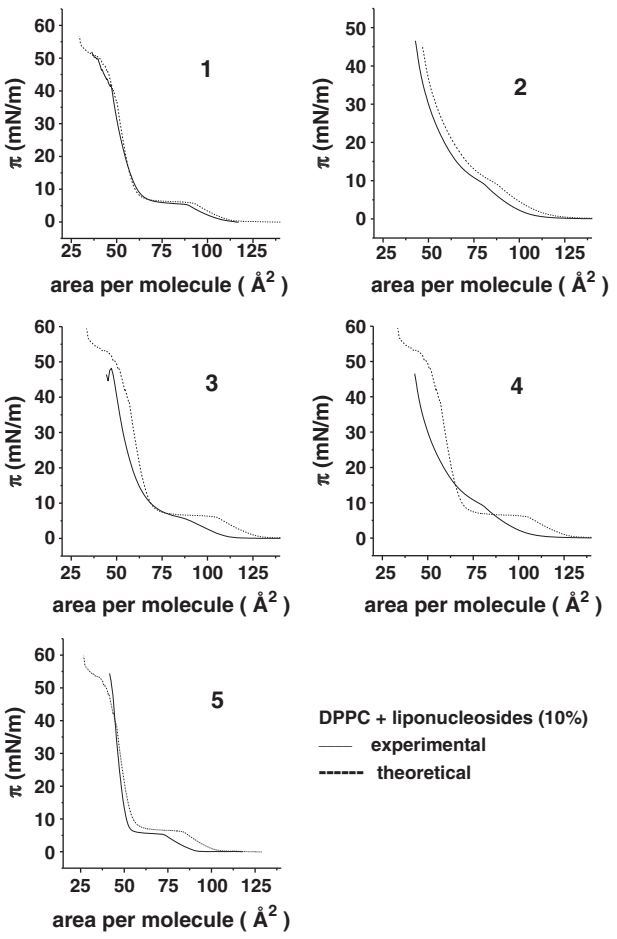

Fig. 5. Comparison between the surface pressure-area (π-A) isotherms of liponucleosides (10% in mol)-DPPC monolayers experimental and theoretical (calculated from isotherms for pure DPPC and pure liponucleoside monolayers).

liquid-expanded phases, typical of pure DPPC, was preserved in all cases. The only significant alteration was the shift of the plateau for larger areas per DPPC molecule. In addition, the presence of liponucleotides increased the monolayer stability in that higher collapse pressures were attained.

Since DPPC and the liponucleosides are amphiphilic, both components in the mixture are likely to contribute significantly to the monolayer properties. We have therefore compared in Fig. 5 the surface pressure-area (π-A) isotherms of liponucleosides (10% in mol)-DPPC monolayers obtained experimentally and theoretically (calculated from the isotherms for pure DPPC and pure liponucleoside monolayers assuming ideal mixtures). For compounds **1**–**4**, there is an increase in the area per liponucleoside when mixed with DPPC, in comparison to the area in the pure liponucleoside monolayer. Even at a high surface pressure of 30 mN/m – which is believed to correspond to the lateral pressure of cell membranes [30] – this tendency is maintained, with the exception of compound 4 at a pressure of ca. 10 mN/m, in which the transition to the liquid-expanded phase takes place. The increase in area indicates a positive value for the mixture excess Gibbs energy, pointing to a non-ideality of the mixing and expansion of the partial molar areas when mixing the two components. ^{2}H NMR data of compounds 1, 3, and 5 incorporated into POPC membranes showed that these molecules can be well incorporated and only slightly alter the chain order of the host membrane [18,31]. On the other hand, for compound **5** there was a reduction in the partial molar area, which could be explained by its much higher surface elasticity. This means that its ability to reach a closely packed arrangement facilitates the mixture into the DPPC monolayer.

Fig. 4B and Table 2 depict the tendency for the reduction of the surface compression modulus of the DPPC monolayer upon mixing with the liponucleosides, indicating that these compounds render the monolayer more flexible. In other words, with the liponucleosides, it is no longer possible to obtain a closely packed structure as for pure DPPC. Again, the exception is compound **5**, which caused the surface compression modulus of DPPC to increase. This is consistent with the finding mentioned above that compound **5** condenses the monolayer, decreasing the occupancy area for both components due to a favorable interaction, and a negative mixture excess Gibbs energy. Also interesting is that compound 2 has a distinct behavior from the other liponucleosides. It induces a significant decrease in the compression modulus of a DPPC monolayer, leading to a more flexible

Table 2
Maximum surface compression modulus (K_{max}) for mixed liponucleoside (10% in mol)-DPPC. E_{max} for pure DPPC is 250 mN/m under the conditions employed in this work.

Liponucleoside	K_{max} (mN/m)
1	176.4
2	146.4
3	121.3
4	197.3
5	384.8

Table 3
Maximum surface potential (ΔV_{max}) for mixed liponucleoside (10 mol%)-DPPC. ΔV_{max} for pure DPPC is 655 mV under the conditions employed in this work.

Liponucleoside	ΔV_{max} (mV)
1	550
2	750
3	490
4	500
5	640

monolayer. This may be attributed to the fact that it is the only compound with two alkyl chains.

With regard to the maximum surface potentials, Table 3 indicates that the behavior of the mixed films is similar to that of the neat liponucleoside films. For instance, compound **4** exhibited the lowest surface potential while compound **2** had the highest one. This applied for the neat liponucleoside films and for that mixed with DPPC.

4. Conclusions

In this paper, we have shown that the lipophilic nucleosides not only form stable Langmuir monolayers, but they can also be incorporated into a phospholipid monolayer that serves as a simplified cell membrane model. For the comparative study the main structural differences to be considered were the type of lipid group, the type of nucleobase, and the number of alkyl chains. While the latter had an important effect for the packing, as one should expect, the type of nucleobase appears not to have an effect. The nucleobase in compound **1** is cytidine while for all other cases it is uracyl. With regard to the type of lipid group, the volume of the tocopherol unit in compound **1** may have been responsible for the similarity in the surface pressure isotherms with compound **2**, in spite of this latter having two chains rather than 1.

All the data of the Langmuir monolayers pointed to a significant molecular-level interaction between the compounds and DPPC, with the nucleosides being miscible and leading to an expansion of the monolayers. Only for compound **5** we observed a significant condensation, which reflects its ability to form well packed monolayers as indicated by its net surface pressure-area isotherms. This has important implications for exploiting molecular recognition in base pairing, with the nitrogen bases anchored to biomembrane models, which may open the way for these materials to be used in biosensors and for medicinal molecular probes based on nucleic acid pairing.

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