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Mendeleev Commun., 2016, **26**, 109–110
Mendeleev Communications

Effect of curcumin on lateral diffusion in lipid bilayers

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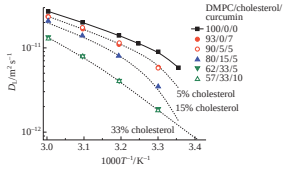
DOI: 10.1016/j.mencom.2016.03.007

Lateral diffusion in dimyristoylphosphatidylcholine lipid bilayers decreases in the presence of cholesterol and curcumin, as measured by ^{1}H NMR spectroscopy, but the mechanisms of action of these two compounds are different.



Curcumin is a natural yellow spice commonly used in Eastern kitchens and traditional medicines[1,2] due to its antioxidant, anti-carcinogenic, antimutagenic and antiinflammatory properties. It is believed that curcumin, like cholesterol, acts on a basic biological level such as biomembranes by changing the physical properties of a membrane rather than by directly binding to membrane proteins.[3] Cholesterol is an essential component of mammalian cell membranes, which can be embedded in the hydrophobic part of the membrane with its hydroxyl group interacting with the polar head groups of membrane phospholipids and sphingolipids.[4,5] Cholesterol increases membrane packing and ordering in a liquid crystalline phase.[6–8] Consequently, membrane fluidity gradually decreases with the concentration of cholesterol, as detected by measuring the lateral diffusion of phospholipids and sphingolipids.[9–11] In this work, we examined the combined effect of both curcumin and cholesterol on lipid lateral diffusion coefficient (D_L), reflecting a more biologically relevant condition compared to those of previous studies.

Figure 1 shows the structures of cholesterol, DMPC and curcumin. Glass-plate-oriented lipid multibilayers were prepared following a previously described procedure.[9,12] The amount of DMPC in each sample was 15 mg, while cholesterol and curcumin concentrations were varied to 33 and 10 mol%, respectively.† This range of concentrations was chosen because of a high solubility of cholesterol (~66 mol%[13]) and a relatively low solubility of curcumin (~10 mol%[14]). To prepare the test sample, a solution of DMPC in ethanol with an amount of cholesterol and curcumin was deposited (25 μl) on approximately 40 glass plates (5×14×0.08 mm). The solvent was evaporated in air and then in a vacuum overnight. The plates were stacked, placed in square, cross-sectioned tubes and hydrated in a humid atmosphere (D_2O) at 35 °C for five days. The degree of hydration of about 23 wt% was controlled by weighing the samples. The process of multi-bilayer formation was confirmed by the ^{1}H NMR spectrum‡ of the sample oriented at a magic angle of 54.7°.[15] The final amount

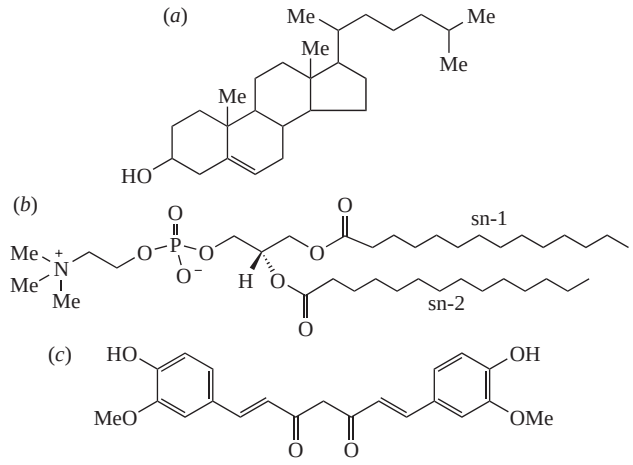


Figure 1 Molecular structures of (*a*) cholesterol, (*b*) DMPC and (*c*) curcumin (keto form).

of water (45 wt%) was adjusted through a piece of filter paper placed on top of the glass stack. Afterward, the sample was sealed.

The NMR diffusion measurements in oriented lipid membranes were described in detail elsewhere.[9] An NMR goniometer probe was used to orient macroscopically aligned bilayers with the lipid bilayer normal at a magic angle (54.7°) with respect to the main magnetic field (Cryomagnet system).[15] For all measurements, a stimulated echo pulse sequence was used.[16] Diffusion decays $A(k)$ were obtained, where $A(k)$ is the spectrum integral, $k = \gamma^2\delta^2 g^2 t_d$, γ is the ^{1}H gyromagnetic ratio, δ is the duration, g is the amplitude of the gradient pulse, $t_d = (\Delta - \delta/3)$ is the diffusion time, and Δ is the duration between identical gradient pulses.

The formation of plain-oriented multi-bilayers in all of the DMPC/cholesterol/curcumin test samples was confirmed by resolved ^{1}H NMR spectra when the bilayers were oriented by their normal at the magic angle at temperatures higher than the main gel-to-liquid phase temperature of DMPC. As the magic

† Commercial DMPC from Avanti Polar Lipids and curcumin (>94% curcuminoid, >80% curcumin) and deuterated water (99.7% D_2O) from Sigma were used.

‡ A Chemagnetic InfinityPlus CMX-360 NMR spectrometer (Agilent) operating at a frequency of 360 MHz was used.