Melatonin directly interacts with cholesterol and alleviates cholesterol effects in dipalmitoylphosphatidylcholine monolayers

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Melatonin directly interacts with cholesterol and alleviates cholesterol effects in dipalmitoylphosphatidylcholine monolayers

Youngjik Choi,[ab] Simon J. Attwood,[c] Matthew I. Hoopes,[d] Elizabeth Drolle,[ab] Mikko Karttunen[bd] and Zoya Leonenko*[abc]

Melatonin is a pineal hormone that has been shown to have protective effects in several diseases that are associated with cholesterol dysregulation, including cardiovascular disease, Alzheimer's disease, and certain types of cancers. Cholesterol is a major membrane constituent with both a structural and functional influence. It is also known that melatonin readily partitions into cellular membranes. We investigated the effects of melatonin and cholesterol on the structure and physical properties of a 1,2-dipalmitoyl-*sn*-*glycero*-3-phosphocholine (DPPC) monolayer as a simple membrane model using the Langmuir–Blodgett (L–B) monolayer technique and molecular dynamics (MD) simulations. We report that melatonin increases the area per lipid and elastic compressibility of the DPPC monolayer in a concentration dependent manner, while cholesterol has the opposite effect. When both melatonin and cholesterol were present in the monolayer, the compression isotherms showed normalization of the area per molecule towards that of the pure DPPC monolayer, thus indicating that melatonin counteracts and alleviates cholesterol's effects. Atomistic MD simulations of melatonin enriched DPPC systems correlate with our experimental findings and illustrate the structural effects of both cholesterol and melatonin. Our results suggest that melatonin is able to lessen the influence of cholesterol through two different mechanisms. Firstly, we have shown that melatonin has a fluidizing effect on monolayers comprising only lipid molecules. Secondly, we also observe that melatonin interacts directly with cholesterol. Our findings suggest a direct nonspecific interaction of melatonin may be a mechanism involved in reducing cholesterol associated membrane effects, thus suggesting the existence of a new mechanism of melatonin's action. This may have important biological relevance in addition to the well-known anti-oxidative and receptor binding effects.

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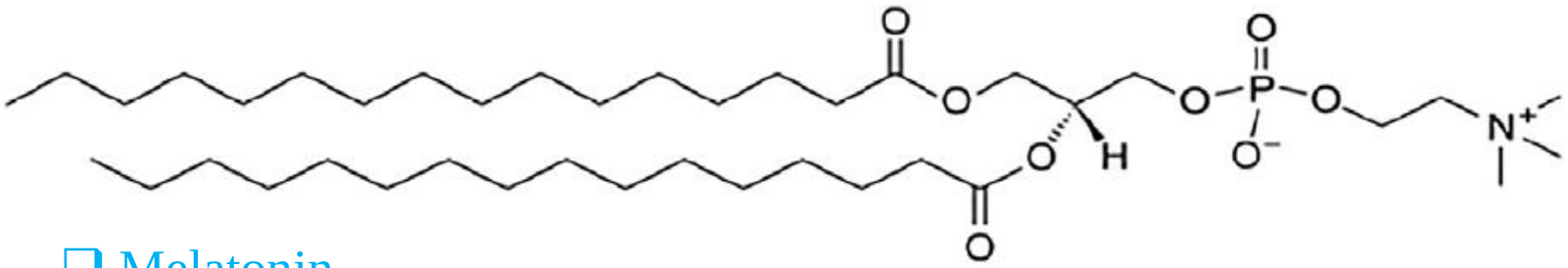
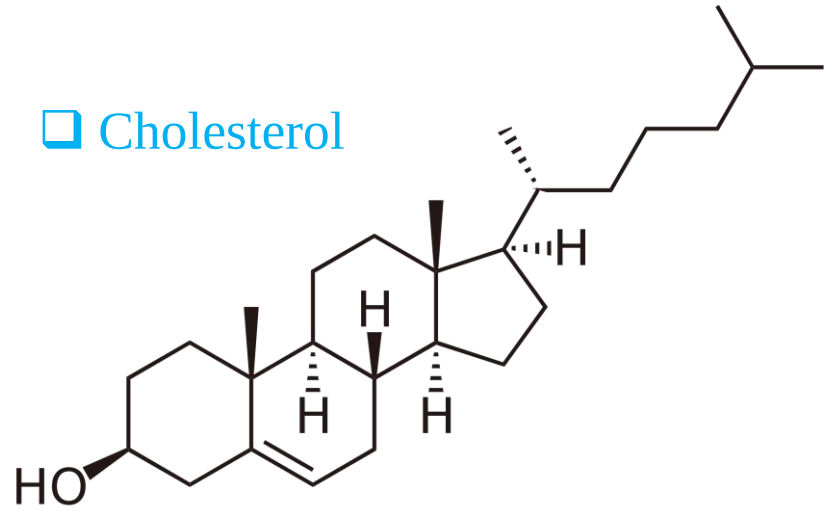
❑Molecular structure

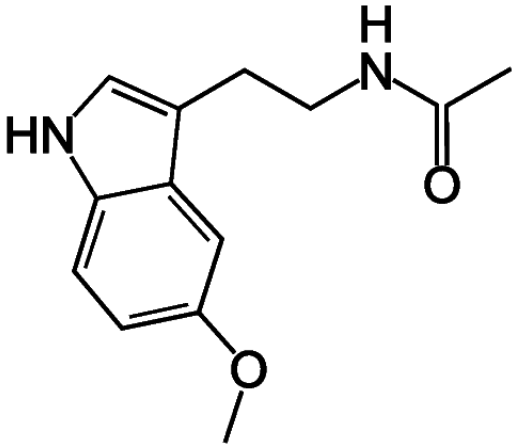
❑ 1,2-dipalmitoyl-sn-glycero-3-phosphocholine (DPPC)



❑ Cholesterol

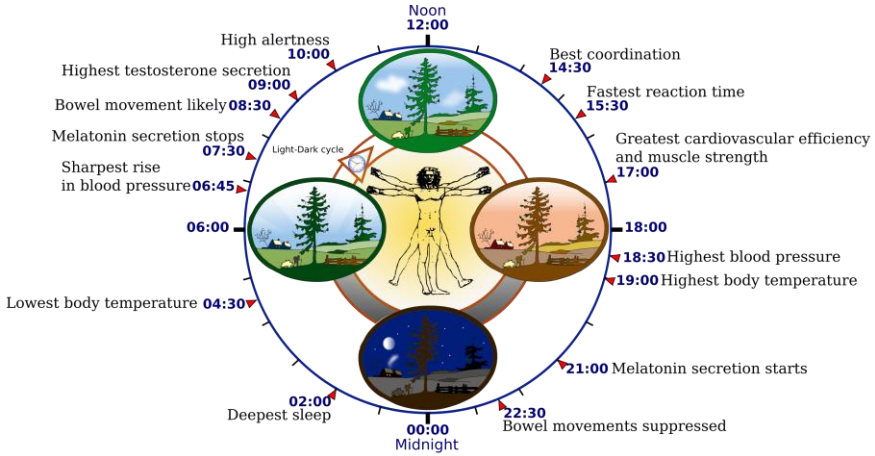


❑ Melatonin

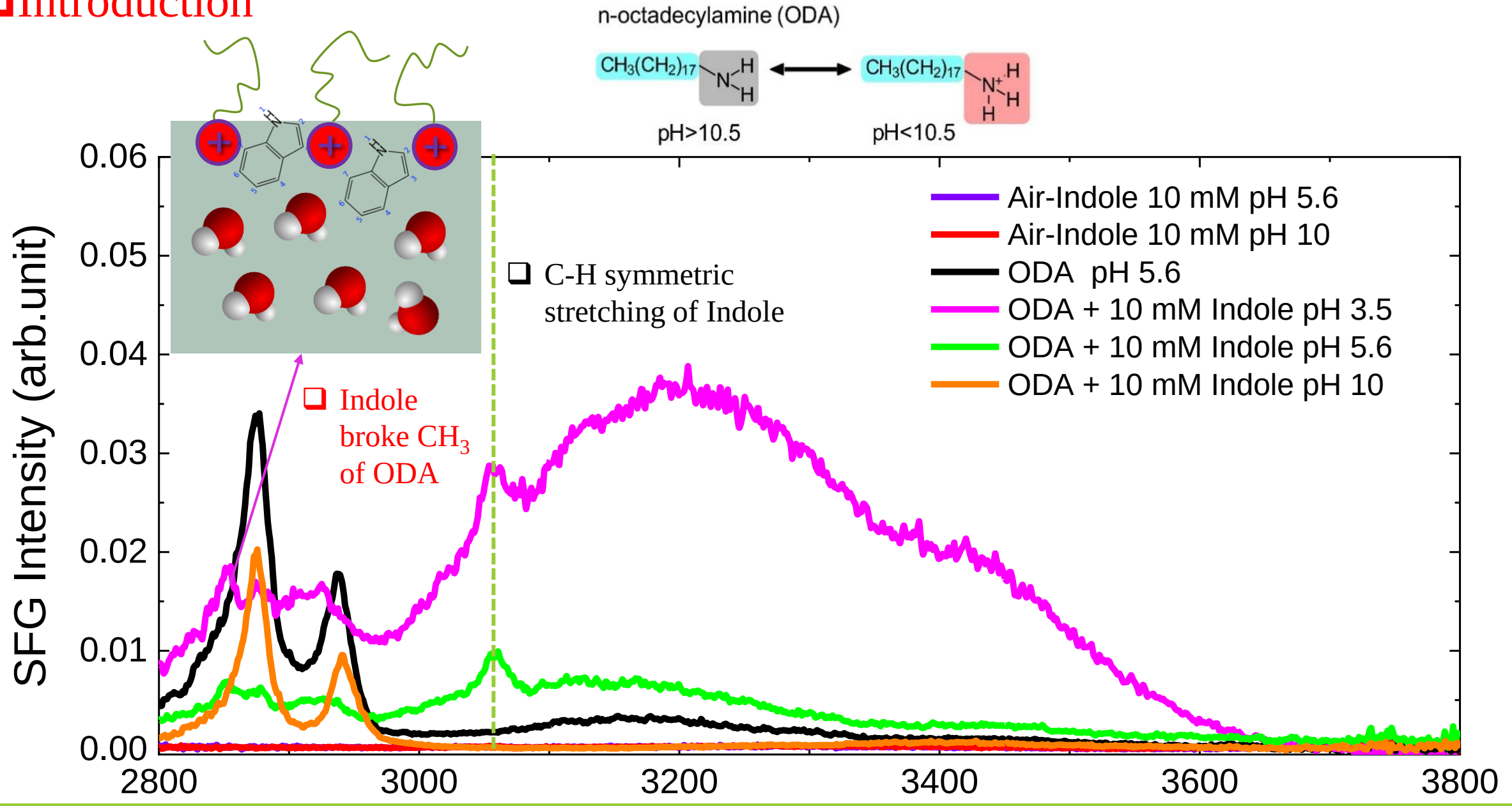


❑ Melatonin is a hormone that your body makes naturally.

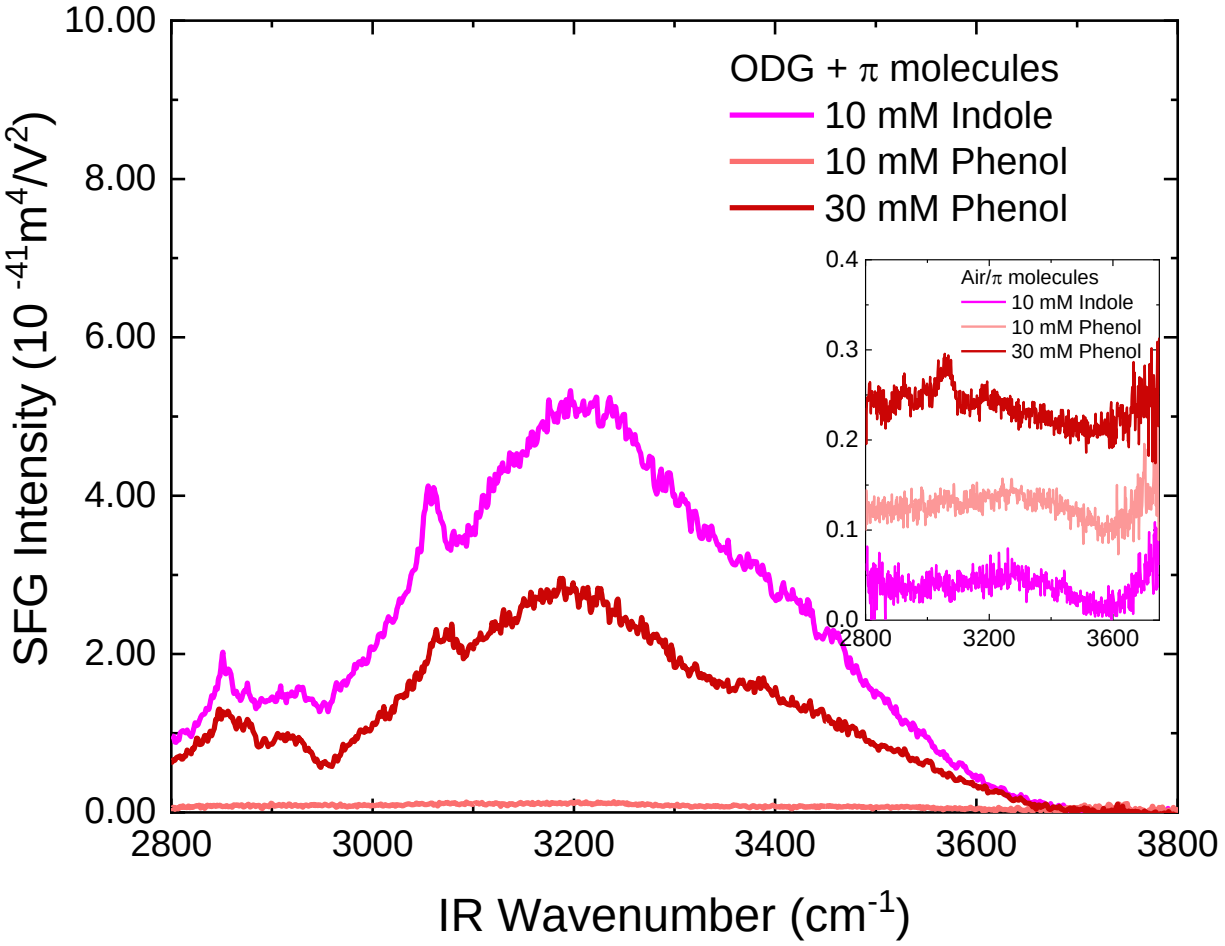
❑ Melatonin works closely with your body's circadian rhythm to help prepare you for sleep. Its levels rise at nighttime.

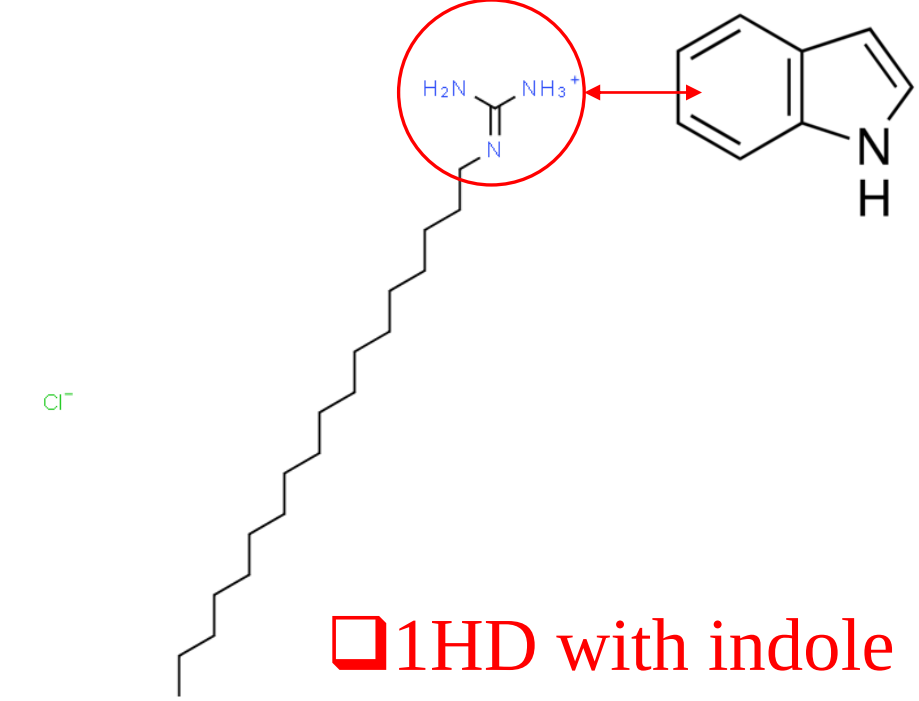


❑Introduction

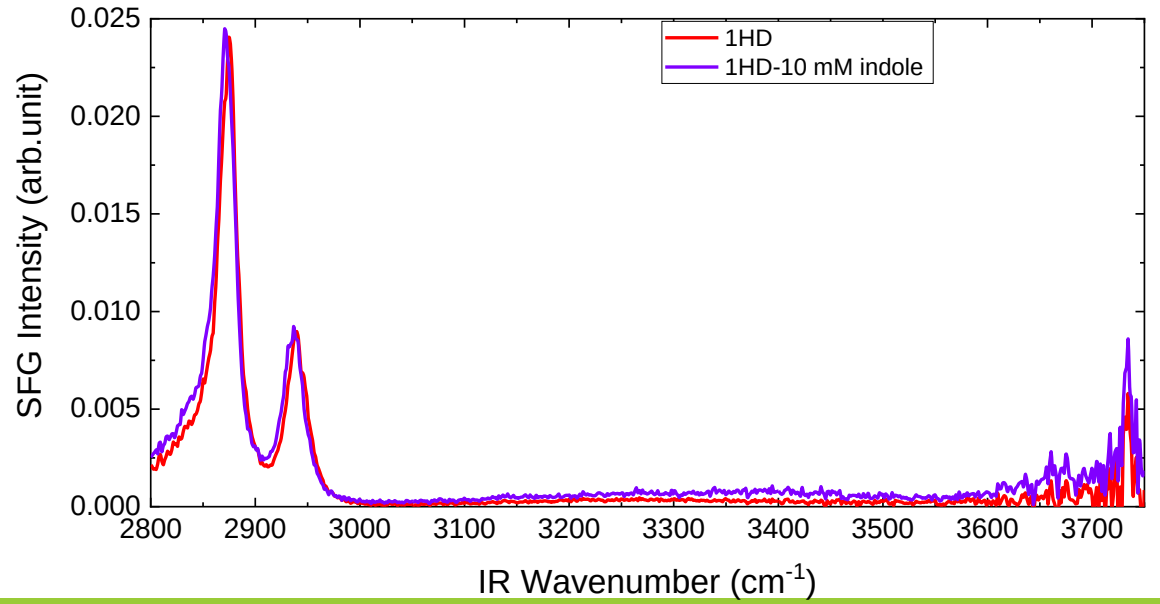


❑ODG with π molecule



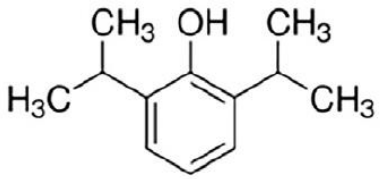


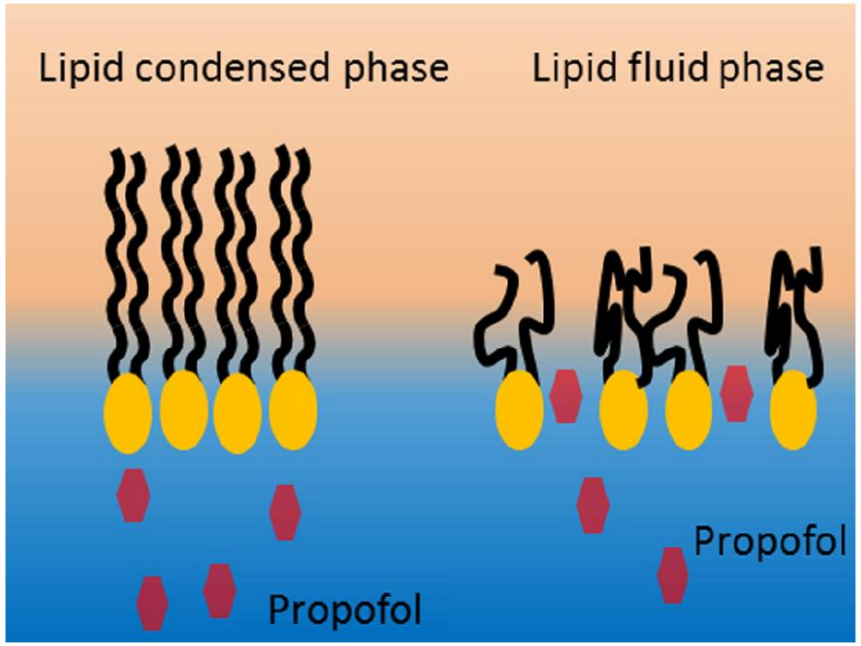
❑1HD with indole



❑Propofol

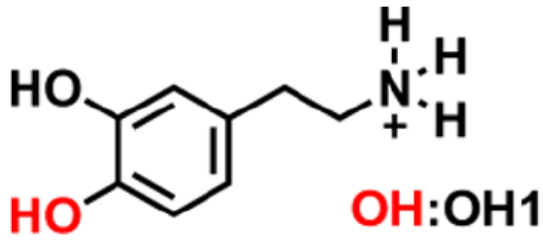
Propofol -2,6-bis(1-methylethyl)phenol

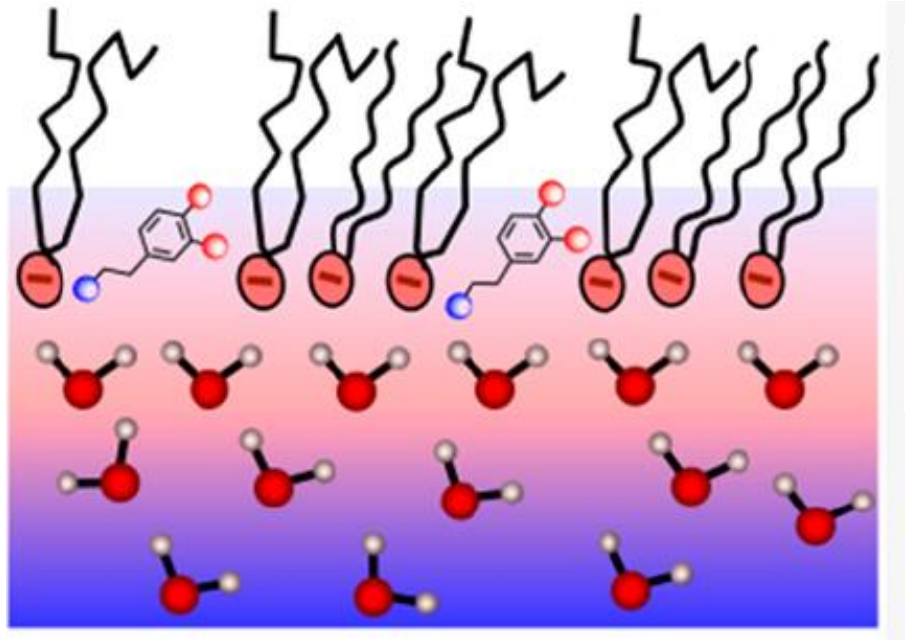




https://doi.org/10.1016/j.jcis.2018.03.052

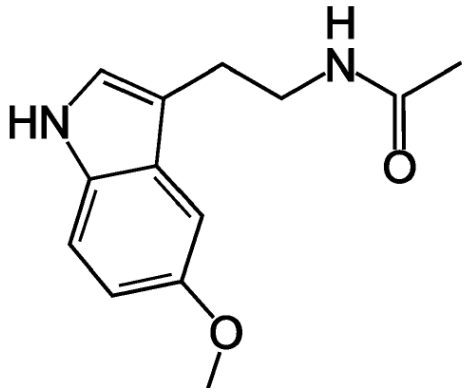
❑Dopamine

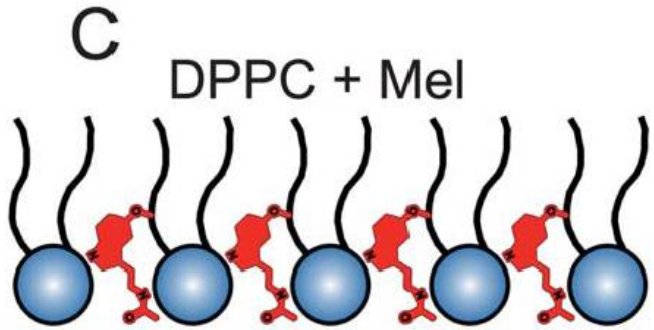


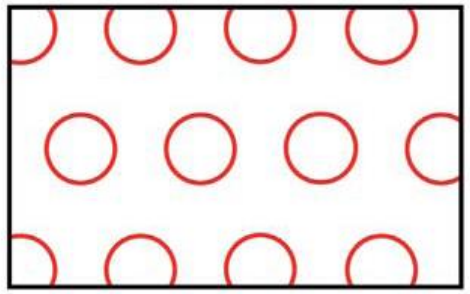


J. Phys. Chem. Lett. 2021, 12, 2871−2879

❑Melatonin







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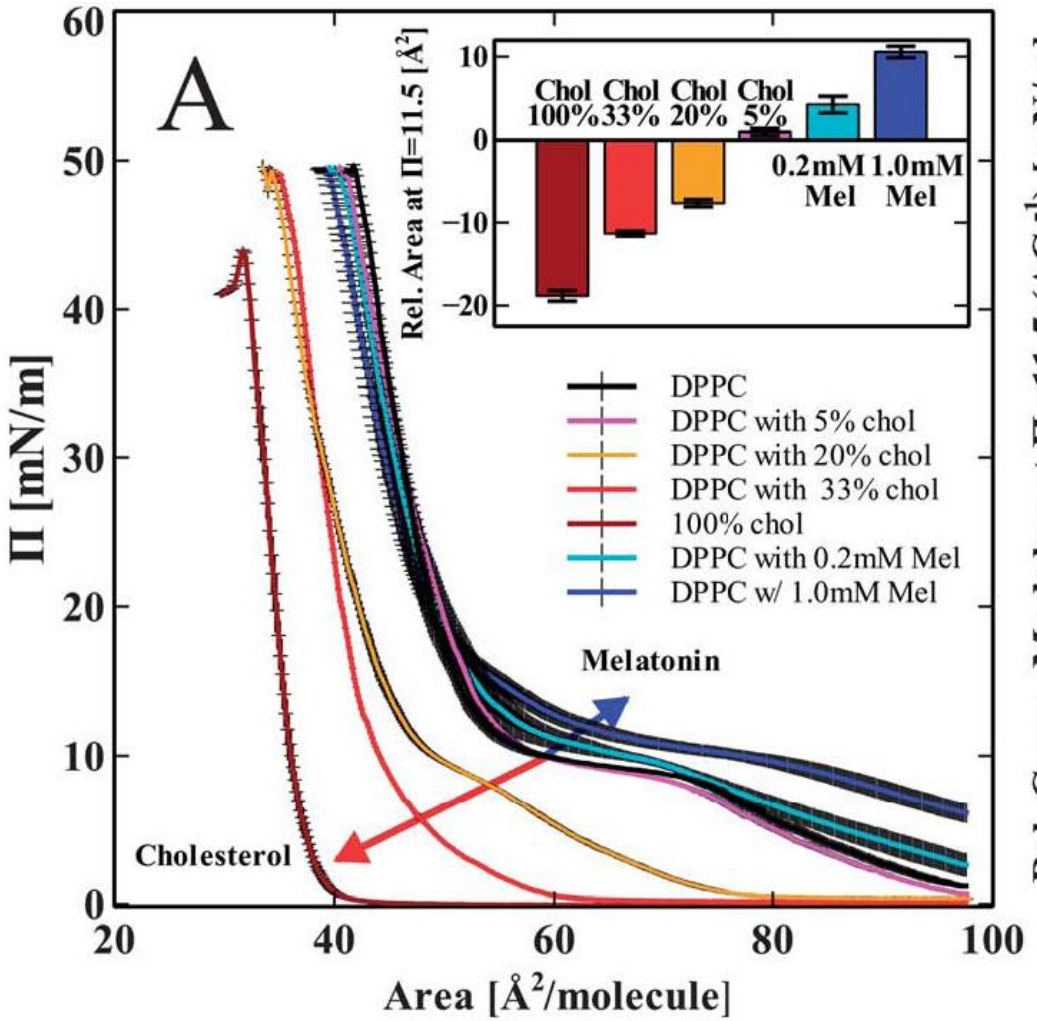
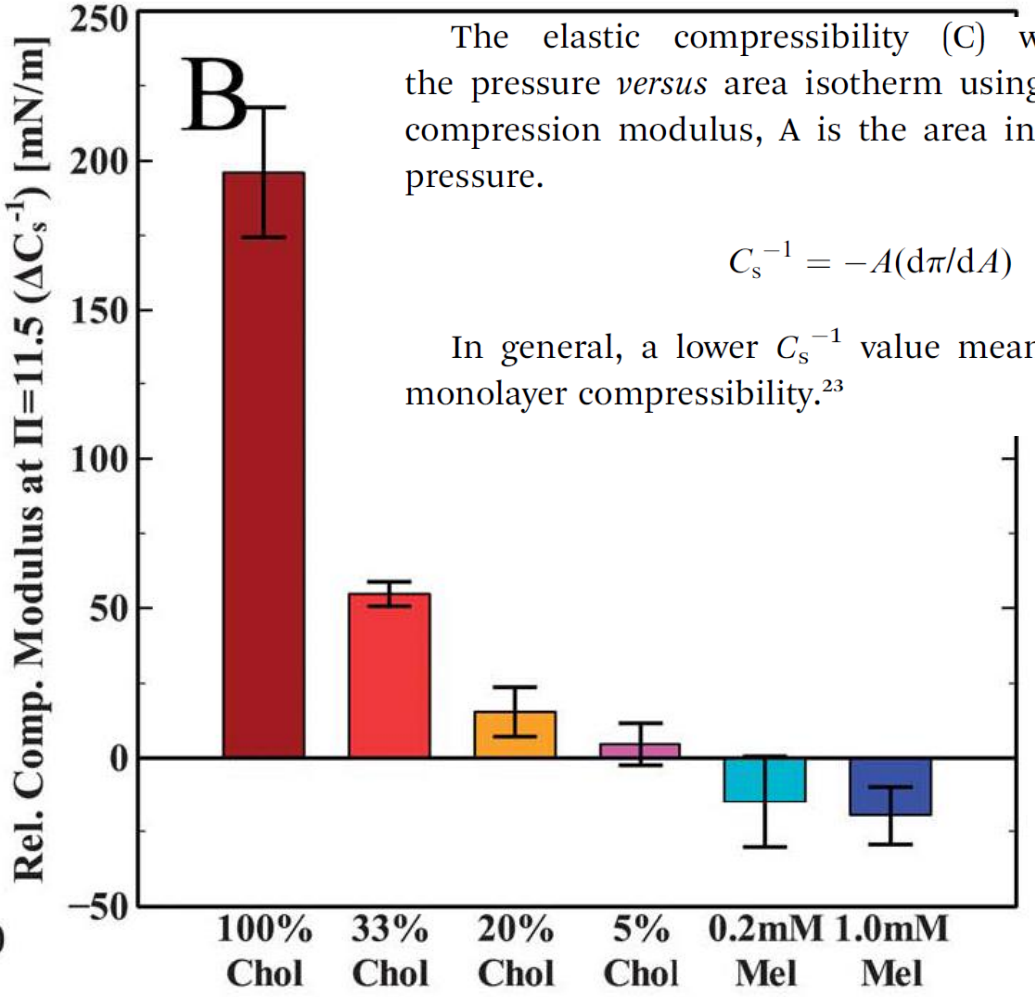
❑Opposite result between DPPC binding with melatonin and cholesterol



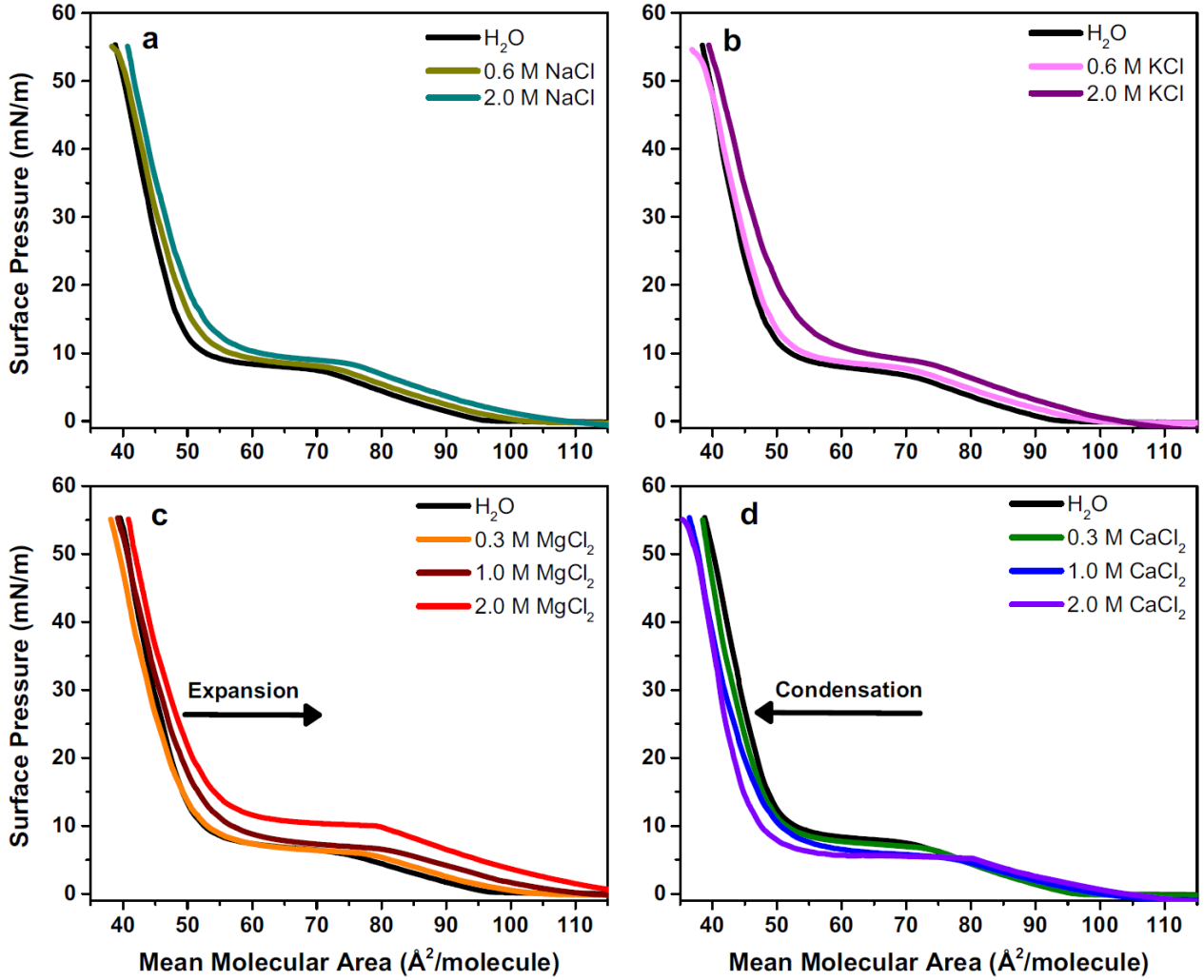


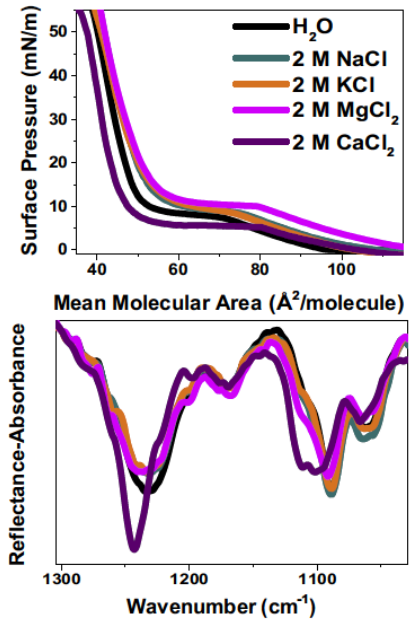
The elastic compressibility (C) was calculated from the pressure *versus* area isotherm using eqn (1). C_s^{-1} is the compression modulus, A is the area in the trough, π is the pressure.

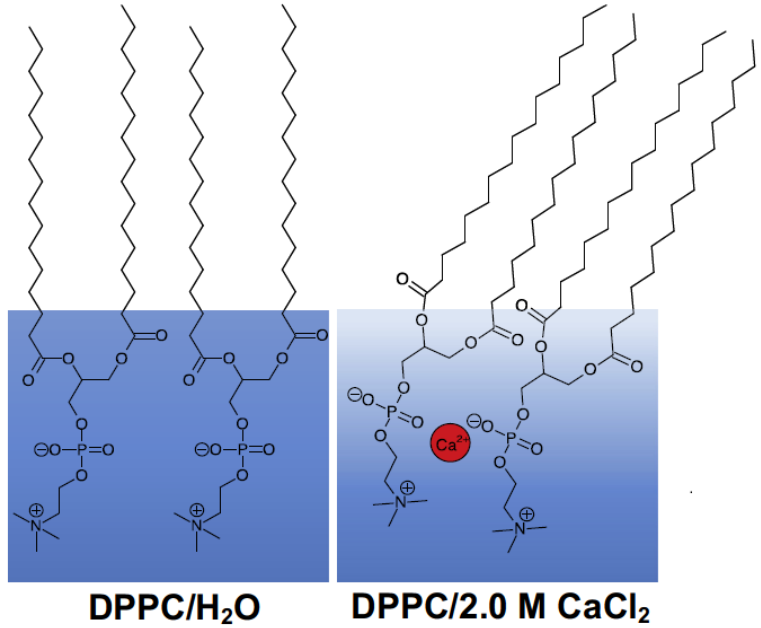
$$C_s^{-1} = -A(d\pi/dA) \quad (1)$$

In general, a lower C_s^{-1} value means an increase in the monolayer compressibility.[23]

❑DPPC binds with mono and divalent salt from Allen's group

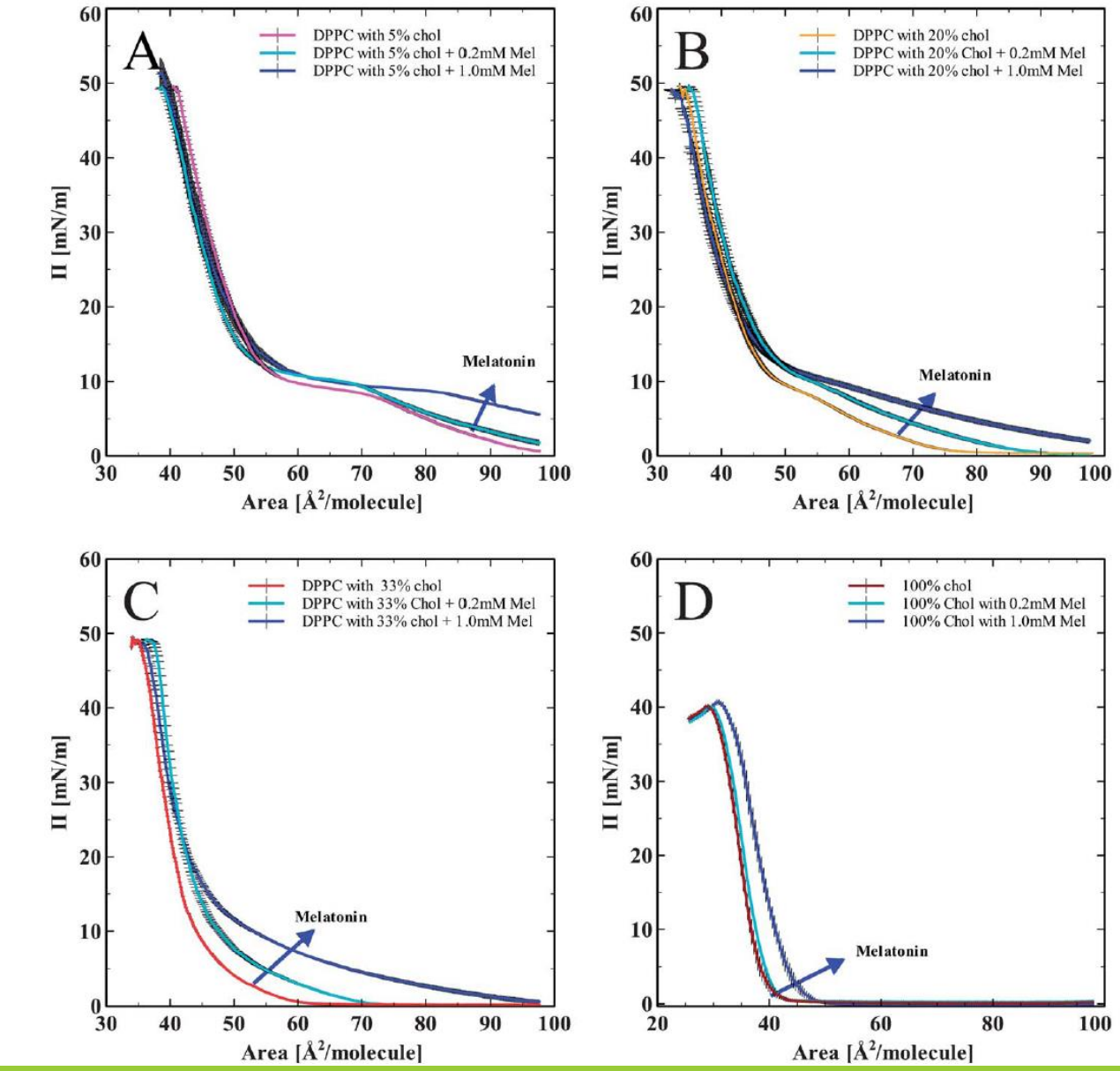






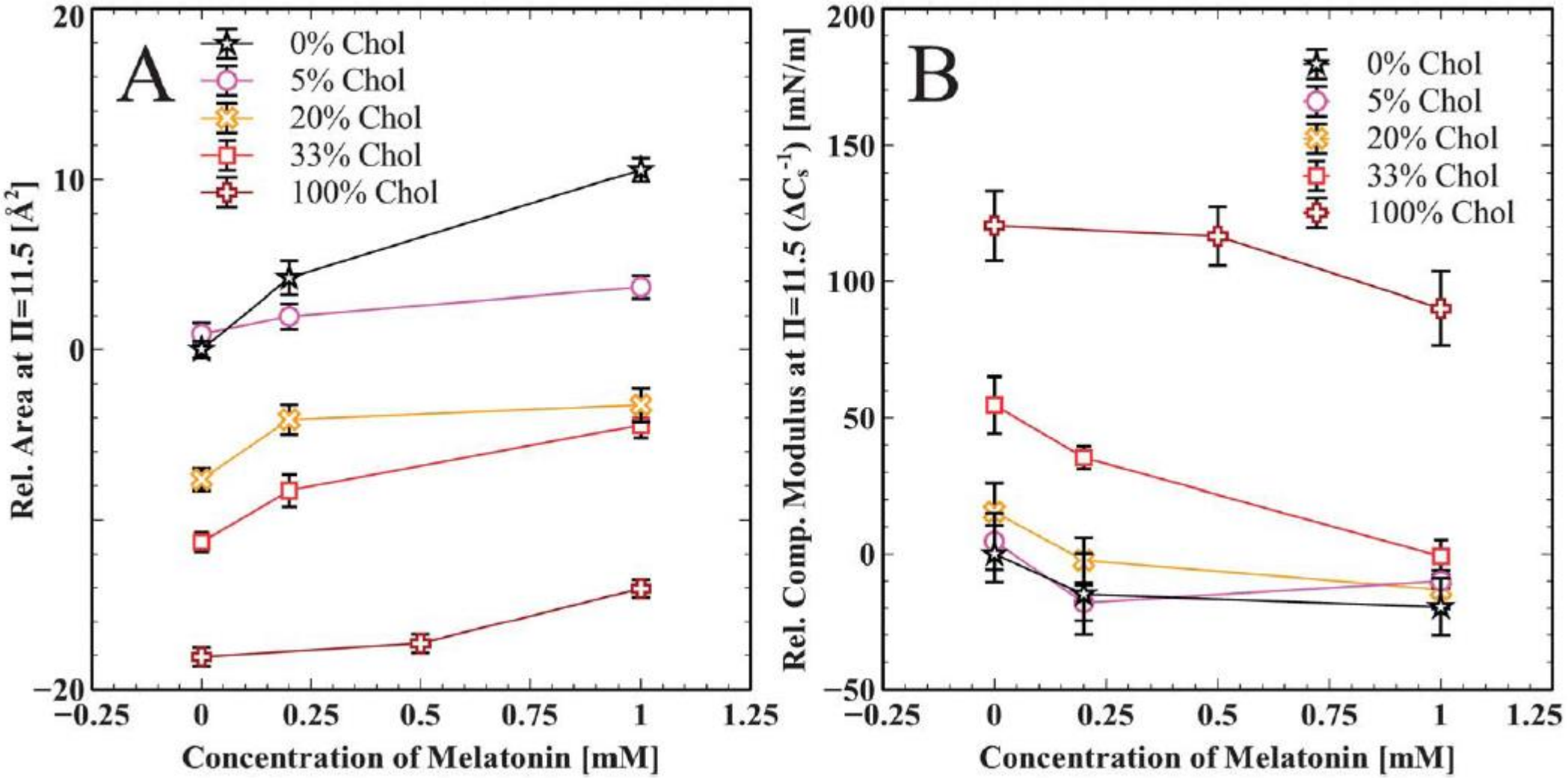
http://dx.doi.org/10.1016/j.jcis.2016.06.016

❑DPPC bind melatonin and cholesterol

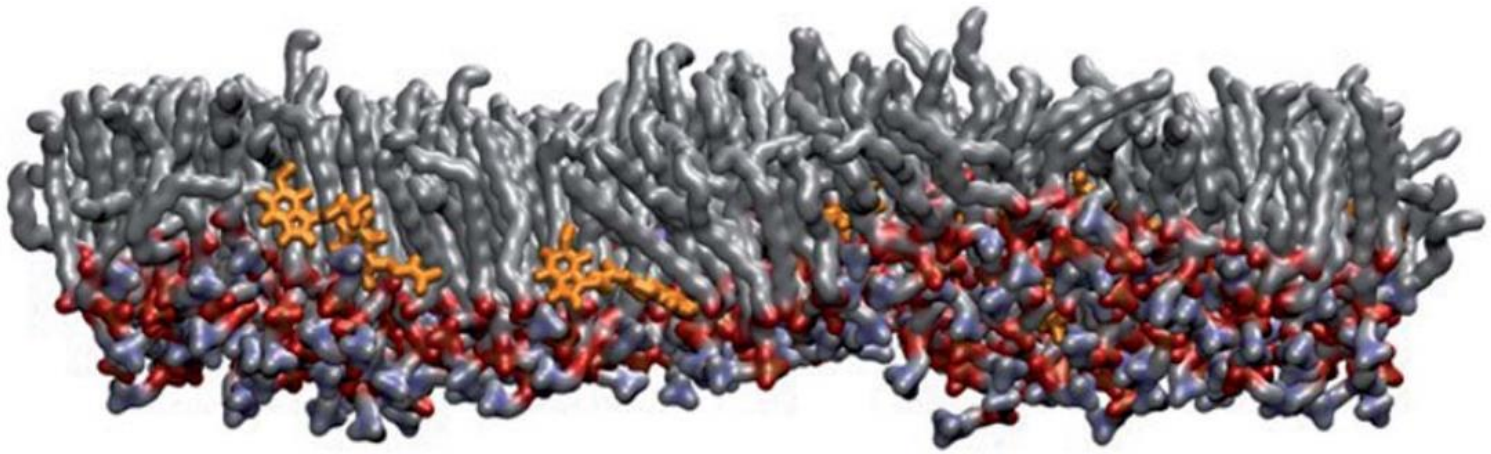


❑Melatonin has effect on both DPPC and cholesterol as seen at the increasing area

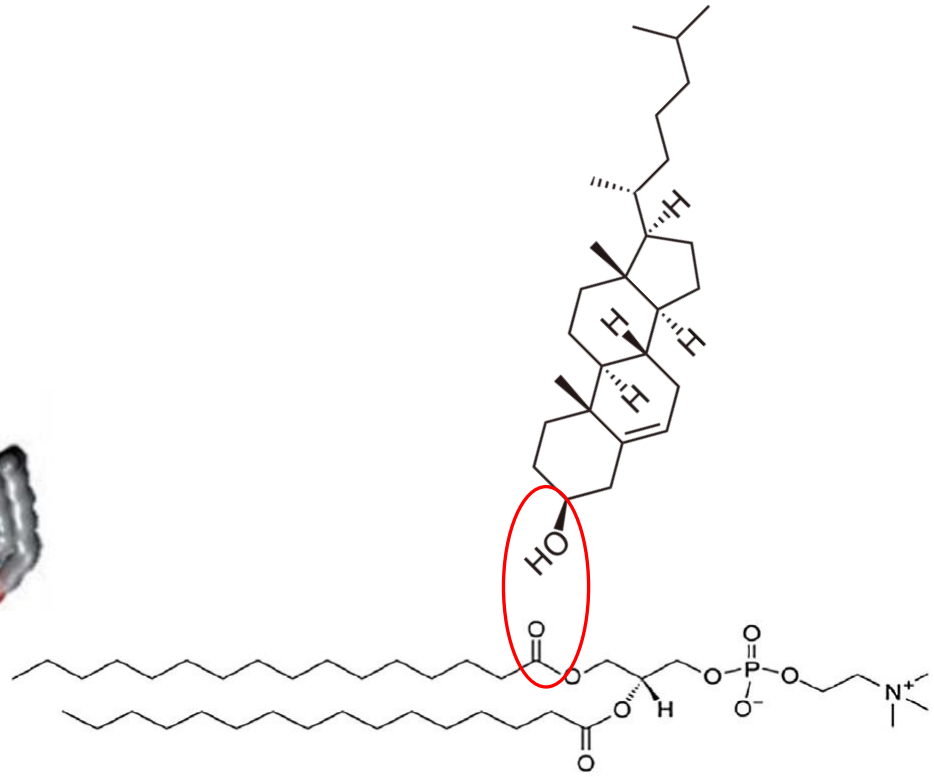
❑Summarize of melatonin effected on DPPC and Cholesterol

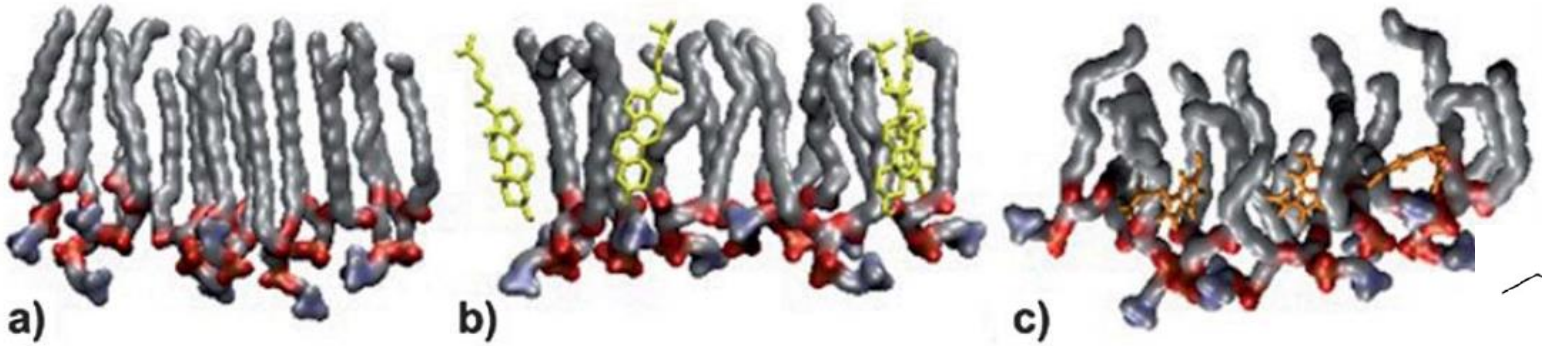


❑MD simulation schematic



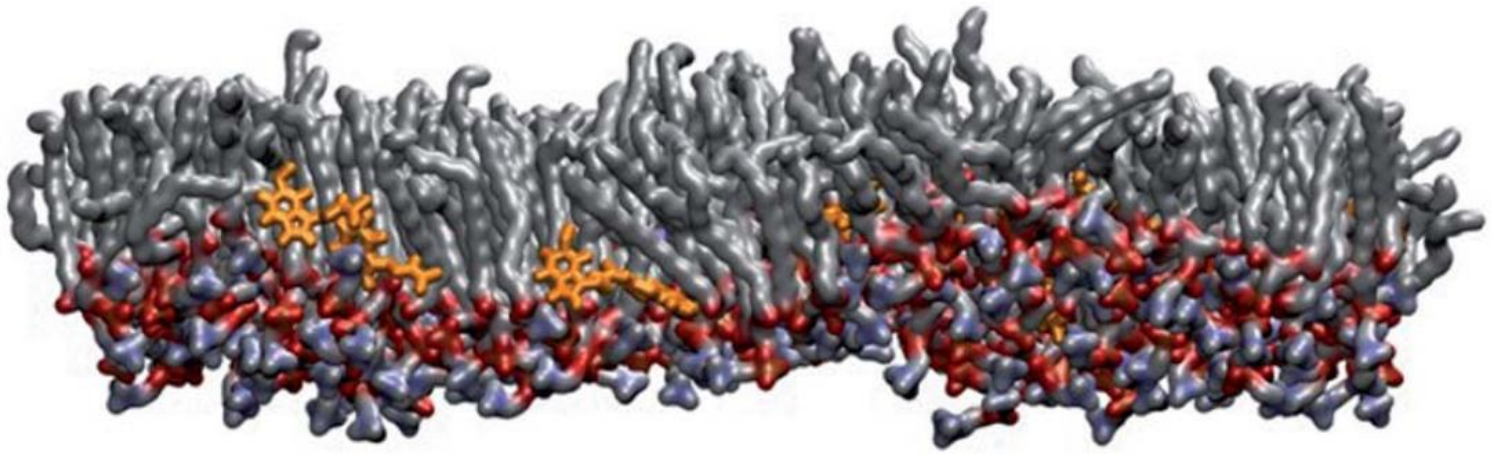
❑Hydroxyl group of cholesterol formed hydrogen bonds with the carbonyl group of DPPC



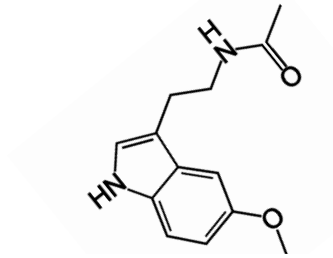


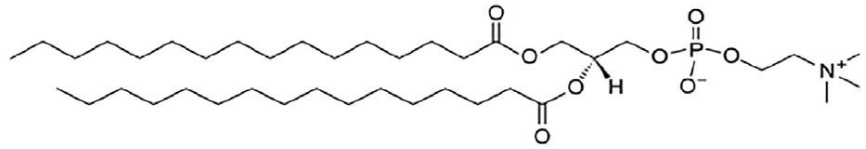
❑DPPC ❑DPPC + Cho ❑DPPC + Mel

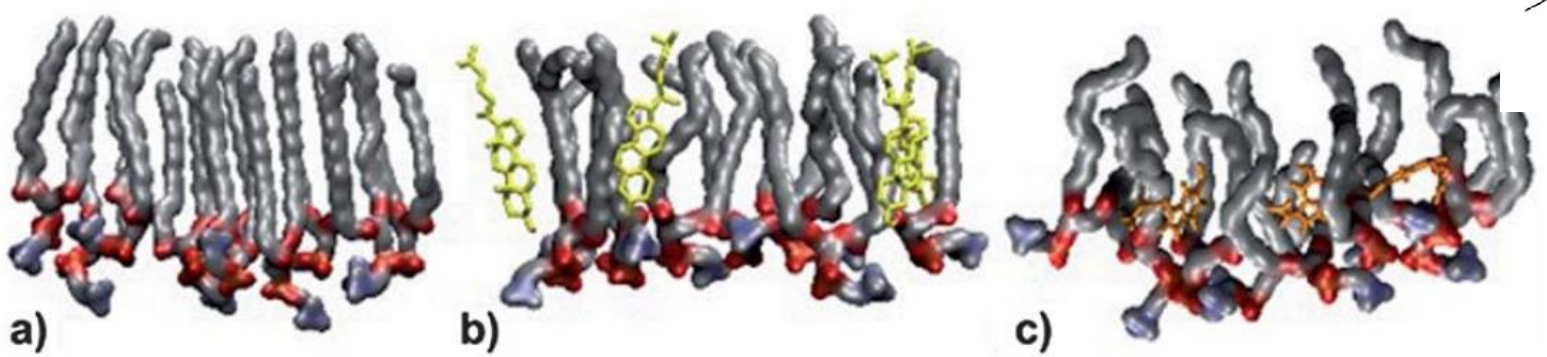
❑MD simulation schematic



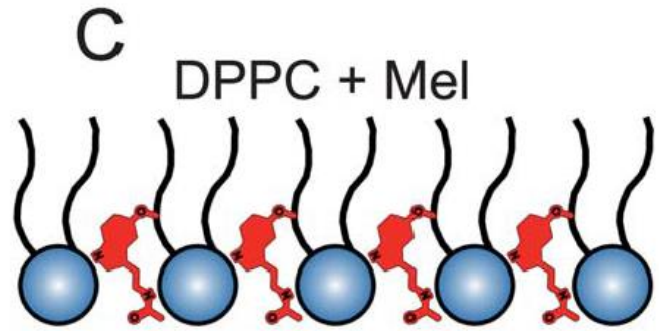
❑Indole group of the melatonin interact with acyl chain of DPPC, and also increase water molecule inside the monolayer



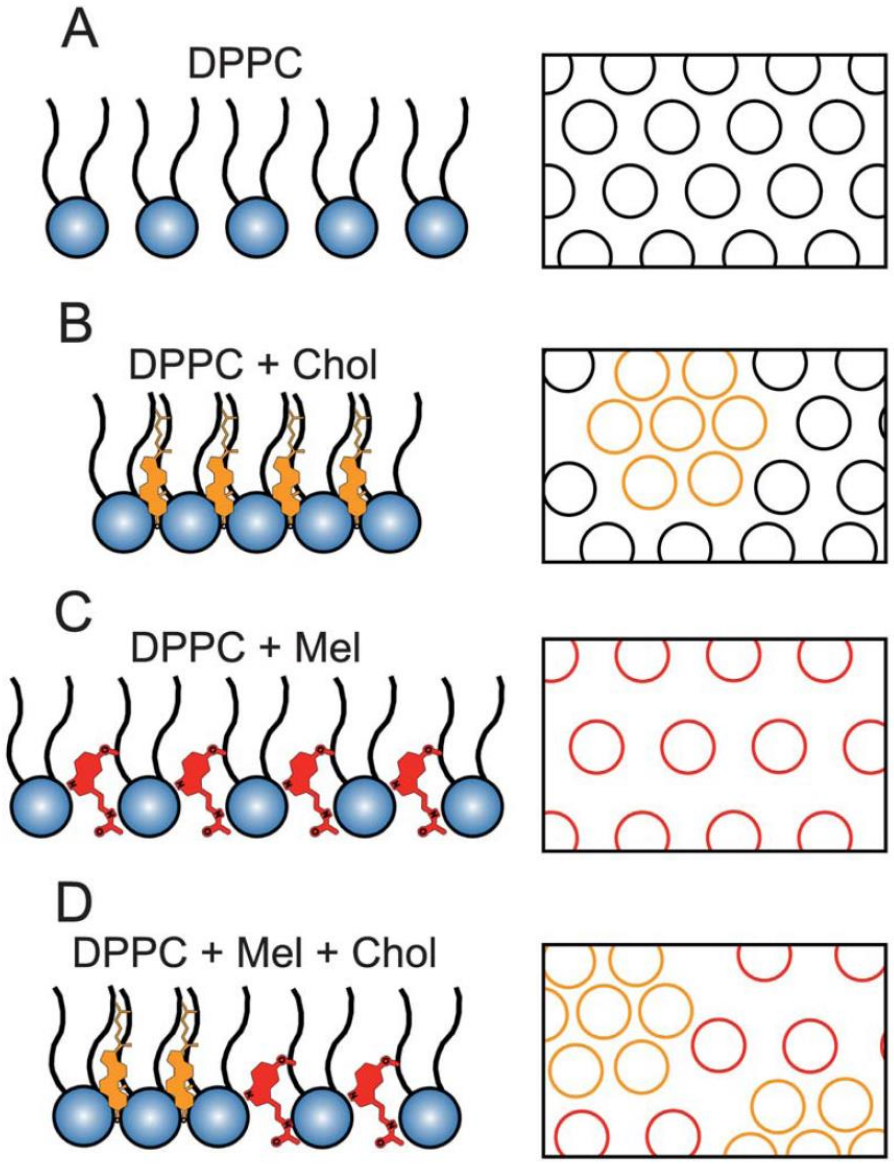




❑DPPC ❑DPPC + Cho ❑DPPC + Mel



❑Discussion and Summarizing



- ❑DPPC-melatonin has increased area which is opposite with DPPC-cholesterol
- ❑Hydroxyl group of cholesterol formed hydrogen bonds with the carbonyl group of DPPC
- ❑Indole group of the melatonin interact with acyl chain of DPPC, and also increase water molecule inside the monolayer

possible that melatonin is able to interact with both cholesterol and the phospholipids through hydrophobic interactions without necessarily strongly influencing the hydrogen bonding among the cholesterol and DPPC molecules. However, Bongiorno *et al.*[8] reported that melatonin's ability to hydrogen bond through its –NH groups is similar to the ability of cholesterol's –OH groups in lecithin reverse micelles. Thus, both the hydrophobic interaction as well as through hydrogen bonding both might be at play. In an analogous manner, hydrophobicity can

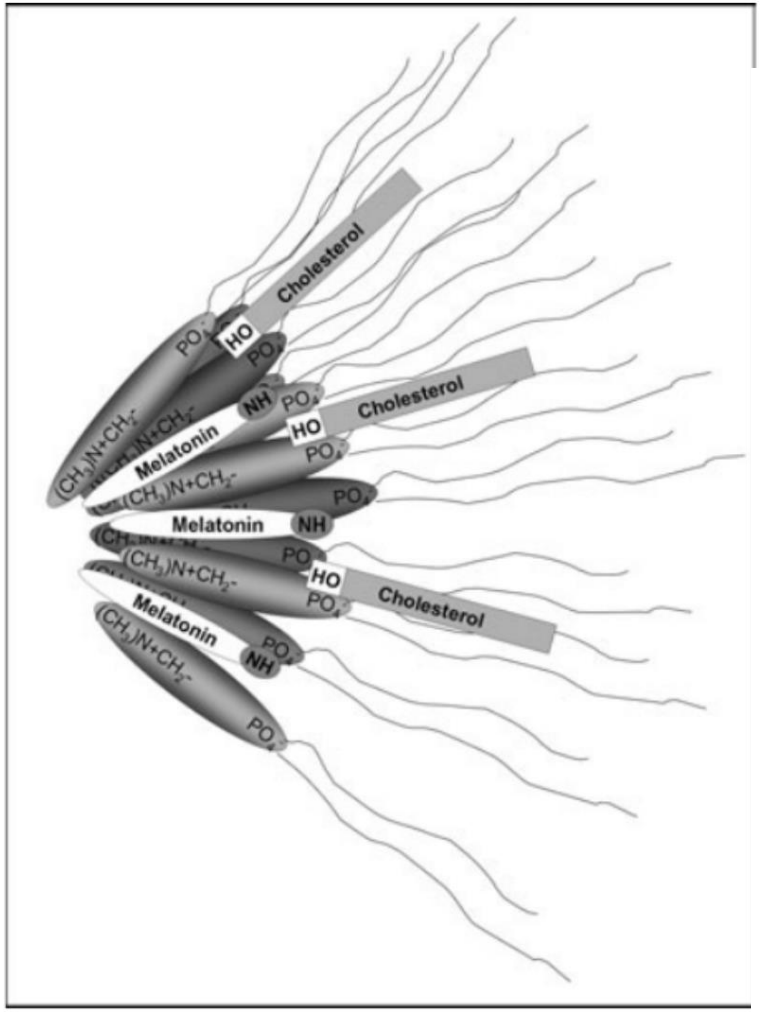
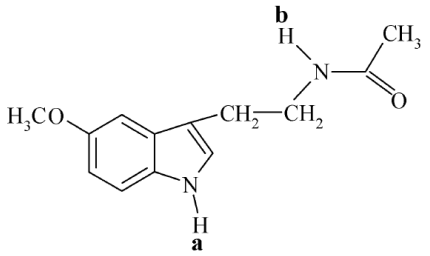
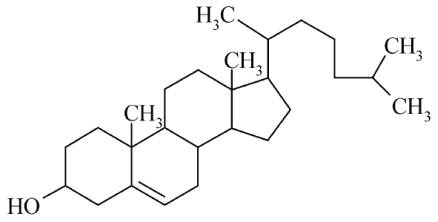


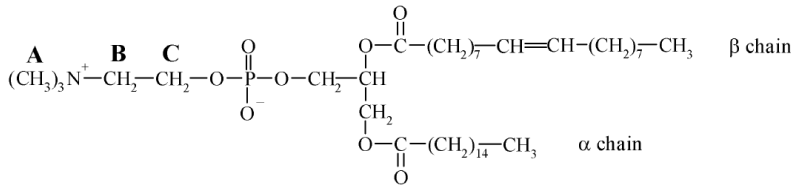
Fig. 8. Schematic representation of the localization of melatonin and CHL in anhydrous reversed micelles.



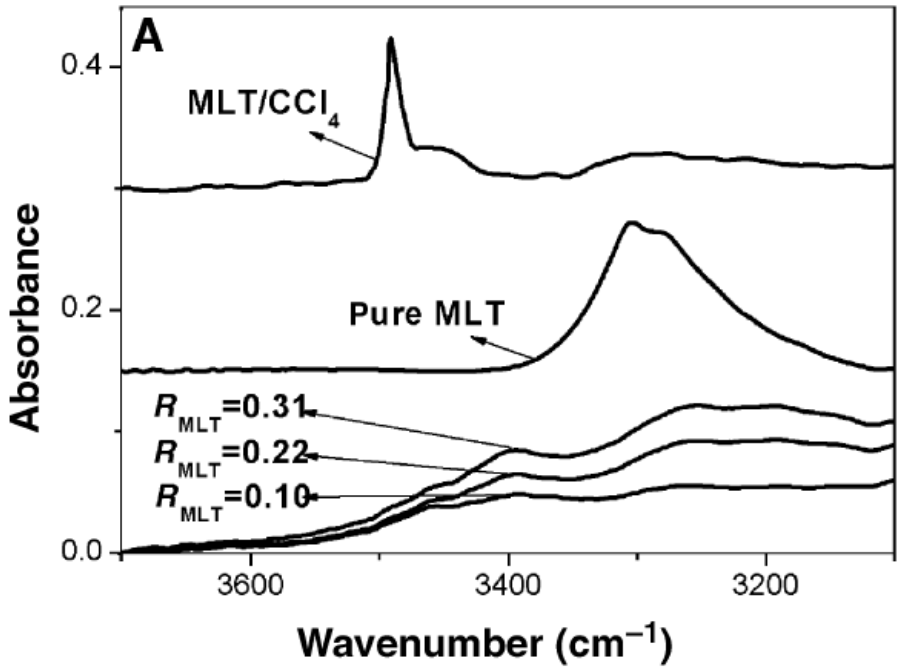
Melatonin



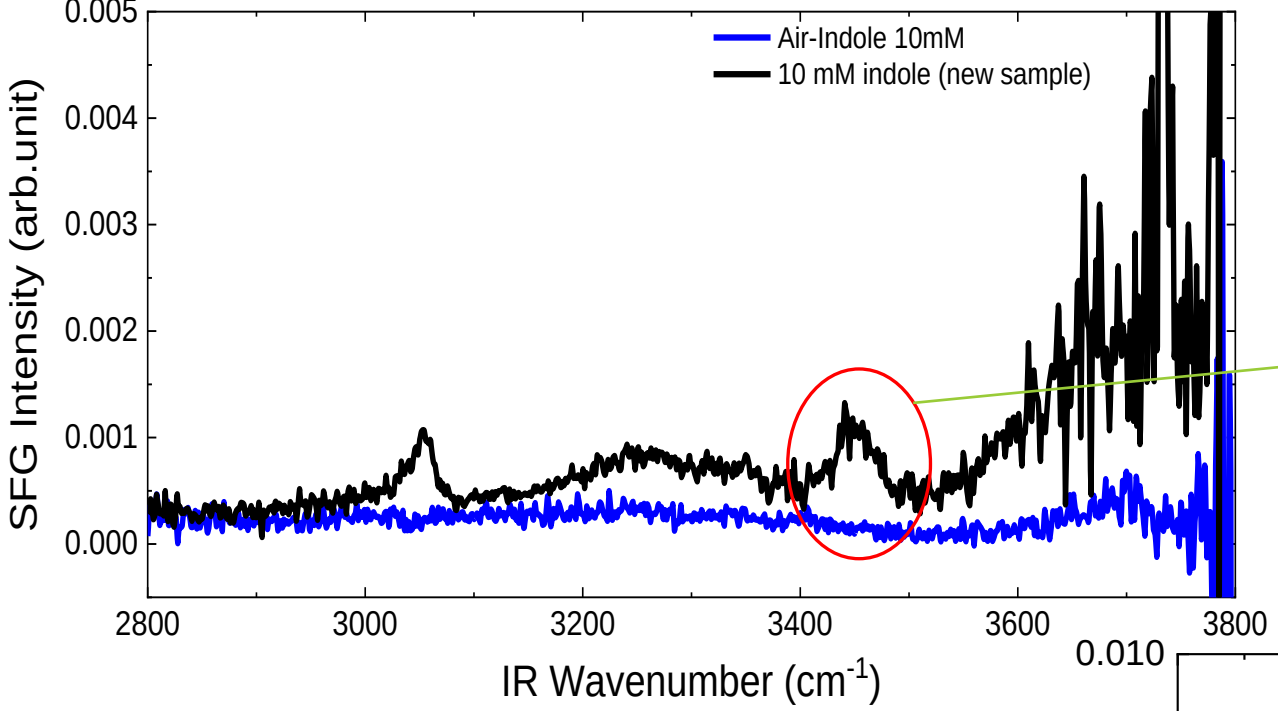
Cholesterol



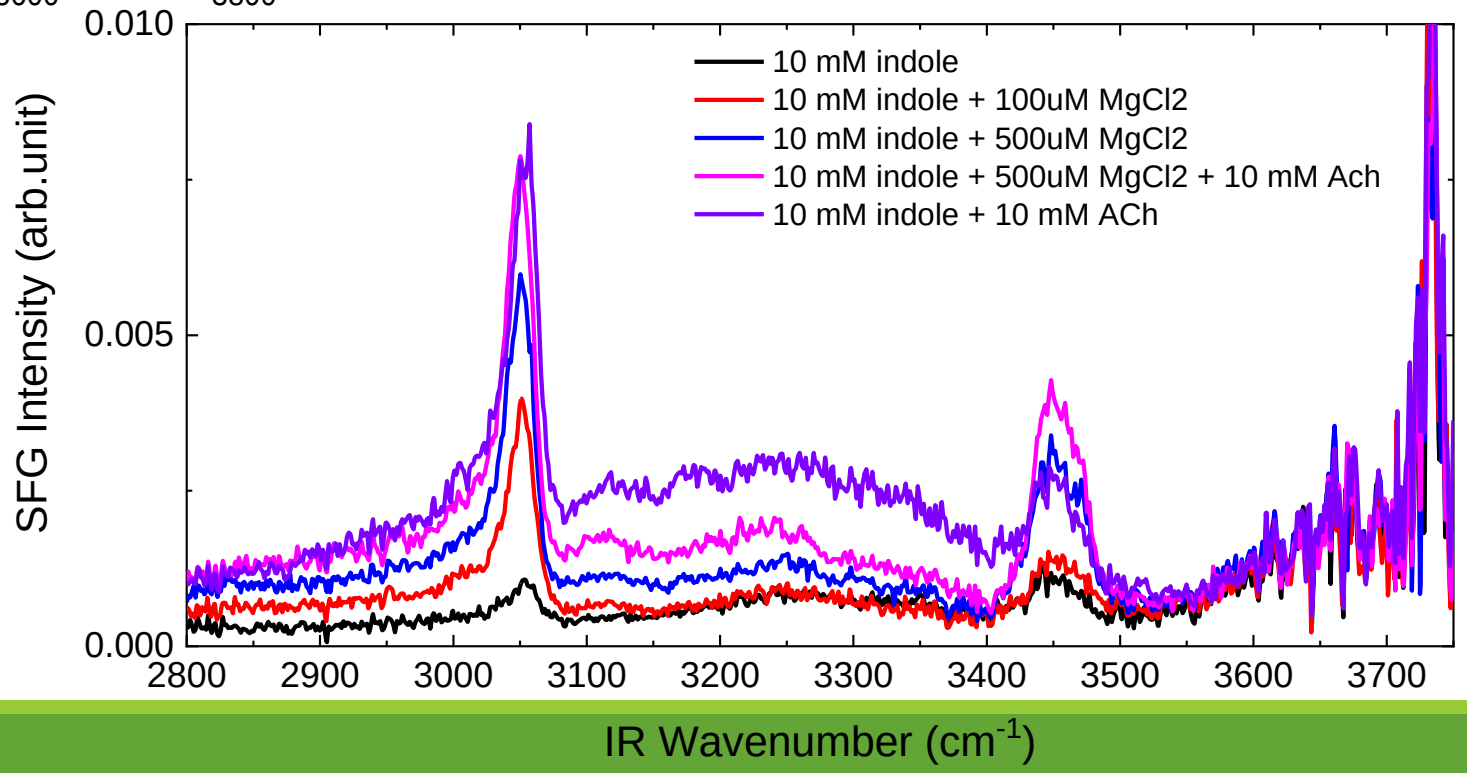
Lecithin

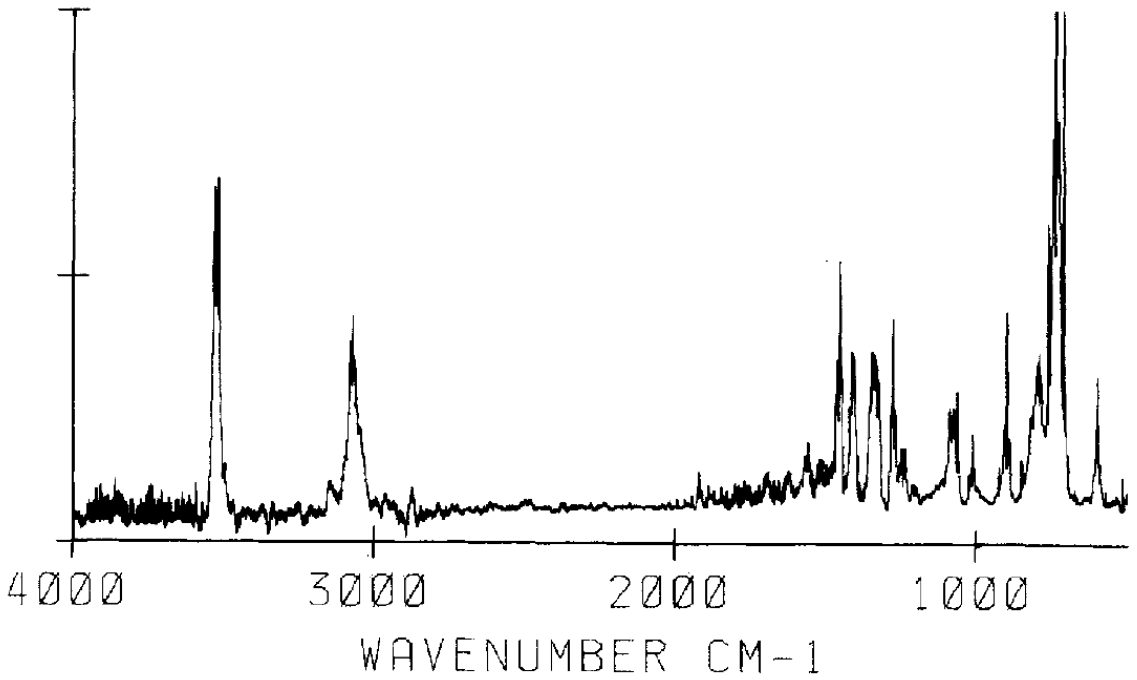


J. Pineal Res. 2005; 38:292–298



NH has peak suspect





in disagreement with the data of Table 4. Another discrepancy with the present work concerns the presence in this range of an additional fundamental at 1300 cm^{-1} corresponding to a weak band observed in both the IR and Raman spectra for liquid indole, probably suggested by AM1 force field calculations. The latter give a calculated frequency of 1310 cm^{-1} with a large calculated intensity for this mode. In solid indole, we observe a weak band (1% relative intensity) at 1303 cm^{-1} in the FT-R spectrum and a shoulder at 1302 cm^{-1} in the FT-IR spectrum. This should rather be assigned to a combination mode corresponding to a calculated frequency of 1304–1300 cm^{-1}, coupling ν_{26} with ν_{28} modes, for which both bands are strong in the Raman but weak in the IR spectrum.

High-frequency modes. These are NH and CH stretching modes. Owing to the hydrogen bonding, the frequency of the former mode exhibits a large shift from 3523.2 cm^{-1} for indole vapour to 3419 and 3398 cm^{-1} for liquid and solid indole, respectively. This corresponds to a weak hydrogen bond when compared with that of pyrazole,[26] where the ν_{NH} mode has the same frequency in the vapour phase but shifts to about 2800 cm^{-1} in solid pyrazole. On *N*-deuteration, the ν_{ND} mode shifts to 2620.0 cm^{-1} for indole vapour, whereas the calculated frequency is 2587 cm^{-1}, as obtained using a scale factor to adjust the ν_{NH} frequency to the experimental value. The deviation $\Delta\nu = 33$ cm^{-1} is mainly due to the anharmonicity of this mode. For comparison with pyrazole vapour, the ν_{ND} mode was observed at 2640 cm^{-1}, calculated at 2583 cm^{-1} ($\Delta\nu = 57$ cm^{-1}), revealing a stronger anharmonic character for its ν_{NH} mode.

In the case of CH stretching modes, six modes are expected for two pyrrolic and four benzenic CH bonds. Two bands were previously observed[1] at 3123 and 3106

Vibrational Spectra of Indole and Assignments on the Basis of *Ab* `Znitio` Force Fields

Table 4. Observed and calculated frequencies (cm^{-1}) for indole

Mode	Solid[a]	Liquid[b]	Vapour[c]	Calculated[d]			Potential energy distributions[e]			
ν_1	3398 s, 1	3419 s, –	3523.2 sB	3523, I	99, R	5	99NH			
ν_2	3122 –, 16	3123 s, –	3117.8 vwB	3131, I	7, R	12	$+61C_2H$	$+38C_3H$		
ν_3	3101 –, 4	3106 s, –	—	3107, I	1, R	6	$-62C_3H$	$+38C_2H$		
ν_4	3062 –, 34	3050 –	3071.7 sA	3063, I	20, R	23	$+38C_6H$	$+33C_7H$	$+14C_8H$	$+13C_5H$
ν_5	3047 w, –	3050 –	3050.7 mB	3051, I	30, R	4	$-40C_8H$	$+27C_5H$	$+19C_6H$	$-14C_7H$
ν_6	3055 –, 34	3050 –	—	3040, I	4, R	11	$+41C_5H$	$+31C_8H$	$-17C_7H$	$-11C_6H$
ν_7	3024 –, 2	3050 –	—	3032, I	0, R	3	$+35C_7H$	$-33C_6H$	$+18C_5H$	$-15C_8H$

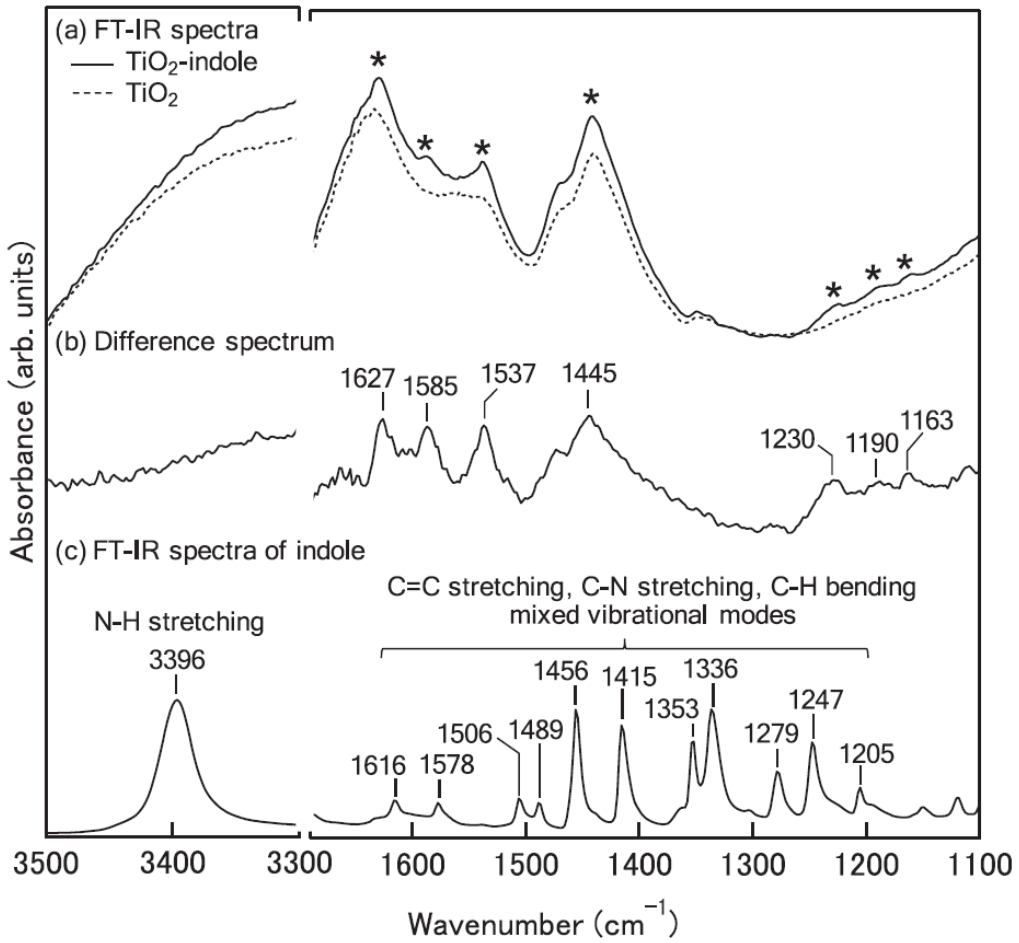


Fig. 3. (a) FT-IR spectra of TiO_2 (dashed curve) and TiO_2-indole (solid curve), (b) difference spectrum between TiO_2 and TiO_2-indole, and (c) FT-IR spectrum of indole.

https://doi.org/10.1016/j.cplett.2019.136974