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ADVANCED MATERIALS

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# Insight into the Behavior of Fluorescent Probes in Lipid Membranes by Molecular Dynamics Simulations

*by*

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In lipid membrane studies, visualization and characterization of membrane domains are important but non-trivial tasks. For studying membrane phases, a diphenylhexatriene (DPH) probe is often used. DPH partitions in both liquid-disordered (Ld, Lα) and liquid-ordered (Lo) phases, but its spectroscopic properties in these phases differ and therefore could be used for phase recognition. Making use of the fluorescence anisotropy decay, the behavior of DPH in lipid membranes was initially described by a wobbling in a cone model,[1] while later several other models were proposed to estimate the orientational distribution. We used molecular dynamics (MD) simulations in order to analyze the orientational distribution of DPH in different lipid phases and to model the anisotropy decay by a rotational autocorrelation function of the transition dipole moment. We calculated the second and fourth order Legendre polynoms $\langle P_2 \rangle$ and $\langle P_4 \rangle$ and showed that the orientational distribution is nearly fully described by these two order parameters. Further, we used the so-called general model[2,3] to fit the rotational autocorrelation function and extracted the $\langle P_2 \rangle$ and $\langle P_4 \rangle$. As an overestimation of $\langle P_2 \rangle$ and $\langle P_4 \rangle$ by the general model has been seen, we suggested a rescaling that leads to a significant improvement of the prediction for the orientational distribution.

Unlike DPH, DiD's transition dipole moment is oriented parallel to the membrane plane.[4] We studied DiD derivatives in lipid membranes of different phases and focused on compounds with acyl tails of varying lengths. The position, orientation and dynamics of these compounds were studied in the membrane as they determine the photoselection. The fluorescence anisotropy decay has been modelled as well. However, the models initially used for DPH, cannot be straightforwardly applied to the DiD family, as the latter expresses intrinsic differences in orientation and behavior with respect to the role model of DPH.

Continuing our work on the DiD compounds, we focused on the ability of DiD to photoisomerize. We parameterized the cyanine backbone both in the ground state (GS) and first excited state (ES). We simulated the excitation and relaxation events and evaluated the isomerization of trans and cis isomers, considering also DiD compounds with different tail lengths. In the ES, the backbones of the individual DiD molecules rotate quickly to a twisted state both in a DMSO solution and in a DOPC membrane. Furthermore, it has been seen that the shorter tails, which consist out of either one or three carbon atoms, rearrange themselves quite easily, in contrast to the longer tails with 18 carbon atoms. The dyes which have rather short tails bear a significant fraction of emerging cis states. For the DiD compound which has two tails of 18 carbon atoms, however, all frames are seen to return back to the trans state, which can be seen as a consequence of the hydrophobicity of these tails. In DMSO, the photoisomerization is not hindered by the ordered membrane structure and we observe a minor contribution of the cis state formed for all studied dyes, including the one with two tails of 18 carbon atoms. In line with previous studies on fluorophores with a flexible cyanine backbone,[5] we also report the presence of a dark twisted state for DiD. In our simulations, we focused on identifying the involved dihedral angle and generally on the description of the mechanism of the photoisomerization of this conformationally versatile probe
in lipid membranes.

**Selected Publications**

(1) Kinosita, K.; Kawato, S.; Ikegami, A. Biophys. J. **1977**, 20 (3), 289–305.
(2) Ameloot, M.; Hendrickx, H.; Herreman, W.; Pottel, H.; Van Cauwelaert, F.; van der Meer, W. Biophys. J. **1984**, 46 (4), 525–539.
(3) van der Meer, W.; Pottel, H.; Herreman, W.; Ameloot, M.; Hendrickx, H.; Schröder, H. Biophys. J. **1984**, 46 (4), 515–523.
(4) Knippenberg, S.; Fabre, G.; Osella, S.; Di Meo, F.; Paloncýová, M.; Ameloot, M.; Trouillas, P. Langmuir **2018**, 34 (30), 9072– 9084.
(5) Widengren, J.; Schwille, P. J. Phys. Chem. A **2000**, 104 (27), 6416–6428.

**Chaired by:**
**Dr. Stefan Knippenberg**