Flip-Flop of Steroids in Phospholipid Bilayers: Effects of the Chemical Structure on Transbilayer Diffusion

The transverse motion of molecules from one leaflet to the other of a lipid bilayer, or flip-flop, represents a putative mechanism for their transmembrane transport and may contribute to the asymmetric distribution of components in biomembranes. However, a clear understanding of this process is still missing. The scarce knowledge derives from the difficulty of experimental determination. Because of its slow rate on the molecular time scale, flip-flop is challenging also for computational techniques. Here, we report a study of the passive transbilayer diffusion of steroids, based on a kinetic model derived from the analysis of their free energy surface, as a function of their position and orientation in the bilayer. An implicit membrane description is used, where the anisotropy and the nonuniformity of the bilayer environment are taken into account in terms of the gradients of density, dielectric permittivity, acyl chain order parameters, and lateral pressure. The flip-flop rates are determined by solving the Master Equation that governs the time evolution of the system, with transition rates between free energy minima evaluated according to the Kramers theory. Considering various steroids (cholesterol, lanosterol, ketosterone, 5-cholesten, 25-hydroxycholesterol, and testosterone), we can discuss how differences in molecular shape and polarity affect the pathway and the rate of flip-flop in a liquid crystalline 1,2-dipalmitoyl-sn-glycero-3-phosphatidylcholine (DPPC) bilayer, at low steroid concentration. We predict time scales ranging from microseconds to milliseconds, strongly affected by the presence of polar substituents and by their position in the molecular skeleton.

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