A Steroid in a Lipid Bilayer: Localization, Orientation, and Energetics

Ranjit Vijayan,*[†] and Philip C. Biggin*

* Department of Biochemistry, University of Oxford, South Parks Road, Oxford OX1 3QU, UK; [†] Life Sciences Interface Doctoral Training Centre, University of Oxford, Parks Road, Oxford OX1 3QD, UK

UMBRELLA SAMPLING SIMULATIONS

All simulations were performed and analysed using the GROMACS version 3.2.1 suite of tools (1) using the GROMOS 43a1 forcefield (2). The topology of a cortisone molecule was generated using PRODRG (3) and partial charges determined in Spartan'02 (4) using semi-empirical AM1 calculations. For the umbrella sampling simulations the reaction coordinate was chosen as the bilayer normal with independent simulations run at 61 windows located 1 Å apart. An umbrella potential using a force constant of 5000 kJ mol^{-1} nm^{-2} (11.95 kcal mol^{-1} Å^2) was applied to the center of mass of the fused-ring cortisone molecule. The simulation box consisted of 128 POPC molecules, 7123 SPC water molecules and one cortisone molecule. Periodic boundary conditions were used and the system coupled to a bath at 300 K and 1 atm pressure using the Berendsen algorithm (5). Particle Mesh Ewald (6) method with a real-space cutoff of 10 Å was used for the electrostatics. To gently introduce the cortisone molecule into the system, at each window, a slow-growth approach was used to transform a non-interacting molecule to a fully-interacting molecule over a period of 0.5 ns. Production simulations were run for 25 ns/window of which the last 5 ns was used for generating a potential of mean force (PMF) profile using the weighted histogram analysis method (WHAM) (7) using Alan Grossfield's implementation of WHAM (http://membrane.urmc.rochester.edu/wham/).

IMAGES

Images were generated using PyMOL (8) and VMD (9) using the Tachyon ray tracer (10).

FIGURES
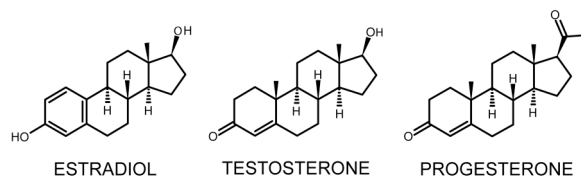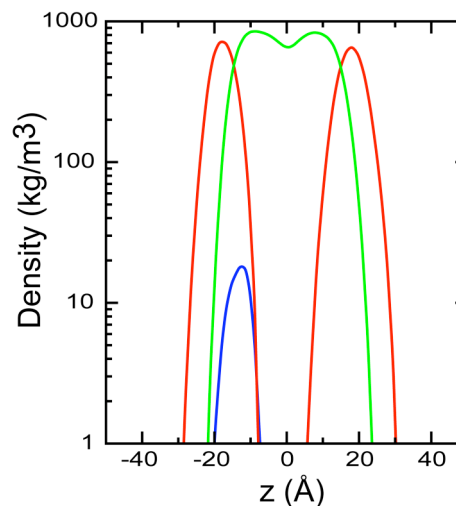

FIGURE 1 Structure of steroid hormones estradiol, testosterone and progesterone. These hormones have a tail that is not as polar as cortisone.

FIGURE 2 Partial densities of the second cortisone molecule, which spontaneously inserts into the lower leaflet of the bilayer at ~20 ns, lipid headgroup and tailgroup.

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