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# Dynamical and structural properties of charged and uncharged lidocaine in a lipid bilayer

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**Abstract**

Molecular dynamics computer simulations have been performed to investigate dynamical and structural properties of a lidocaine local anesthetic. Both charged and uncharged forms of the lidocaine molecule were investigated. Properties such as membrane area per lipid, diffusion, mass density, bilayer penetration and order parameters have been examined. An analysis of the lidocaine interaction with the lipid surrounding according to a simple mean field theory has also been performed. Almost all examined properties were found to depend on which of the two forms of lidocaine, charged or uncharged, is studied. The overall picture is a rather static behavior determined by the lipids for the charged molecules and more mobile situation of the uncharged form with higher diffusion and lower orientational and positional order.


*Keywords:* Lidocaine; Lipid membrane; Molecular dynamics

## 1. Introduction

Lidocaine-family drugs are widely used as local anesthetics in medical treatment to prevent or relieve pain. The anesthetic action of lidocaine is based on its ability to block $Na^+$ voltage-gated ion channels in the nervous system [1–3]. The specific molecular mechanism of this action is still poorly understood. This effect is often ascribed to a direct binding of lidocaine to $Na^+$ channel [4–6]. Significant amount of evidence has been also presented for the influence of lidocaine on membrane properties [7–9] which may also trigger the conductivity of ion channels.

In aqueous solution lidocaine molecules exist as a mixture of uncharged and positively charged (protonated) species depending on the pH value of the solution (the pK value of lidocaine is estimated to be between 7.5 and 9) [10]. Inside membranes the balance is shifted in favor of the uncharged species [11]. It is assumed that the anesthetic action of lidocaine (as well as other local anesthetics) is related to its protonated form [4]. The role of the uncharged form may also be important: due to its higher hydrophobicity, the uncharged form has higher membrane-water partition coefficient [11] and thus can faster penetrate and diffuse in membranes.

Experimental results providing information about molecular interactions of lidocaine with surrounding lipid membrane are rather fragmented. Fourier-transform infrared spectroscopy (FTIR) studies [12] have shown that local anesthetics are positioned in the membrane-water interface region and may compete for the water molecules with lipid headgroups. The presence of lidocaine leads also to a more fluid character of the lipid membrane and decreases transition temperature to the gel phase [9,12]. EPR and NMR spectroscopy studies of the uncharged lidocaine in phosphatidylcholine membrane have been reported [13,14] and a model for a preferential location of lidocaine near the glycerol region has been suggested.

In this paper we report, to our knowledge, the first computer simulation study of structural and dynamical properties of lidocaine molecules in a lipid bilayer. During the last decade, molecular dynamics simulations have been extensively used to study many properties of lipid membranes [15–20] including cases where some other components (cholesterol [21], methanol or ethanol [22]) where added. Molecular simulations enable us

*Abbreviations:* DMPC, Dimyristoylphosphatidylcholine; EPR, Electron paramagnetic resonance; FTIR, Fourier-transform infrared spectroscopy; MSD, Mean square displacement; MFT, Mean field theory; NMR, Nucleic magnetic resonance; PME, Particle mesh Ewald; RDF, Radial distribution function; SPC, Simple point charge.

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to follow every detail of the molecular motion and thus provide a unique insight into machinery behind all molecular processes. In this work we address questions relevant for general understanding of interaction of lidocaine molecules with surrounding lipids: location of lidocaine in membrane, diffusion, hydration, formation of hydrogen bonds. Also, orientational order of lidocaine and lipid molecules is investigated and analyzed using a simple mean field theory. We consider both charged and uncharged forms of lidocaine molecules and compare their properties.

## 2. Simulation details

Two different lipid bilayer systems, each consisting of 128 (64 × 2) dimyristoylphosphatidylcholine (DMPC) lipids, 3655 water molecules and 12 lidocaine molecules were simulated. The system with charged lidocaine contained also 12 chloride ions to balance the charge. In addition to the systems containing lidocaine molecules, one system containing a pure fully hydrated bilayer was simulated as a reference.

For DMPC lipids, we used the united atom model for hydrocarbon groups. Previous studies of phospholipid bilayers have shown that both united atom and all-atom force fields yield generally similar results, while the united atom model provides more than three-fold saving of the computer time due to a significantly lower number of atoms. The lipid force field parameters for bonded and non-bonded interactions as well as atomic partial charges are based on the GROMOS force field [16], with modification by Berger et al. [17]. The DMPC molecular structure with the names of atoms referenced in the text is shown in Fig. 1. For water the simple point charge (SPC) model was used [23].

As for the lipids, the united atom model was used to describe lidocaine (except the polar H atom in the charged form). Though all-atomic model, including possibly polarization effects, may be important for correct presentation of pi-interactions in the aromatic ring, we did not include these effects in order to keep consistency with the used lipid model. Similar united atom model was previously used in DPPC–cholesterol simulations [21]. The lidocaine molecular structure and interaction parameters were prepared using the *prodrg* server [24]. The interaction parameters were taken from the GROMOS force field included into GROMACS simulation package [25]. The partial atom charges for the both forms were assigned according to the charges of similar molecular fragments found in the GROMOS force field, with modifications based on Hartree–Fock quantum chemical calculations carried out for optimized geometries of these molecules using

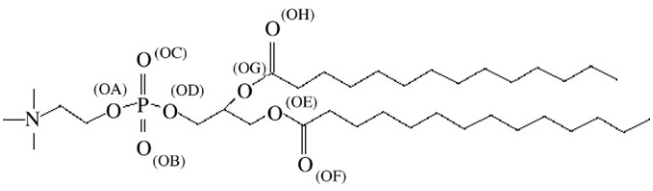


Fig. 1. The DMPC molecule with atom names used in the text.

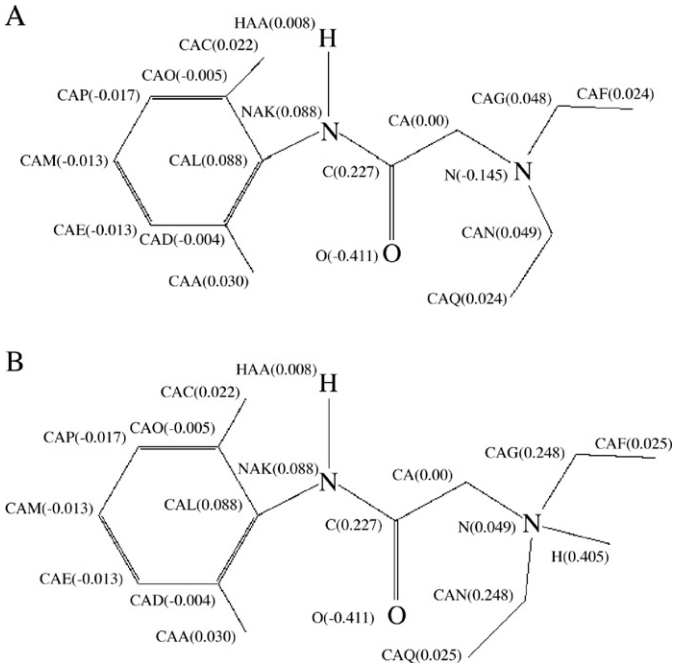


Fig. 2. Uncharged (A) and charged (B) lidocaine with atom names used in the text.

6–31* basis set. The lidocaine molecules with partial charges and atom names are shown in Fig. 2.

The starting configuration for the lipids was taken from our previous simulation [20], where the lipids were in the liquid crystalline phase. The lidocaine molecules were inserted in close vicinity to the membrane surface and with an equal number of molecules on both sides of the bilayer. Then water molecules were added in necessary amount not overlapping with the already placed components. The systems were energy minimized and in each case a 1 ns pre-equilibration run with isotropic cell fluctuations was carried out. The starting configuration of the reference neat bilayer system (including water) was used from the previous simulation [20] without modifications.

All simulations were preformed with the Gromacs simulation package v. 3.2 [25]. All bond lengths were kept constant at their equilibrium values using the LINCS algorithm [26]. The time step was set to 2 fs.

The temperature in the simulated systems was set to 310 K and was regulated separately for lipids and for water/lidocaine using the Nose-Hoover thermostat [27]. This temperature corresponds to the liquid crystalline structure of the neat DMPC bilayer. It is also known that addition of local anesthetics decreases the temperature of transition to the gel phase [12] that is why the bilayer remains in the liquid crystalline phase even upon addition of lidocaine. The pressure was set to 1 atm and was regulated by the Parrinello-Rahman barostat [28] semi-anisotropically with two degrees of freedom: one along the $Z$ dimension and another in the $XY$ plane. The relaxation constants were set to 0.4 ps for the thermostat and 2.0 ps for the barostat.

The long range electrostatic forces were treated by using the Particle Mesh Ewald (PME) algorithm [29]. In a number of methodological studies it was demonstrated that the Ewald