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A comparison of sulfur mustard and heptane penetrating a dipalmitoylphosphatidylcholine bilayer membrane

Thomas J. Müller*, Florian Müller-Plathe

Theoretische Physikalische Chemie, Eduard-Zintl-Institut für Anorganische und Physikalische Chemie, Technische Universität Darmstadt, Petersenstrasse 20, 64287 Darmstadt, Germany

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ABSTRACT

In the present molecular dynamics simulations we study the chemical warfare agent sulfur mustard (bis(2-chloroethyl) sulfide) and the alkane heptane inserted into a dipalmitoylphosphatidylcholine (DPPC) bilayer, a generic model for a biological membrane. We investigate the diffusion, the orientation, the preferred positioning, and the end-to-end distance of the solutes within the membrane as well as the corresponding coupling times. We compare results of equilibrium simulations and simulation at different external forces, which drag the solutes through the membrane. These properties lead to a general comparison of the rotational and translational behaviors of the two solutes during the penetration of the membrane. We show that sulfur mustard, due to its atomic charge polarization, its bigger flexibility and its smaller molecular volume, is the faster moving molecule within the membrane. In last consequence, we show that this leads to different limits for the transport mechanism as observed in these simulations. For heptane the hindrance to penetrate into the membrane is significantly higher than for sulfur mustard. In contrast to heptane molecules, which spend the most of the time penetrating the tail groups, sulfur mustard needs more time to escape the tail group–head group interface of the membrane.

1. Introduction

Although French, German and British chemists were working with sulfur mustard (bis(2-chloroethyl) sulfide, CAS number 505-60-2) in the 19th century [1], the oily liquid became famous in the 20th century under the names mustard gas and yperite as a persistent chemical warfare agent which was first used by the Germans to win a tactical victory against English troops in the battle near Ypres in 1917 during World War I. The warfare agent caused many deaths but far more painful casualties for which it became famous [2]. During the 20th century sulfur mustard was used in military conflicts by many nations around the world. The most recent documented usage of sulfur mustard was in 1988 against the Kurds in Iraq. Currently several nations still have old stocks of sulfur mustard [3]. The most recent official declaration of previously unreported stockpiles was made by Libya in 2004 [1].

At room temperature sulfur mustard is a oily fluid. Due to impurities weaponized sulfur mustard is brownish (yellow to black) with a slight odour of garlic, mustard and rubber. Pure $C_4H_8C_{l2}S$ is a colorless viscous liquid with a melting point at 14 °C. Sulfur mustard is barely soluble in water while it has a high solubility in organic solvents like acetone and ether, fats and oils. [4,5] Exposure to sulfur mustard causes skin and eye injuries and can also damage the respiratory system. Since sulfur mustard is a potent alkylating agent, it causes vesication of epidermal surfaces (blisters). At high dose exposure, it is genotoxic, mutagenic and carcinogenic. This toxicity is related to the ability of sulfur mustard to spontaneously form onium compounds which react with electron rich sulfhydril (–SH) and amino ($-NH_2$) groups of proteins, nucleic acids and other tissue macromolecules [6].

The severe impact of sulfur mustard on the human health comprise the majority of the work published in peer-reviewed literature. Detection, description of poisoning effects and treatment are a major part of the contributions. Physicochemical contributions, however, are quite sparse. Recently, Shukla et al. performed quantum calculations on the reaction path of nitrogen mustard derivates on DNA [7]. While the reaction schemes for reactions within the cell have been studied in detail, there is, to our best knowledge, no study about the transport mechanisms. The dependence of the toxicity on the intake path (oral, inhalation, dermal and eye) is well known but how the molecules get into the cells, where they attack DNA, is not reported. General knowledge about the membrane penetration of sulfur mustard is also important for the decontamination process, since often emulsions or more recently microemulsions [8] are used as decontamination agents.

This work starts investigating the transport process at a basic level. To act as an alkylating agent, the molecule has to travel across several membranes to get to the DNA. Since membranes are

* Corresponding author. Tel.: +49 6151 16 5289; fax: +49 6151 16 6526.
E-mail address: t.mueller@theo.chemie.tu-darmstadt.de (T.J. Müller).

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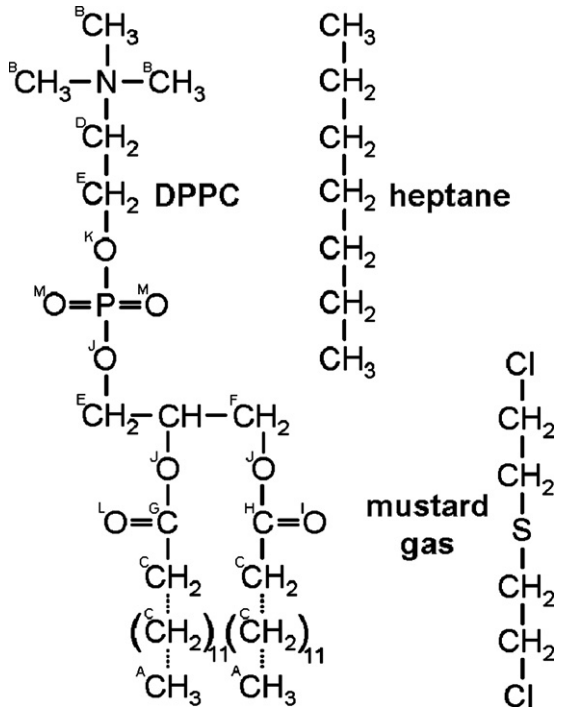

Fig. 1. Schematic specification and naming convention of the simulated molecules.

generally barriers to transport processes, we investigate in this computer simulation some aspects of the physicochemical behavior of sulfur mustard molecules in a model dipalmitoylphosphatidylcholine (DPPC) bilayer membrane, like their orientation, their preferred localization, and the forces required to move them. For reference, we compare these results to the structurally comparable *n*-heptane molecules in the same DPPC membrane (cf. Fig. 1).

For this type of study computer simulations, in our case molecular dynamics, provide several advantages. They are not only hazardless to execute, but also allow the necessary detailed insight into the system at the atomistic level. Computer simulations are a well established and often used method to study small molecules within membranes. Next to water, which is one of the most investigated molecules [9–11], because it is also of importance as the solvent of biological membrane systems, other relevant biological molecules like different sugars [12–14], helical structures [15], or anaesthetics [16] are topics of recent research. Computer simulations are often used to characterize the interactions between small molecules and biological membranes [17,18] and gas permeability with and without channels [19].

The present work is aimed at a qualitative understanding of the microscopic structures and processes only, as for the most part, there are no experimental values of sufficient accuracy to compare with. The understanding of motion patterns is important. A secondary goal is the investigation and elucidation of qualitative differences between the semi-hydrophobic sulfur mustard, which contains a few hetero atoms and the completely hydrophobic *n*-heptane. Using a united atoms approach for this study both molecules consist of seven atoms and are also comparable in size. But the force field description of the two molecules differ significantly in their partial charges (which sulfur mustard has and heptane has not). As we are at present not after quantitative transport coefficients, we use off-the-shelf force field parameters without further optimization, which are deemed good enough for both objectives.

2. Method

The simulation package which was chosen for this investigation is YASP, which was initially written by Müller-Plathe [20] and has recently been parallelized by Tarmyshov and Müller-Plathe [21].

The motion of the atoms in this program is based on a potential built of six different parts [22]:

$$V_{\mathrm{tot}} = V_{\mathrm{LJ}} + V_{\mathrm{Coulomb}} + V_{\mathrm{angle}} + V_{\mathrm{torsion}} + V_{\mathrm{hd}} + (V_{\mathrm{bond}}) \tag{1}$$

the non-bonded potentials were based on Lennard–Jones interaction V_{LJ} (applying the Lorentz-Berthelot mixing rules [23]) and the Coulomb interaction of partial charges V_{Coulomb}. The truncation error induced by using a cutoff radius was reduced applying a reaction field correction. Of the bonded potentials we used the harmonic angle potential V_{angle}, the harmonic dihedrals potential V_{hd}, and the cosine based torsion potential V_{torsion} while we did not use the harmonic bond potential but fixed the distances between bonded atoms using the SHAKE algorithm [24].

To change from simulations at constant number of particles, constant volume and constant energy (NVE) to simulations at constant temperature (NVT) a Berendsen thermostat was applied to couple the system temperature to an external bath. To perform simulations at constant pressure (NPT) instead of constant volume we use additionally a Berendsen manostat [25].

In addition to equilibrium simulations, YASP also allows the user to apply constant external forces F to selected atoms. This method has previously been applied to study the gas sorption and transport of small gas molecules in polyisobutylene [26]. Here it is applied to study the transport of heptane and sulfur mustard in an inhomogeneous system. The external forces are balanced in a way to conserve the total linear momentum and to avoid a drift of the system. The system responds with a flux of molecules J (which depends on the simulation box volume V, and the velocity of the particles v_i) to the applied external force (here applied in the z direction). From this flux the diffusion coefficient D can be calculated, knowing the Boltzmann constant k_{B}, the number density ρ of the penetrant molecules, the temperature T, and the external force F_z [22,27]:

$$J = \frac{1}{V}\sum_i (-1)^i v_i \tag{2}$$

$$D_{zz} = \frac{k_{\mathrm{B}}T}{\rho F_z}\langle J(t \to \infty)\rangle \tag{3}$$

This description will be compared to the diffusion coefficient calculated from the mean square displacement in equilibrium simulations using the Einstein relation:

$$D = \frac{1}{2\mathrm{dim}}\lim_{t\to\infty}\frac{d}{dt}\langle|\mathbf{r}(t) - \mathbf{r}(0)|^2\rangle \tag{4}$$

In this expression t is the time, $\mathbf{r}$ are the coordinates of the atoms and, when treating small molecules, the molecule's center of mass. Finally, dim is the number of spatial dimension accessible to the diffusing particle. While in homogeneous bulk the particle can diffuse in all three dimensions (dim = 3), it is inhibited in a bilayer to wander in the z direction (dim = 2).

We are looking at three different properties of the solutes in this paper: the position of a molecule, which was always characterized by the central atom (S in sulfur mustard, and CH_2 at position 4 in heptane), the end-to-end distance (ee), and the angle of the molecule to the z axis (the axis perpendicular to the membrane), which is calculated from the end-to-end vector and the z axis. For calculating distributions, the first two properties do not need any further modification. The orientation angle to the axis is different, since projecting the total orientation onto the z axis neglects the orientation in x and y directions. There are more possible orientations perpendicular to the z axis, than along it. To correct this effect of the