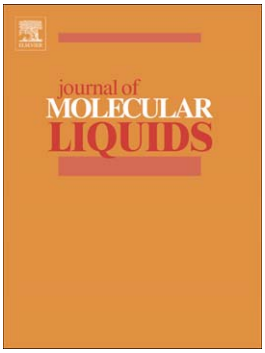

Interaction of anticancer drug doxorubicin with sodium oleate bilayer: insights from molecular dynamics simulations

Tymofii Yu.Nikolaienko

PII: S0167-7322(16)32077-3
DOI: doi:10.1016/j.molliq.2016.11.065
Reference: MOLLIQ 6612

To appear in: *Journal of Molecular Liquids*

Received date: 29 July 2016
Revised date: 17 November 2016
Accepted date: 19 November 2016

Please cite this article as: Tymofii Yu.Nikolaienko, Interaction of anticancer drug doxorubicin with sodium oleate bilayer: insights from molecular dynamics simulations, *Journal of Molecular Liquids* (2016), doi:10.1016/j.molliq.2016.11.065

Interaction of anticancer drug doxorubicin with sodium oleate bilayer: insights from molecular dynamics simulations

Tymofii Yu.Nikolaienko[a*]

[a] Taras Shevchenko National University of Kyiv, Faculty of Physics,
64/13, Volodymyrska Street, City of Kyiv, Ukraine, 01601; Tel: +38 097 452 45 57; E-mail: tim_mail@ukr.net

Abstract

The structure of a complex spontaneously formed by the molecule of anticancer drug doxorubicin hydrochloride (DOX) and sodium oleate (OLA) bilayer via non-covalent interactions has been investigated by means of molecular dynamics simulations. It has been shown that non-covalent interactions in the studied system are as strong as to achieve the binding free energy of 55 kJ/mol, which is sufficient to ensure thermodynamic stability of the complex. The spatial structure of the formed complex (orientation of DOX molecule relative to OLA bilayer, atomic composition of the nearest environment of DOX, the conformation of DOX molecule) have been studied in details. The calculated potential of mean force acting between DOX and OLA bilayer has been shown to arise from forces of short-range nature which are most likely to be the solvent-mediated (hydrophilic/hydrophobic) interactions.

Keywords: molecular dynamics; drug delivery; non-covalent interactions; potential of mean force.

1. Introduction

It is generally believed that one of the most efficient ways to enhance the biological effect of drugs and to reduce their side effects is making the drug delivery targeted[1]. This is especially important for extremely toxic drug substances[2,3], and/or in the situations when very high drug doses are required as, for example, in cancer treatment. Making drug delivery targeted relies on ‘drug vectors’, that is, requires attaching a drug molecule to such a ‘carrier particle’ whose movement inside the living organism can be controlled. Although very different ways of the drug vectors (carrier particle) preparation are possible (e.g., employing diverse host-guest interactions that lead to cage-like molecular assemblies able to strongly entrap their cargo[4]), they often take advantage of self-organization abilities of amphiphilic molecules[5,6] (see Table 1 in [7] for the list of basic structures and materials used in nanoparticle formulations). In some cases the carrier is (self-)assembled directly from amphiphilic molecules in solution[1], while in other cases these molecules are used to cover an existing ‘core’ and, possibly, to make its surface biocompatible[8,9]. One way or another, the conjugation of drug molecule with the structures formed by amphiphilic molecules is ubiquitous in the structures used for targeted drug delivery.

However, the details of the physics involved in the interactions between drug molecules and amphiphilic structure often remain obscure[10]. It is worth noting that the systems involving these interactions can also find their applications beyond the field of targeted drug delivery, e.g., for removing cytostatic drugs (in particular, doxorubicin) or cytostatic residues from waste waters or other aquatic environments [11].

In this paper we investigate, by means of molecular dynamics simulation, the structure of a complex which is spontaneously formed by a molecule of anticancer drug doxorubicin (DOX) and sodium oleate (OLA) bilayer due to non-covalent interactions, i.e., without formation or breakage of chemical bonds, that is, without chemical modification of the drug molecule itself. We show that non-covalent interactions in the studied system are sufficiently strong to ensure thermodynamic stability of the complex and, what is more, our results suggest that the mechanism of binding to the amphiphilic bilayer revealed for DOX is equally possible for other